Health & Fitness Journal
of Canada

Volume 8 **September 30, 2015** **Number 3**

ARTICLE

Progressive high volume aerobic training increases arterial augmentation index.

Jamie F. Burr[1], David Jenkins[2], Jeff Coombes[2], and Wade L. Knez[3]

Abstract

Objectives: This paper examines high-volume aerobic exercise participation on the temporal stability of augmentation index (AIx). *Methods:* Six participants (25 ± 4 yr, VO_2max = 56.0 ± 7.2 mL·kg^{-1}·min^{-1}) and a control group matched for age, height, weight and sex progressed from a modest weekly training load (4.9 ± 1.9 hr) of moderate/vigorous mixed modality physical activity to 18.3 ± 0.4 hr over a period of 8 wk. A control group maintained regular exercise and lifestyle. Resting AIx, blood pressure and 30 km cycling time trials were tracked bi-weekly, with aerobic power measured pre- and post-intervention. VO_2max improved significantly (5.4%), while peripheral/central blood pressure, and resting HR remained unchanged. Performance improved significantly at week 2 and 4 with no improvement at weeks 6-8. The AIx of the training group increased significantly between weeks 0, 4, and 8, while no changes occurred in the control. A progressively increasing volume of aerobic exercise training for 8 wk, appears to increase AIx, likely owing to an uncompensable training load induced stress. **Health & Fitness Journal of Canada 2015;8(3):3-13.**

Keywords: Cardiovascular, Augmentation index, Pulse wave, Overtraining, Ultra-endurance

From [1]Human Health and Nutrition Sciences, University of Guelph, Guelph ON, Canada; [2] School of Human Movement Studies, University of Queensland, Brisbane; [3] Research and Education Centre, Aspetar; Qatar Orthopaedic and Sports Medicine Hospital, Doha, Qatar. Email: burrj@uoguelph.ca

Introduction

The health benefits of regular moderate intensity physical activity are irrefutable (Warburton et al., 2006). Epidemiological data shows regular moderate intensity physical activity to decrease cardiovascular morbidity and mortality (Paffenbarger et al., 1986). Furthermore, improvements in arterial risk factors have occurred in response to both short (Heffernan et al., 2007) and long-term habitual participation (Tanaka et al., 1998). Notwithstanding, there is evidence to suggest that people who regularly train for and compete in prolonged endurance events are not immune from cardiovascular risk. Historically, in fact, approximately 75% of cardiovascular events recorded during marathon racing occurred in runners with existing disease (Noakes et al., 1984). Recent data examining acute alterations in well recognized vascular mediated risk factors show no effect on arteries following participation in the marathon (42.2 km) (Burr et al., 2014b; Vlachopoulos et al., 2010b), whereas participants running ultra-endurance marathon running races (>120km, up to 40 consecutive hours) acutely revealed significant alterations after a race (Burr et al., 2012). Similarly, exposure to downhill running, which is used to impose a particularly potent exercise stress, has been shown to induce a delayed arterial stiffening that coincides with the timing of maximal muscle soreness and the typical inflammatory response (peak at 48 hr) (Burr et al., 2014a). This inflammatory effect is commonly observed after prolonged running (Kim et al., 2007).

Despite differing acute effects of the marathon and ultra-marathon, habitual participation in both lengths of race are associated with baseline alterations in vascular risk factors when compared to normative age matched controls (Burr et al., 2013; Vlachopoulos et al., 2010b), and some recent data suggests a correlation of sub-clinical myocardial damage with frequent marathon running (Mohlenkamp et al., 2008); a finding that remains controversial.

Seemingly contradictory data showing both beneficial and potentially detrimental effects of aerobic exercise on cardiovascular health may suggest that the body responds differently to exercise stimuli at differing points on the volume spectrum. Given the increasing popularity of long-distance aerobic exercise events (Knechtle et al., 2010) and the current lack of knowledge in relation to the dose-response to prolonged exercise, this is an important area of investigation, and this pilot work represents an important starting point. Understanding the effects of increasing exercise volume on vascular function could inform optimal training and racing practices from both a performance and clinical perspective. Subsequently, we sought to examine the effect of an increasing aerobic exercise stimulus on arterial wave reflections, as measured using augmentation index (AIx) in a small group of athletes capable of steadily increasing exercise volume. We hypothesized that a steady increase in training volume over a period of 8wk would lead to increases in resting AIx.

Methods

We incorporated an interventional pre-post design with a parallel control group. Owing to the intensive demands of this intervention, groups could not be randomly assigned (see below), thus a case-control design is well suited to examine the effects of increasing volume on cardiovascular wave reflections, our main outcome of interest.

