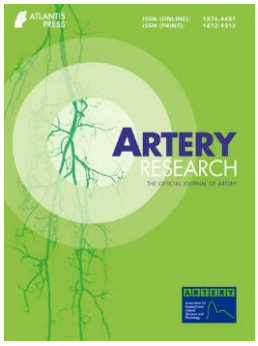

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New insights into cardiovascular risk from the exercise central waveform

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Summary Numerous studies in healthy individuals with normal office blood pressure (BP) have shown that a hypertensive response to exercise predicts the future onset of hypertension, as well as cardiovascular morbidity and mortality, independent of office BP. The mechanisms underlying the predictive value of exercise BP are incompletely understood. However, it has been proposed that the additional cardiovascular stress imposed by exercise may unmask the presence of concealed hypertension. A new non-invasive method of exercise arterial pressure waveform analysis (and central BP estimation) may provide additional clinical information, as well as insight into mechanisms, beyond the BP obtained by traditional upper arm cuff methods.

Exercise brachial blood pressure (BP) and cardiovascular risk

While the risk of vascular mortality is strongly related to resting office BP, there is an increasing acceptance that central BP and indicators of vascular stiffness derived from tonometry are more prognostically valuable.[1] Most of the research relating BP to cardiovascular risk and the effect of treatment has focused on seated office BP as well as home BP and 24-h ambulatory BP monitoring (24 ABPM). However, some investigators have explored the predictive value of exercise brachial BP, either recorded during submaximal exercise, at peak exercise, or in the recovery period afterwards. A consistent finding is that, independent of resting office BP, an exaggerated BP response predicts cardiovascular morbidity and mortality,[2–8] as well as, left ventricular mass[9,10] and the future development of essential hypertension,[11–13] in normotensive individuals. Unfortunately, due to the varied methods between investigations, there is little uniformity as to what constitutes an exaggerated exercise BP. Nonetheless, the values that

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exceed the upper limits (>2SD) of normal exercise systolic BP (SBP) are ≥210 mm Hg in men and ≥190 mm Hg in women.[14]

It is not known why exercise BP appears to be more clinically informative than resting BP. Some suggest that exercise brachial BP is more akin to the BP response to daily life[4] and, therefore, more representative of the chronic burden of BP. There is general agreement that exercise BP is not as susceptible to the intrinsic (e.g. nervousness) or extrinsic (e.g. talking) factors known influence office BP. Lund-Johansen[15] proposed that the extreme challenge to the vascular system during exercise (i.e. increased heart rate, stroke volume and peripheral vasodilation) may unmask the presence of hypertension; perhaps in a similar fashion to the unveiling of coronary stenosis by exercise stress echocardiography. However, a limitation of previous investigations that have assessed the association between cardiovascular risk and exercise BP in individuals with normal BP is that office BP has been used to determine normotension. This method fails to identify the presence of masked hypertension, which is a relatively common condition (14.5% prevalence) in patients attending a hypertension outpatients clinic.[16]

Our group recently performed 24 ABPM in 81 untreated patients free from coronary artery disease who had office BP (<140/90 mm Hg) and a hypertensive response to exercise (as defined above). There was a high prevalence (62%) of masked hypertension (defined as 24 ABPM SBP ≥ 130 mm Hg) and, in these patients, left ventricular mass index was significantly increased (the principal sign of organ damage associated with hypertension) compared to normotensive patients with exaggerated exercise BP. These data are of relevance to clinicians supervising exercise stress tests, who should be aware that high exercise BP warns of the likely presence of hypertension irrespective of the apparently normal office BP values. Moreover, since masked hypertension is associated with cardiovascular and all-cause mortality,[17] these findings provide evidence as to why exaggerated exercise BP (independent of office BP) foreshadows poor long-term cardiovascular outcome. On the other hand, the isolated focus on brachial BP may overlook potentially important information gleaned from the exercise central BP waveform.

