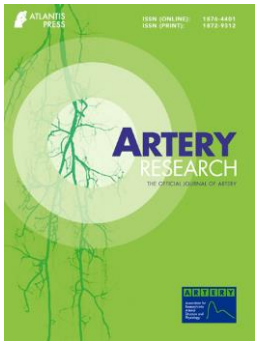

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The clinical importance of exercise blood pressure

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Abstract Clinical exercise stress testing is a common medical test performed in cardiology and exercise physiology clinics the world over. Measurement of blood pressure (BP) during testing is mandated. Whilst systolic BP should normally rise with incremental exercise, and diastolic BP remains relatively stable, abnormal responses can occur. Low BP or 'exercise hypotension' is a known signal of underlying cardiovascular disease and sign of poor prognosis. On the other hand, observational evidence suggests an exaggerated BP response is also associated with heightened cardiovascular disease risk. Historically, research has focused on the BP response to peak or maximum exercise intensities. However, exaggerated BP during submaximal exercise (light-to-moderate intensity) may expose the presence of high BP otherwise not detected by traditional resting measurement in the clinic. Exaggerated exercise BP is related to subclinical cardiovascular disease risk markers such as raised arterial stiffness and impaired cardiac structure and function. The mechanisms underlying such associations are complex, but physiological insight has been gained from studying changes in arterial haemodynamics in response to dynamic exercise. Similarly, there are several known modifiers of the exercise BP response, including age, disease status and aerobic capacity. An area of continued focus is to establish if modifiers, such as aerobic capacity, also modify associations between exercise BP and clinical outcomes throughout the life-course. Future work is also directed towards filling a crucial evidence gap, providing population-based thresholds of exercise BP that are associated with acute and longer-term outcomes. This should pave the way for pragmatic research aimed towards enhancing the clinical use of exercise BP.

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Introduction

Clinical exercise stress testing is frequently performed in cardiology and exercise physiology clinics the world over. This incremental or 'graded' form of exercise testing is generally carried out to establish presence of exercise induced myocardial ischaemia and/or arrhythmia, or for the assessment of aerobic and functional capacity. The measurement of blood pressure (BP) before, during and in recovery from exercise forms a mandatory requirement of each test.[1,2] Irrespective of exercise test mode (which may take the form of a treadmill, cycle, step or walk protocol), systolic BP should normally rise with incremental exercise, theoretically reaching maximal value towards peak intensity.[3] Diastolic BP should remain relatively stable, likely reducing at higher exercise intensities in response to reduction in systematic vascular resistance. Nonetheless, irrespective of BP status at rest, abnormal exercise BP responses can occur. Several lines of evidence suggest that abnormal exercise BP holds clinical relevance in the prediction of cardiovascular risk, as well as revealing the presence of high BP otherwise missed by traditional resting measures.[4] The aim of this paper was to summarise (our) recent work underlying the clinical importance of (abnormal) exercise BP (with a focus on exercise hypertension); whilst describing current and future research endeavours that will enhance clinical use.

The clinical importance of abnormal exercise BP

Exercise hypotension

Clinical exercise guidelines define exercise hypotension as a drop in systolic BP below pre-testing value, or an increase with subsequent decrease in systolic BP of >10 mmHg with increasing exercise intensity.[1,2] A relatively common condition in individuals referred for clinical exercise testing (prevalence estimates > 6%),[5] exercise hypotension is known to be associated with presence of underlying cardiac disease (such as left ventricular dysfunction, ischaemic heart disease and aortic outflow obstructions). Thus, it has been incorporated into exercise testing guidelines as an absolute indication to terminate a clinical test on safety grounds. The clinical importance of exercise hypotension may not only be acutely relevant, but may signify future cardiovascular risk. Indeed, we recently undertook a systematic review and meta-analysis and found that a hypotensive response to clinical exercise stress testing predicts longer-term (average follow-up of 4.4 years) fatal and non-fatal cardiovascular events and all-cause mortality.[6] Of particular note, data indicated the prognostic significance of exercise hypotension irrespective of disease status, modality of exercise testing (treadmill or cycle protocols), exercise intensity, or definition of exercise hypotension.[6] More recently, data from the Henry Ford Exercise Testing (FIT) Project indicated that a reduction in systolic BP during exercise testing was associated with elevated incidence of cardiovascular events (myocardial infarction) and all-cause mortality.[7] This association held following adjustment for important cardiovascular risk factors (including aerobic capacity).