Participants

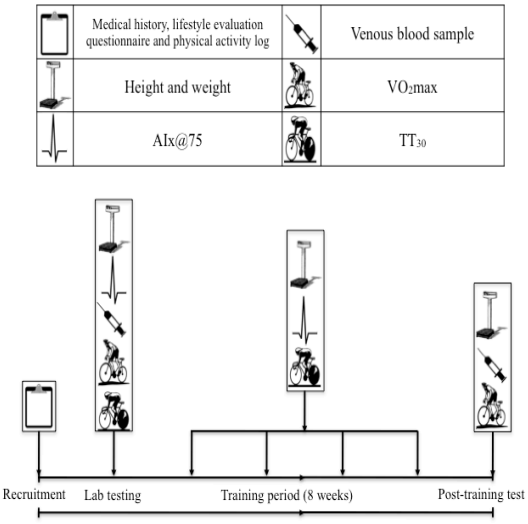
A total of 12 participants (8 male, 4 female) were employed for this study; 6 who were committed to initiating intense prolonged training for 8 wk in preparation for long distance endurance racing (triathlon) and 6 who represented a recreationally active control group matched for age, height, weight, blood pressure and sex. Given the pilot nature of this investigation, the control group was essentially included as a match to our pre-selected cases, intended only to exclude the possibility that extraneous life factors that were completely unrelated to the exercise intervention were responsible for a population wide effect of any observed alterations. It is recognized that this is not a perfect control, but was deemed acceptable for initial proof of concept, with the understanding that a full RCT would be preferable for a future full-scale follow-up study.

All participants provided written informed consent in accordance with the declaration of Helsinki, and this study was approved by the institutional review board for human research. The training group was comprised of moderately-trained subjects (VO_2max = 56.0 ± 7.2 $mL \cdot kg^{-1} \cdot min^{-1}$) that already participated in a modest amount of mixed modality endurance training (triathlon), a requisite trait for identification of an ability to progress from shorter distance races up to the “ultra” distance category. Although the selection of these athletes meant that they were already somewhat more

trained than the recreational norm at baseline, recruiting unmotivated, non-training participants would have resulted in an unacceptable risk of injury, low adherence, burnout, and/or dropout. The control was group comprised of recreationally active members of the general population, who were normally active but did not engage in structured exercise training to increase fitness or performance. Matching participants for both age and fitness presented a challenge as age matched participants are not expected to have fitness >50 $mL \cdot kg^{-1} \cdot min^{-1}$ according to normative means, and if trained controls were available, the effect of continued training or detraining would have been a concern. Participants were instead matched on sex and age, both of which also have important influences on vascular form and function and which were stable for the study duration. Despite being of somewhat lower fitness at baseline, the control group was important to account for possible alterations in fitness or outcome measures that occurred as a result of non-training related factors. Exclusion criteria for participants included the presence of known cardiovascular risk factors such as obesity, diagnosed cardiovascular disease, poor blood lipid profile, diabetes, alcohol dependence/abuse, and the use of any medications or vitamin supplements.

Upon recruitment and following the submission of the informed consent, the physical activity participation and medical status of each participant was obtained by questionnaire. Laboratory testing (measures of blood pressure, 30 km trial time, blood sampling and pulse wave analysis for AIx) was completed at baseline and each 2 wk during the 8 wk training period. An overview of the experimental design and study period is shown in Figure 1. All testing took place in a climate controlled exercise laboratory (~21^0C, 40-60% RH, 760-770 mmHg). At the initial visit participant height and mass were recorded along with baseline cardiovascular measures. The next visit required both groups to participate in a maximal aerobic fitness test (VO_2max), which was repeated following the 8wk intervention. For cardiovascular measures and performance tests, participants were instructed to report to the laboratory having abstained from alcohol, caffeine and tobacco use following a 12 hr fast and refraining from exercise for 36 hr.

Figure 1. Diagramatic representation of the methodological timeline.



Both the control and training groups underwent pulse wave analysis to determine the AIx, which is a ratio calculated from the blood pressure waveform and accounts for the augmentation of the forward waveform when it meets with reflected waves returning from distal portions of the vascular tree (Shimizu and Kario, 2008). Among other factors, as the stiffness of

the vessel increases, the velocity of wave propagation also increases, and thus reflected waves return more quickly. By altering these temporal patterns, it becomes more likely that the arrival of the wave coincides with systole, and the work of the myocardium is consequently increased owing to the greater afterload (Laurent and Boutouyrie, 2007). This technique has well documented limitations for certain applications (Laurent et al., 2006) including acute exercise (increased heart rate affects timing of pulse waves) and for comparisons across the age span and differing body sizes, and between genders. However, these methodological considerations were largely inconsequential for the current investigation as we employed only resting data collection, in a repeated measure age and gender matched experimental design. At rest, both the training and control groups displayed AIx values, which fit within the normative population values included with the measurement software (SphygmoCor, Atcor Medical, Sydney, Australia). Descriptive participant characteristics are presented in Table 1.