Exercise central BP: non-invasive estimation

In 1968 Rowell et al.[18] recorded pressure waveforms at the aortic arch and radial artery in four healthy young men using indwelling catheters. Readings were obtained at rest and during graded treadmill exercise to exhaustion. The ratio of brachial to central pulse pressure (pulse pressure amplification) increased significantly and, while the average difference in the SBP between central and peripheral sites was 21 mm Hg at rest, this rose to 82 mm Hg at peak exercise (SBP is always higher in the arm). The investigators concluded that the pressure disparity between the heart and arm with exercise may have major clinical significance because an excessive brachial BP rise during an exercise stress test could either be due to local peripheral vasoconstriction or increased central BP. In the former situation, the estimation of central systolic stress would be greatly overestimated by the use of upper arm cuff BP during exercise. In the ensuing decades since these comments were made there has been little advancement to determine their clinical relevance. Clearly the lack of progress has been due to the limited application of the invasive method to measure central BP in large study populations.

The advent of non-invasive radial tonometry to estimate central BP by a generalised transfer function (GTF), even in response to haemodynamic perturbations, offered potential for widespread use.[19] However, concerns were raised about the validity of a GTF and we sought to test this during exercise by simultaneous acquisition of invasive ascending aortic pressure waveforms (by catheter) as well as estimated central pressure derived by GTF from the radial artery (by servo-controlled tonometry and customised software; SphygmoCor 7.1, AtCor Medical, Sydney, Australia).[20] Thirty patients undergoing diagnostic coronary artery angiography were studied at rest and during supine exercise using a portable cycle ergometer. Central SBP ranged from 77 mm Hg at rest to 229 mm Hg during exercise, whereas only a moderate increase in heart rate was elicited (15 ± 7 bpm) due to most patients receiving beta blocker medication. There was a strong correlation between invasive and non-invasive central SBP at rest and exercise (for both $r = 0.995$; $p < 0.001$). The mean difference (±SD) between measures for central SBP was low at rest (-1.3 ± 3.2 mm Hg) and, although higher during exercise (-4.7 ± 3.3 mm Hg), was still within national standards for measuring BP.[21] Therefore, it appeared that the GTF was robust in the context of light to moderate exercise (recent work also suggests that the technique has good reproducibility).[22]

Conversely, in a study of 30 healthy young men, Payne et al.[23] found that a radial-to-carotid GTF underestimated central SBP (-5.8 ± 2.1 mm Hg; $p = 0.01$) in the immediate period after exercise in which mean heart rate was raised 59 bpm above resting levels. Additionally, they suggested that the use of an exercise-specific GTF may improve central pressure estimations. Stok et al.[24] also tested the validity of a finger-to-aorta GTF in seven cardiac patients performing graded supine cycling to a maximal intensity averaging 51 bpm above that of rest. The mean difference between measured and GTF-estimated central SBP during all grades of exercise was -6.3 ± 6.4 mm Hg. These investigators concluded that the finger-aorta GTF changed with exercise and was unreliable for synthesising central pressure in this setting, particularly at higher heart rates.

While the design of all three studies were dissimilar, the mean differences in GTF-derived central SBP were markedly lower (<7 mm Hg)[20,23,24] than the actual aorta-to-peripheral SBP difference that may be experienced during exercise (>80 mm Hg).[18] It would, therefore, appear possible that, despite inaccuracy and refinement required, the use of a GTF to estimate central BP may provide prognostically useful information beyond that of exercise brachial BP. Moreover, recent work by Munir et al.[25] suggests that the second systolic peak of the radial waveform (P2) is analogous to ascending aortic SBP, thereby identifying a central haemodynamic marker that may be acquired from a non-transformed peripheral waveform. This offers an appealing alternative to the GTF approach, although it remains to be tested whether P2 is readily identifiable in the smoothly declining late

systolic portion of the radial waveform that typically occurs with higher intensity exercise.