Exercise hypertension

The clinical importance of exaggerated BP responses to clinical exercise testing has been long-debated. Precise definitions of exercise hypertension are unavailable, although several large studies have indicated that irrespective of normal BP at rest some individuals will experience an abnormal increase in BP (more likely for systolic BP) which at peak exercise intensity is associated with adverse cardiovascular outcomes.[8,9] We conducted a systematic review meta-analysis compiling all available data on subjects without a history of hypertension (in-clinic BP $\leq$ 140/90 mmHg) and cardiovascular disease.[10] In data from 46,314 subjects followed for 15 $\pm$ 4 years, we found that independent of age, sex, resting BP and multiple traditional cardiovascular risk factors, that exaggerated BP during submaximal intensity exercise was associated with a 36% increased cardiovascular event and mortality rate. Moreover, each 10 mmHg increase in exercise systolic BP at submaximal intensity was associated with a 4% increased annual event rate.[10] Despite expectation, the BP response to peak intensity exercise was not predictive of outcome. Thus, within otherwise healthy individuals, the signal for heightened risk may be stronger for exercise BP recorded at a submaximal intensity when measurements may be more practically feasible and reliable. Nonetheless, whilst some attempt at defining exercise hypertension at submaximal exercise workloads (submaximal exercise systolic BP in the range of 150–180 mmHg) has been made from small selected study samples,[11–14] more definitive conclusions on thresholds are required in order to be able to fully elucidate its prognostic importance.

Exercise hypertension is likely a precursor to future development of established hypertension, which may underlie its aforementioned prognostic value. Indeed, multiple longitudinal studies have indicated that exercise hypertension in those with apparently normal BP (in-clinic BP $\leq$ 140/90 mmHg) predicts incident hypertension.[13,15–18] To consolidate this evidence, we recently integrated data from 23,207 normotensive subjects followed for an average 5.3 $\pm$ 2.1 years, in the form of a meta-analysis.[19] Our primary finding was that exercise hypertension independently predicted future development of hypertension, irrespective of exercise mode (i.e. treadmill, step or cycle) or intensity, and independently of resting BP.[19]

One of the limitations of studies included in our meta-analysis was that in-clinic measures of BP were used to define those with normal BP at baseline, and the outcome of incident hypertension at follow-up. It is well known that true BP control cannot be confirmed in the absence of an out-of-clinic (ambulatory or home monitoring) BP, because white coat hypertension (erroneously high BP in the clinic) or masked hypertension (erroneously normal BP in the clinic) cannot be ruled out. Thus, risk related to the exercise BP response could have been potentially over- or under-estimated in our meta-analysis. We aimed to address the magnitude of this limitation in a study of non-selected individuals undergoing clinical exercise stress testing. One

hundred individuals free of coronary artery disease completed a standard clinical Bruce treadmill exercise stress test protocol, followed by 24-h ambulatory BP monitoring. The exercise systolic BP response to early stress test stages (light-to-moderate exercise intensity) revealed the presence of hypertension defined according to ambulatory BP guidelines.[12] The key finding was that 75% of individuals with a stage 1 (light intensity) exercise systolic BP $\geq$ 150 mmHg had hypertension defined by 24-h ambulatory systolic BP $\geq$ 130 mmHg. This same threshold of exercise systolic BP $\geq$ 150 mmHg (at stage 1 of the test) predicted the presence of hypertension confirmed by ambulatory monitoring, independent of age, sex and in-clinic resting BP.[12]