Prior to cardiovascular measures, participants were instructed to sit quietly for a period of 30 min. Systolic (SBP) and diastolic (DBP) brachial blood pressures were measured in triplicate using the left arm supported at the height of the heart, with an Omran (T4)-Digital Blood Pressure Monitor. All BP measures were taken prior to the tonometric tracking of arterial pulse, which was used for the calculation of AIx (SphygmoCor Pulse Wave Analysis System, SCOR-Px, Software Version 6.x.). Pulse contours were collected from the left radial artery of the participants' stabilized forearm using a high fidelity Millar strain gauge transducer (Millar instruments, Houston, TX). The participant's wrist was slightly hyperextended and braced during measurement while manual palpation was used to locate the strongest pulse, which was selected for tonometer placement. A 30 s measurement of arterial pulse was collected for analysis, with stringent controls for the quality of the captured signal. The final operator index was 94.2 ± 1.3%. To control for the relatively minor effect of differing day-to-day resting heart rates, all measures were corrected to a heart rate of 75 bpm. Subendocardial viability ratio, a measure of myocardial oxygen supply and demand, was calculated using values from pulse wave analysis.

Table 1: Baseline data for age, height, mass, BP, AIx@75, cholesterol, VO_2max and resting HR (mean ± SD).

Variable	Training	Control
Age (yrs)	24.5 ± 4.7	24.5 ± 4.3
Height (cm)	174.2±7.5	174.7±7.9
Mass (kg)	68.7 ± 3.7	73.8 ± 12.9
SBP (mmHg)	112.7 ± 15.1	112.7 ± 14.1
DBP (mmHg)	62.0 ± 5.0	74.5 ± 2.9
AIx@75	-15.5±11.9	-3.5±14.9
Cholesterol (units)	4.2 ± 0.6	4.3 ± 0.9
VO_2max ($mL \cdot kg^{-1} \cdot min^{-1}$)	56.0 ± 7.2	43.2 ± 8.2
Resting HR (bpm)	49.9 ± 5.4	55.7 ± 4.3

SBP, systolic blood pressure; DBP, diastolic blood pressure; AIx@75, augmentation index at 75 bpm.

VO_2max was assessed using a progressive-load cycle test on an electro-magnetically braked ergometer (Lode, Groningen, Netherlands). The test was initiated with 100 W load and increased 30W every 3 min until volitional fatigue. Attainment of a true maximal value was confirmed by the presence of a plateau in oxygen consumption, defined as an increase of less than 100 $mL \cdot min^{-1}$ with increasing workload, and an RER > 1.15.

To minimize possible variations in efficiency and performance during the test, participants were instructed to pedal at an approximate cadence of 90 rpm for both tests. Direct gas analysis for O_2 and CO_2 was performed on expired air using electro-chemical analyzers (Ametek S-3A/1 and CD3A, Pittsburgh, USA) calibrated with known gas concentrations. Flow was quantified from inspired air using a turbine ventilometer (Morgan Mark 2, England), connected to a standard two-way breathing valve (Hans Rudolph, Kansas City, USA).

Throughout the 8 wk training intervention, the training group consistently increased their training exercise volume from 4.9 ± 1.9 to 18.3 ± 0.4 hr·wk^{-1} (mean bi-weekly training increase of 3.8 ± 1.4 hr·wk^{-1}), while the control group maintained their non-training behaviour. Training involved the modalities of triathlon, which are cycling, swimming and running. The progressive duration exercise bouts were performed in a prolonged fashion as an athlete would use to prepare for a long distance event (Ironman), and intensity was thus sub-maximal with the majority of training time at or below the aerobic adaptation zone of approximately 75% VO_2max. Individual training sessions, were not tracked as overall volume was the focus. Bi-weekly measures of brachial BP, AIx and body mass were performed on both training group and control group to track changes over time. Additionally, the training group's exercise performance was measured at baseline and bi-weekly for 8 weeks using a simulated 30km time trial. Participants used their own properly fitted road bicycles mounted on a stationary trainer (Cyclosimulatory CS-1000; Cateye Co. Ltd., Osaka, Japan). During the time trial, participants were provided feedback on heart rate and elapsed distance, but not time.