Exploring the clinical value of exercise central BP

Only a few studies have been published in the field of exercise pressure waveform analysis. We recently recorded radial artery waveforms by hand-held tonometry at rest and immediately after maximal treadmill exercise in 153 healthy subjects (aged 54 ± 10 years; 60% male). Radial waveforms were calibrated using a standard mercury sphygmomanometer and central BP was estimated by the SphygmoCor GTF. To determine if exercise central BP provided information that may be incremental to brachial BP measures, the subjects were stratified into quartiles of exercise brachial SBP and the estimated exercise central SBP was then compared between quartiles. Inter-quartile comparison of the aorta-to-brachial SBP difference (calculated by brachial SBP − central SBP) was also assessed. As shown in Fig. 1, there was significant overlap of both central SBP and aorta-to-brachial SBP differences between quartiles of exercise brachial SBP. Indeed, it was possible for an individual with exercise brachial SBP in the second quartile to have central SBP within the range of subjects in all other quartiles (shaded area). Notably, exercise BP's were distinct from resting central BP measures. The average aorta-to-brachial SBP difference during exercise was 41 ± 11 mm Hg (range 16—69 mm Hg) which was significantly greater than in the resting state 11 ± 5 mm Hg (range 2—26 mm Hg; $p < 0.001$). Principally, these data show that the exercise brachial SBP does not predict the central SBP response; a finding which lends support for the concerns expressed by Rowell and colleagues.[18]

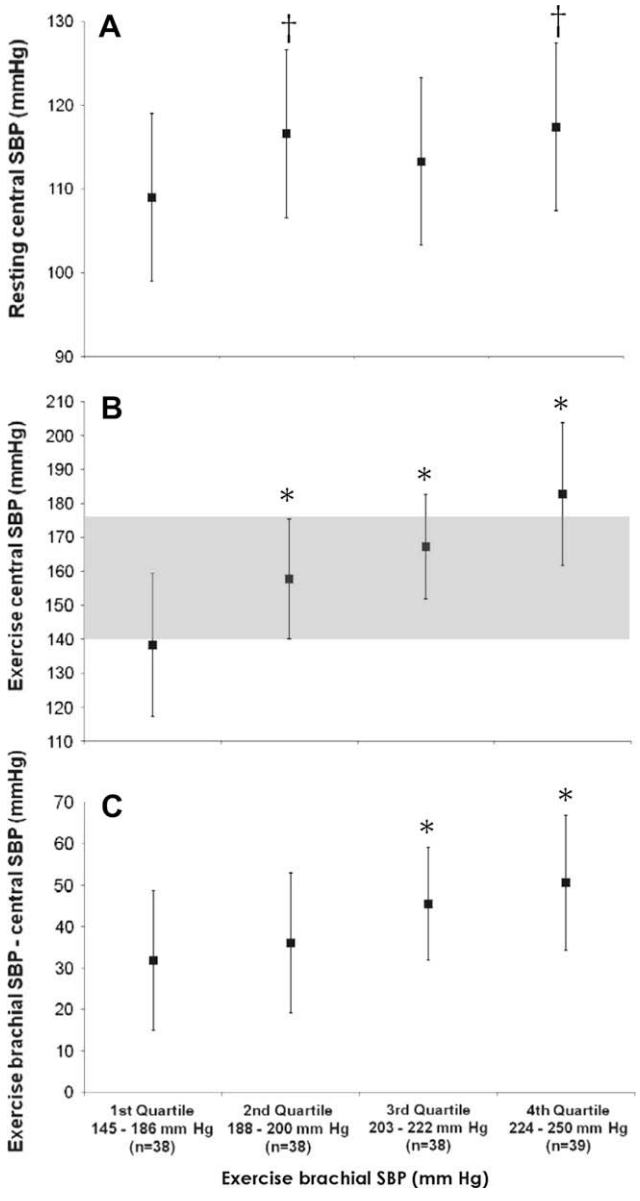

Figure 1 Resting central systolic blood pressure (SBP; panel A), exercise central SBP (panel B) and the exercise brachial—central SBP difference (panel C) between quartiles of maximal exercise brachial SBP in 153 healthy individuals. The shaded area indicates the cross over in exercise central SBP between the 2nd brachial SBP quartile and all other quartiles. Data are mean $\pm$ 2SD. *$p < 0.001$ and †$p < 0.05$ compared with the 1st quartile. For exercise central SBP there is a significant difference ($p < 0.001$) between all quartiles.