It has been hypothesised that a hypertensive response to light-to-moderate intensity exercise may reveal the presence of hypertension missed by in-clinic (resting) BP. Indeed, exercise of a light-to-moderate intensity reflects the level of activity undertaken during daily life, and thus may be more indicative of true BP load than a single BP measure at rest.[20] Our work and that of others has shown a high proportion of individuals with exercise hypertension also have masked hypertension,[11,21,22] a condition defined as normal in-clinic BP but raised out-of-clinic BP.[23] Those with masked hypertension have a greater rise in BP during exercise, and these individuals are at increased cardiovascular risk, as indicated by associations with markers of organ damage (including raised left ventricular mass) and cardiovascular events and mortality.[24] Thus, a hypertensive response to exercise of a light-to-moderate intensity may be a useful signal to clinicians of likely increased risk related to BP, otherwise undetected at rest. Indeed, exercise hypertension has been added to some consensus documents as an indication to perform out-of-clinic BP monitoring to ascertain true BP control.[23,25]

Whilst the risk related to exercise hypertension is underscored by associations with high BP, it is also appears related subclinical cardiovascular disease, which is expected if indeed exercise hypertension is synonymous with chronic hypertension. Raised exercise systolic BP is associated with altered cardiac structure and function (including raised left ventricular mass and systolic dysfunction).[22,26,27] Others have also found independent associations between exercise BP and arterial structure and function (including aortic stiffness and endothelial dysfunction),[28] as well as metabolic irregularities including glucose control and dyslipidaemia.[29–31] The majority of studies have identified links to subclinical cardiovascular disease risk markers in older-middle aged adults. However, we recently studied a large cohort of adolescents (17-year old boys and girls) and found post-exercise (submaximal intensity) systolic BP to be positively associated with raised left-ventricular mass and aortic stiffness, independent of body composition and resting BP (data presently unpublished). Thus, it appears that even in earlier life, abnormal exercise BP may allude to heightened BP-related cardiovascular risk.

If risk associated with exercise hypertension is apparent from early life, then strategies are needed to prevent the development of the condition and to intervene to reduce the associated cardiovascular risk. Aerobic and strength training programs lower submaximal intensity exercise systolic BP in those with untreated hypertension and prehypertension.[32] However, the effect of lifestyle modifications including exercise on exercise BP in those with a more advanced cardiovascular disease is unknown. We undertook a post-hoc analysis of individuals with type 2 diabetes (with a high prevalence of exercise hypertension) who participated in a randomised trial of exercise and lifestyle intervention to determine whether it could improve exercise BP compared to usual care.[33] Whilst absolute exercise BP values were not improved following the 12-month intervention, we demonstrated that in those without exercise hypertension at baseline, exercise and lifestyle diminished the rate of exercise hypertension development by comparison to usual care. Perhaps more importantly, we showed that in those with established exercise hypertension at baseline, exercise and lifestyle intervention was not sufficient to reverse the condition.[33] Thus, exercise hypertension may represent a more advanced cardiovascular condition that requires a more targeted approach to improve among this population and in the short term.

Factors influencing exercise blood pressure

Several factors may influence the BP response to clinical exercise testing. Peak systolic and diastolic BP, as well the difference from resting values have been shown higher in men compared with women, and increased with age in both sexes.[3] Disease status may also influence BP response, with those at already increased cardiovascular risk (e.g. type 2 diabetes, masked hypertension) having substantially greater prevalence of exercise hypertension,[11,34] and those with established coronary artery disease having greater prevalence of exercise hypotension.[5] The specific mechanisms underlying (abnormal) exercise BP are multifactorial.[35] Fundamentally, neural cardiovascular control (sympatric drive) will modify cardiac inotropy and vascular function during exercise, subsequently influencing exercise haemodynamics. Whilst it is beyond the scope of this paper to detail all these factors, the primary (simple) mechanism driving exercise BP can be viewed as a balance (imbalance) between cardiac output and systemic vascular resistance. Restriction to the level of systemic vasodilation in response to dynamic exercise may increase systolic BP (i.e. failure for sufficient vascular 'run-off'). On the other hand, an inadequate increase to cardiac output to meet the metabolic demands of exercise, or excessive systemic vasodilation may cause a drop in systolic BP.