Statistical analyses

All statistical analyses were performed using SPSS (21.0). A one-way analysis of variance (ANOVA) for repeated measures was used to assess the main effects of each Group (training group or control group) and Time (0 h, 2, 4, 6, and 8 wk) on changes in mass, BP, cholesterol, resting HR, training volume and 30km time trial. Where a significant interaction was found, post-hoc pairwise comparisons were performed. Pearson's correlation coefficient was used to examine potential relationships between training volume and AIx@75. Mauchly's test was used to assess for sphericity and in case of violation Greenhouse-Geisser epsilon correction was used to adjust degrees of freedom. Statistical significance was accepted at $p < 0.05$.

Results

Table 2 displays the mean (±SD) of the changes in the training group over the 8-week experimental period. No changes were observed in control group on any variable throughout the 8 weeks of the experimental period. For the training group, no changes were observed in body mass, SBP, DBP or resting HR. Blood lipids, which are associated with baseline cardiovascular risk, remained unaltered through to week 8. However, the increase in training volume resulted in an increase in VO_2max of the training group by 5.4% ($p = 0.006$) from baseline to week 8.

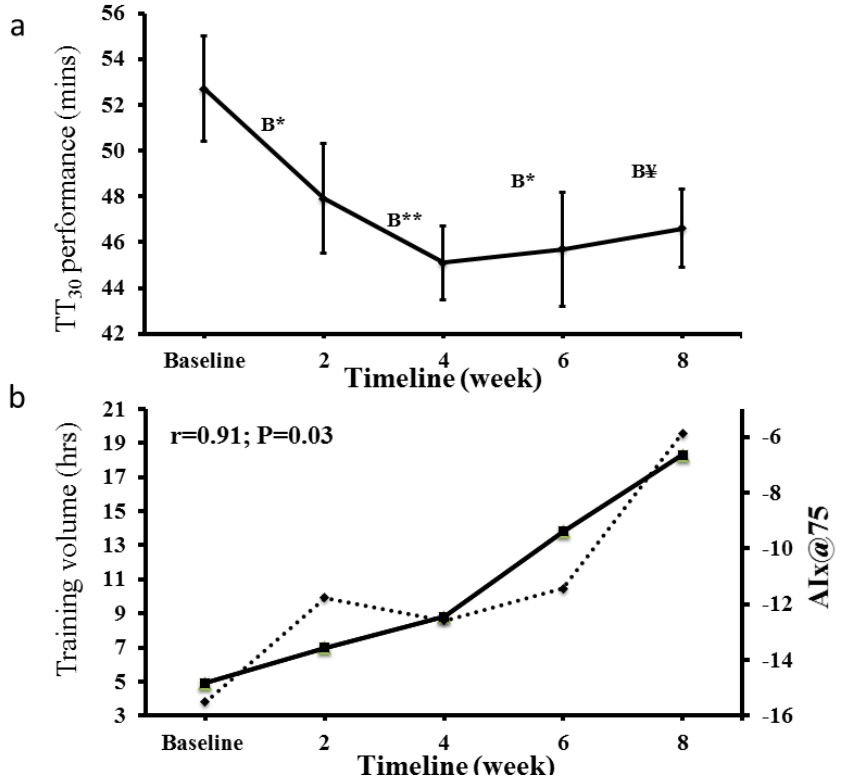
Figure 2 shows that bi-weekly 30 km time trial performance improved in week 2 and again in week 4 followed by a plateau in weeks 6 and 8. Each 30 km time trial performance was significantly faster than baseline.

Table 2: Resting values of mass, SBP, DBP, HR, TC, TRIG, LDL, HDL and AIx@75 for the training group (mean ± SD).

Variable	Training week 0	2	4	6	8
Mass (kg)	68.7±3.7	68.6±9.1	68.3±8.9	68.2±9.0	67.8±8.8
SBP (mmHg)	112.7±14.1	115.3±11.0	114.3±11.1	113.7±8.0	114.5±8.9
DBP (mmHg)	62.0±5.0	60.7±5.4	65.8±3.2	60.7±4.4	62.3±4.4
Resting HR (bpm)	49.9±5.4	51.1±9.5	47.2±9.0	49.0±7.8	50.3±10.3
TC	4.19±0.58	4.36±0.94	4.42±0.74	4.50±0.74	4.10±1.14
TRIG	1.33±0.88	1.32±0.90	1.03±0.74	1.15±0.44	1.35±0.65
LDL	2.23±0.80	2.46±0.68	2.68±0.62	2.69±0.79	2.3±1.0
HDL	1.4 ±0.2	1.3±0.3	1.27±0.3	1.29±0.26	1.2±0.3
AIx@75	-15.5±11.9	-11.7±9.4	-12.6±9.4	-11.4±9.6	-5.8±8.4*B, *4

SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TRIG, triglycerides; LDL, low density lipoprotein; HDL, high-density lipoprotein; AIx@75, augmentation index at 75 bmp. *p < 0.05. *B=significantly difference between week 8 & baseline; *4=significantly difference between week 8 and week 4.

Figure 2 a (top): Changes in time trial performance over the 8-week study period. Figure 2b (bottom) Pearson correlation coefficient of training volume (dotted line) and AIx@75 (solid line) of the project timeline.

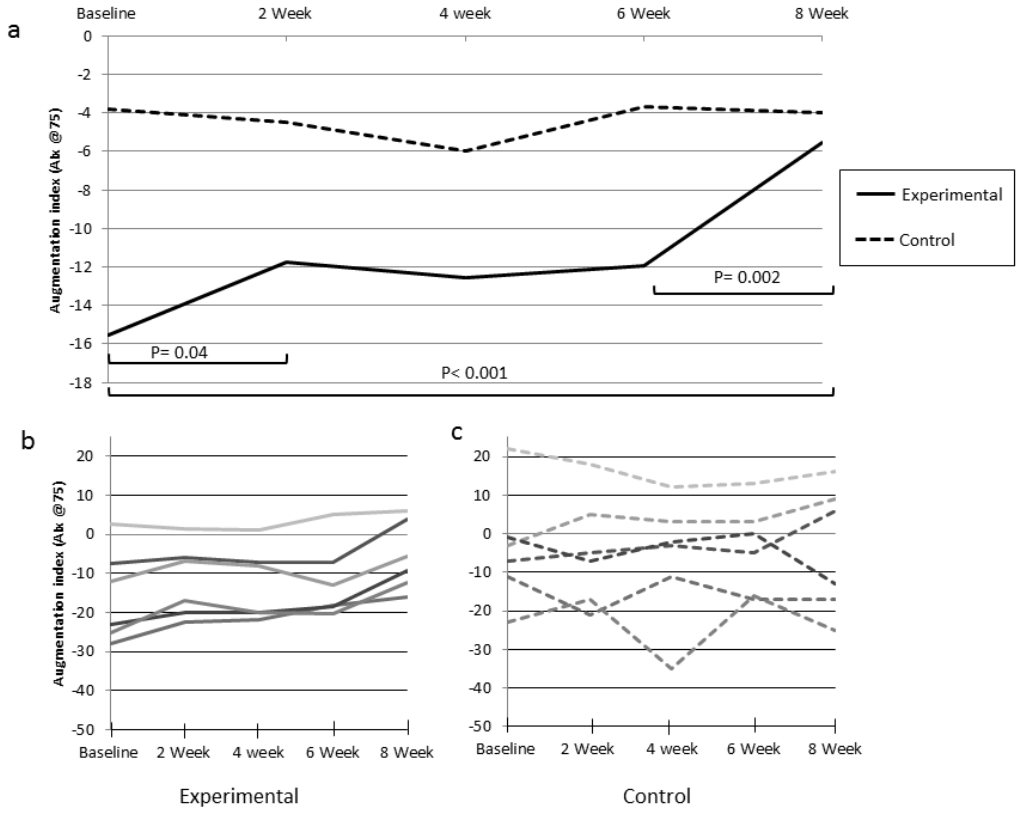


*p < 0.05; **p < 0.01; ¥p < 0.001. B = significantly different baseline to time trial. Error bars = SD.

Although the training group was (by selection) habitually more active than the control group at baseline, the difference in AIx was not statistically significant. The training group significantly changed AIx from baseline after 8wk of progressively increasing volume aerobic exercise training ($p < 0.001$). An initial increase was observed from baseline to the first follow-up at week 2, which was followed by a plateau and an additional increase in stiffness at week 8. No changes from baseline or at any other time point were observed in the control group (Figure 3). Figure 3 demonstrates that no significant changes occurred in the control group, whereas arterial stiffness increased from baseline to 8wk in the training group, with significant increases noted at the 2wk and 8wk time points.

Figure 2 (part b) shows that the increase in the AIx observed over the study period was significantly correlated with the increase in the associated bi-weekly training volume ($r = 0.91$; $p = 0.03$). Although showing signs of a trend toward declining values ($p = 0.058$), no changes were evident in the subendocardial viability ratio of participants as a result of training.

Figure 3. a) Mean temporal changes in augmentation index (arterial stiffness) of the experimental and control groups measured bi-weekly from baseline through 8wk. Individual participant responses of the experimental and control groups are shown in figures b and c respectively.