Fundamental changes to 'output' and 'resistance' (as described) during exercise will affect arterial wave travel and modify the exercise BP waveform morphology. Using the novel approach of wave intensity analysis applied to invasively acquired ascending aortic pressure and flow velocity waveforms (captured at the time of coronary catheterisation), we described the influence of pressure wave travel in the generation of BP during dynamic aerobic exercise.[36] Despite traditional expectation for an increase in reflected wave intensity contributing to aortic BP augmentation, our data indicated minimal change of wave reflection in response to exercise. Indeed, the overwhelming driver of exercise aortic BP was elevation in intensity of the forward compression wave (indicative of increased left ventricular ejection) and forward decompression wave (indicative of enhanced late systolic

deceleration of left ventricular ejection).[36] We also performed pressure wave separation using the reservoir-excess pressure paradigm. In the first application of this model to BP waveforms captured during exercise, our results indicated that whilst reservoir pressure remained relatively similar from rest to exercise, the aortic BP increase was largely attributable to an increased excess (or wave-related) pressure component. This was an important finding, and may underlie some of the prognostic value of exercise hypertension,[10] since elevations to excess pressure have been shown to be a strong and independent (of traditional hypertension-related risk factors) predictor of cardiovascular events and mortality.[37]

Evidence gaps and future directions

Whilst the clinical importance of exercise BP is apparent from our (and others) observational research, a crucial evidence gap in the field is the absence of thresholds of exercise BP associated with outcomes. In the absence of such thresholds, clinicians supervising exercise stress testing are unable to determine the true level of risk associated with a given (abnormal) BP response, and therefore creates difficulty in making definitive clinical decisions from exercise BP results. We are in the early stages of a large collaborative study (the EXERcise stress Test collaboratION; the EXERTION study) aimed at creating population-based thresholds of exercise BP, via construction of a nationwide (Australian) clinical exercise stress testing database linked to clinical outcomes and death. Analysis of a small section of this data ($n = 717$ individuals without a prior history of cardiovascular disease) using change-point analysis indicates that a submaximal (stage 2 Bruce protocol) exercise systolic BP beyond a threshold of 170 mmHg is associated with an increased rate of cardiovascular related hospital admissions. Nonetheless, this is a preliminary analysis and results will need to be confirmed within the full study cohort, a target of >200,000. Creation of such a large database will enable us to not only determine long-term risks associated with abnormal exercise BP, but also provide much needed evidence for thresholds outlined in exercise testing guidelines as indications to terminate testing. Creation of exercise BP thresholds will also enable pragmatic research studies aimed at establishing how incorporation of exercise BP into decision making within clinical practice may improve the detection and management pathways related to high BP.

Aerobic capacity is a strong determinant of exercise BP.[38] Nonetheless, the influence of aerobic capacity on the exercise BP response (in particular at submaximal intensities), and subsequent association with adverse outcomes (including hypertension and cardiovascular events and mortality) remains to be fully elucidated. Several studies are underway to determine how aerobic capacity and indeed physical activity patterns across the life course may alter exercise BP, both concurrently and in the future.

Summary and conclusion

Our research (and that of others) suggests abnormal exercise BP has clinical importance beyond resting BP. Both exercise hypotension and hypertension are associated with adverse cardiovascular outcomes including events and mortality. Exercise hypertension predicts future development of hypertension, whilst revealing the presence of underlying high BP missed by traditional in-clinic BP at rest. Several important evidence gaps remain to be filled; including the development of population-based clinical thresholds of exercise BP associated with outcomes. Whilst this will enhance the clinical relevance of exercise BP in the future, abnormal exercise BP should still act as a warning signal of likely increased cardiovascular risk related to BP that warrants follow-up care to ascertain true BP control, and/or lifestyle intervention to lower risk.

Conflicts of interest

There are no conflicts of interest to declare.

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