Discussion

We evaluated the effects of a gradually increasing exercise volume on measures of performance and AIx in moderately trained athletes. The major novel finding of this investigation was that 8wk of aerobic exercise training with a progressive volume of exposure led to an increase in AIx. At present, the implications of an increase in AIx in moderate to well-trained athletes is poorly understood, but within the general population AIx has been associated with clinical events independent of peripheral BP (Vlachopoulos et al., 2010a), and predicts CVD mortality, at least in men (Janner et al., 2013). Altered wave reflections may acutely affect ventricular vascular coupling and cardiac afterload, thus increasing myocardial oxygen demand (Laurent and Boutouyrie, 2007). In the current investigation, all participants were relatively young, fit and healthy and no statistically significant changes were observed in subendocardial viability ratio at rest. It is worth noting that even if the apparent trend toward a decline in subendocardial viability ratio reached significance, values remained high (230 vs. 200) and as such would still be considered healthy. Although the transient augmentation of waveforms that might commonly accompany any exercise that alters pressure and pulse rate is likely of little import to immediate health, a more sustained increased work of the myocardium during rest could be potentially deleterious. Given the recent evidence of select populations of endurance athletes who present with unaltered AIx, but higher resting levels of resting aortic pulse wave velocity compared to age matched controls (Vlachopoulos et al., 2010b) it is clear that these cardiovascular risk factors may be differentially affected by exercise training and lifestyle factors. Recognizing the well-established evidence that aerobic exercise causes favorable cardiovascular health outcomes with increasing benefits as participation progresses from low to moderate volumes of exercise; the current data suggests that this relationship may not be infinitely linear. Rather, there may exist an upper limit to the increasing benefits accrued from higher levels of training. Alternatively, given the progressive and non-periodized training load used in the present study, this data may also suggest a potential use of AIx measures for detecting stress responses or "over-training", but further work to determine such a diagnostic role is required.

Training effects

During the training period we observed significant improvements in the aerobic fitness and 30km time trial performance of the training group. The observed speeds during the time trial were similar, albeit slightly slower, than previous literature in regular male time trialing athletes (Ham and Knez, 2009); but suggested maximal efforts nonetheless. As the participants in the training group were not elite cyclists, the gains in time trial performance evident at the first and second time trials following baseline may represent a combination of an improvement in the athletes' training status as well improvement in their time trialing ability, including pacing and efficiency. It is interesting to observe that increasingly greater amounts of training did not lead to further improvement throughout the last 4wk of the trial, which can be one indication of overtraining in endurance sport athletes (Budgett, 1998). It is also well known that continued

stressful training with inadequate rest can lead to inflammation, illness, injury, and maladaptation (Budgett, 1998).

A notable limitation of the current study was that only AIx was tracked, and information on pulse wave velocity or endothelial function would further our understanding of the relationship between exercise volume and global vascular alterations. As such, future training studies should consider tracking these variables as well. Unavoidable differences between our control and experimental groups at baseline weaken the utility of our control; however, it should be noted that this group would be more, not less, susceptible to alterations as a result of non-training exercise exposures or extraneous stimuli and none were observed. It is also important to point out that even as a case- study, which ignores the control, the observed effects in the experimental group notably increase our understanding of the human vascular response to exercise. To get around the issue of randomizing untrained athletes to such an extreme training regime (and risking dropout, injury etc) future studies could also employ a "detraining" model amongst high level athletes at the initiation of the off-season, with the control continuing training and the experimental group adopting complete cessation.

Currently, the underlying causes and long term consequences of exercise induced alterations in wave reflections remain incompletely understood, and this is an area warranting of further research. It has been postulated that the effects may be mechanistically related to oxidative and inflammatory pathways (Knez et al., 2006), and these types of compensatory reactions to stress have the potential to cause the body to react with an increased arterial stiffness, which in turn would affect the timing of returning waves. A strong relationship has been established between vascular stiffness and oxidative stress in patients with coronary artery disease (Delles et al., 2008) and the link between inflammation and acute changes in vascular stiffness has been demonstrated experimentally using an induced human model (Vlachopoulos et al., 2005). It is also feasible that some alterations in AIx may be attributable to changes in autonomic nervous system activity, which are known to be altered by "over-reaching" exercise (Le Meur et al., 2013) and inflammatory stress responses (Perring and Jones, 2012), and could in turn affect baseline arterial tone. Complimentary data not reported in the current investigation (Knez et al., 2013) from these same subjects indeed supports a link with increased levels of oxidative stress. Further research investigating the temporal stability of these alterations and the effects of de-training on arterial properties will greatly aid in our understanding of the implications of the observed aerobic exercise induced augmentation of pulse waves.

Conclusions

When exposed to a progressively increasing high volume of aerobic exercise training over a period of eight weeks, the AIx of moderately trained athletes increased from baseline. This increase in pulse wave augmentation is likely related to a stress response resulting from high training loads that exceed the tolerable stresses of the normal resting state. This alteration likely indicates a state of imbalance, such that the body's ability to cope with the training stress is overwhelmed.

Practically, this finding should not be interpreted to suggest that aerobic exercise necessarily has deleterious effects on cardiovascular health and should thus be avoided; particularly as the health implications of increased AIx following exercise are, at present, poorly understood. Rather, we suggest that these findings indicate the possible existence of a volume of exercise training that may be too great a load for the body to handle without proper preparation, and that this load appears to be greatly above a level of activity that one could undertake without purposeful effort. Augmentation index may, thus, offer potential as a tool to monitor training related stress.

Acknowledgements

The author's acknowledge no funding relationships or conflicts of interest.

Authors' qualifications

The authors' qualifications are as follows: Jamie F. Burr PhD; David Jenkins PhD; Jeff Coombes PhD; Wade L. Knez, PhD.

References

Budgett, R. (1998). Fatigue and underperformance in athletes: the overtraining syndrome. *British journal of sports medicine, 32*(2), 107-110. Retrieved from http://bjsm.bmj.com/content/32/2/107.full.pdf

Burr, J. F., Boulter, M., and Beck, K. (2014a). Arterial stiffness results from eccentrically biased downhill running exercise. *Journal of science and medicine in sport / Sports Medicine Australia*. doi:10.1016/j.jsams.2014.03.003; 10.1016/j.jsams.2014.03.003

Burr, J. F., Bredin, S. S., Phillips, A., Foulds, H., Cote, A., Charlesworth, S., Ivey, A. C., Drury, T. C., Fougere, R., and Warburton, D. E. (2012). Systemic arterial compliance following ultra-marathon. *International Journal of Sports Medicine, 33*(3), 224-229. doi:10.1055/s-0031-1297956

Burr, J. F., Drury, C. T., Phillips, A. A., Ivey, A., Ku, J., and Warburton, D. E. (2013). Long-term ultra-marathon running and arterial compliance. *Journal of science and medicine in sport / Sports Medicine Australia*. doi:10.1016/j.jsams.2013.04.018; 10.1016/j.jsams.2013.04.018

Burr, J. F., Phillips, A. A., Drury, T. C., Ivey, A. C., and Warburton, D. E. (2014b). Temporal response of arterial stiffness to ultra-marathon. *International Journal of Sports Medicine, 35*(8), 658-663. doi:10.1055/s-0033-1358478; 10.1055/s-0033-1358478

Delles, C., Zimmerli, L. U., McGrane, D. J., Koh-Tan, C. H., Pathi, V. L., McKay, A. J., Steedman, T., Dargie, H. J., Hamilton, C. A., and Dominiczak, A. F. (2008). Vascular stiffness is related to superoxide generation in the vessel wall. *Journal of hypertension, 26*(5), 946-955. doi:10.1097/HJH.0b013e3282f7677c; 10.1097/HJH.0b013e3282f7677c

Ham, D. J., and Knez, W. L. (2009). An evaluation of 30-km cycling time trial (tt30) pacing strategy through time-to-exhaustion at average tt30 pace. *The Journal of Strength & Conditioning Research, 23*(3), 1016-1021.

Heffernan, K. S., Collier, S. R., Kelly, E. E., Jae, S. Y., and Fernhall, B. (2007). Arterial stiffness and baroreflex sensitivity following bouts of aerobic and resistance exercise. *International Journal of Sports Medicine, 28*(3), 197. Retrieved from https://www.thieme-connect.com/DOI/DOI?10.1055/s-2006-924290

Janner, J. H., Godtfredsen, N. S., Ladelund, S., Vestbo, J., and Prescott, E. (2013). High aortic augmentation index predicts mortality and cardiovascular events in men from a general population, but not in women. *European journal of preventive cardiology, 20*(6), 1005-1012. doi:10.1177/2047487312449588; 10.1177/2047487312449588

Kim, H. J., Lee, Y. H., and Kim, C. K. (2007). Biomarkers of muscle and cartilage damage and inflammation during a 200 km run. *European journal of applied physiology, 99*(4), 443-447. doi:10.1007/s00421-006-0362-y

Knechtle, B., Knechtle, P., and Lepers, R. (2010). Participation and performance trends in ultra-triathlons from 1985 to 2009.

Scandinavian journal of medicine & science in sports. doi:10.1111/j.1600-0838.2010.01160.x

Knez, W. L., Coombes, J. S., and Jenkins, D. G. (2006). Ultra-endurance exercise and oxidative damage : implications for cardiovascular health. *Sports medicine (Auckland, N.Z.), 36*(5), 429-441.

Knez, W. L., Jenkins, D. G., and Coombes, J. S. (2013). The Effect of an Increased Training Volume on Oxidative Stress. *International Journal of Sports Medicine*(EFirst).

Laurent, S., and Boutouyrie, P. (2007). Arterial stiffness: a new surrogate end point for cardiovascular disease? *Journal of nephrology, 20 Suppl 12*, S45-50.

Laurent, S., Cockcroft, J., Van Bortel, L., Boutouyrie, P., Giannattasio, C., Hayoz, D., Pannier, B., Vlachopoulos, C., Wilkinson, I., Struijker-Boudier, H., and European Network for Non-invasive Investigation of Large, A. (2006). Expert consensus document on arterial stiffness: methodological issues and clinical applications. *European heart journal, 27*(21), 2588-2605. doi:10.1093/eurheartj/ehl254

Le Meur, Y., Pichon, A., Schaal, K., Schmitt, L., Louis, J., Gueneron, J., Vidal, P. P., and Hausswirth, C. (2013). Evidence of Parasympathetic Hyperactivity in Functionally Overreached Athletes. *Medicine and science in sports and exercise*. doi:10.1097/MSS.0b013e3182980125

Mohlenkamp, S., Lehmann, N., Breuckmann, F., Brocker-Preuss, M., Nassenstein, K., Halle, M., Budde, T., Mann, K., Barkhausen, J., Heusch, G., Jockel, K. H., Erbel, R., Marathon Study, I., and Heinz Nixdorf Recall Study, I. (2008). Running: the risk of coronary events : Prevalence and prognostic relevance of coronary atherosclerosis in marathon runners. *European heart journal, 29*(15), 1903-1910. doi:10.1093/eurheartj/ehn163

Noakes, T. D., Opie, L. H., andRose, A. G. (1984). Marathon running and immunity to coronary heart disease: fact versus fiction. *Clinics in sports medicine, 3*(2), 527-543.

Paffenbarger, R. S., Hyde, R. T., Wing, A. L., and Hsieh, C. C. (1986). Physical activity, all-cause mortality, and longevity of college alumni. *The New England journal of medicine*.

Perring, S., and Jones, E. (2012). Assessment of changes in cardiac autonomic tone resulting from inflammatory response to the influenza vaccination. *Clinical physiology and functional imaging, 32*(6), 437-444. doi:10.1111/j.1475-097X.2012.01147.x; 10.1111/j.1475-097X.2012.01147.x

Shimizu, M., and Kario, K. (2008). Role of the augmentation index in hypertension. *Therapeutic advances in cardiovascular disease, 2*(1), 25-35. doi:10.1177/1753944707086935; 10.1177/1753944707086935

Tanaka, H., DeSouza, C. A., and Seals, D. R. (1998). Absence of age-related increase in central arterial stiffness in physically active women. *Arteriosclerosis, Thrombosis, and Vascular Biology, 18*(1), 127-132. Retrieved from http://atvb.ahajournals.org/content/18/1/127.full.pdf

Vlachopoulos, C., Aznaouridis, K., O'Rourke, M. F., Safar, M. E., Baou, K., and Stefanadis, C. (2010a). Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta-analysis. *European heart journal, 31*(15), 1865-1871. doi:10.1093/eurheartj/ehq024; 10.1093/eurheartj/ehq024

Vlachopoulos, C., Dima, I., Aznaouridis, K., Vasiliadou, C., Ioakeimidis, N., Aggeli, C., Toutouza, M., and Stefanadis, C. (2005). Acute systemic inflammation increases arterial stiffness and decreases wave reflections in healthy individuals. *Circulation, 112*(14), 2193-2200. doi:10.1161/CIRCULATIONAHA.105.535435

Vlachopoulos, C., Kardara, D., Anastasakis, A., Baou, K., Terentes-Printzios, D., Tousoulis, D., and Stefanadis, C. (2010b). Arterial stiffness and wave reflections in marathon runners. *American journal of hypertension, 23*(9), 974-979. doi:10.1038/ajh.2010.99

Warburton, D. E., Nicol, C. W., and Bredin, S. S. (2006). Health benefits of physical activity: the evidence. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne, 174*(6), 801-809. doi:10.1503/cmaj.051351