Example radial and centrally derived waveforms between individuals with similar exercise brachial BP, but different central BP are illustrated in Fig. 2. In another study, the association between these large central-to-peripheral BP disparities during exercise on the structural characteristics of the heart was examined in a cross-sectional analysis of 73 patients with type 2 diabetes compared with 73 controls.[26] Data were recorded at rest and in response to maximal treadmill exercise. Patients with type 2 diabetes had significantly higher exercise brachial and estimated central BP compared with controls, as well as an increased prevalence of a hypertensive response to exercise (51% versus 22%; $p < 0.01$). This was not unexpected given that vascular dysfunction and large artery stiffness are features known to accompany diabetes and may exacerbate exercise BP. Indeed, others have shown that these patients have raised brachial DBP[27] during light exercise. However, regardless of disease status, people with a hypertensive response to exercise had increased left ventricular relative wall thickness (0.41 ± 0.09 versus 0.36 ± 0.08; $p < 0.05$) and a higher prevalence of left ventricular hypertrophy (35% versus 16%; $p < 0.05$). Moreover, after accounting for other confounding variables (including resting brachial SBP), exercise central SBP was independently associated with left ventricular relative wall thickness ($\beta = 0.22$; $p = 0.006$). Thus, in addition to brachial BP values, clinical information relevant to cardiovascular risk may be derived from maximal exercise central BP.

A potential shortcoming of assessing the response to maximal aerobic exercise is that it is rarely undertaken by the general population, let alone by patients with disease that has manifest, at least in part, due to inactivity. Could it then be that central haemodynamic estimations during light to moderate activity, similar to that experienced during daily life, may elicit information to improve the precision of risk related to BP? In a study of healthy young men performing cycle exercise at 50%, 60%, 70% and 80% of

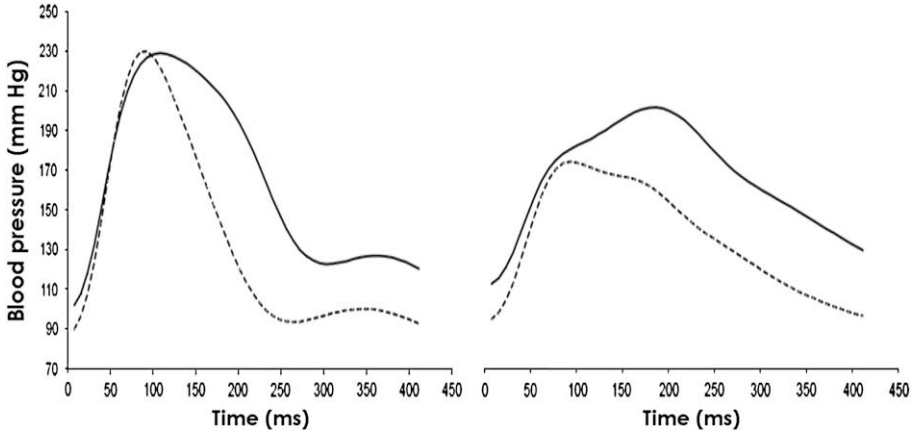

Figure 2 Example maximal exercise radial (left panel) and estimated central (right panel) pressure waveforms from two middle-aged men with a hypertensive response to exercise and similar brachial systolic blood pressures (229 and 230 mm Hg). However, one subject has central systolic blood pressure 27 mm Hg higher (198 mm Hg; solid lines) than the other (171 mm Hg; dotted lines).

maximal heart rate, it was found that pulse pressure amplification increased significantly from baseline at all exercise intensities, with the largest increase occurring at 60% intensity.[28] Furthermore, augmented pressure and augmentation index decreased in a step-wise fashion as exercise intensity increased. Importantly, brachial pulse pressure and brachial SBP increased significantly more than central pulse pressure and central SBP ($p < 0.001$ for both), again indicating that the central BP response to exercise could not be predicted from the upper arm BP, even during light exercise.

Following on from this, it was hypothesised that vascular structural and functional degeneration associated with ageing and hypercholesterolaemia may result in larger changes to central waveform indices than standard cuff BP readings during light exercise.[29] Healthy young men (aged 29 ± 5 years), healthy older men (aged 57 ± 5 years) and older men with high blood cholesterol (aged 59 ± 7 years) had central BP estimated (using radial tonometry) at rest and during cycle exercise at 60% of age predicted maximal heart rate $[(220 - \text{age}) \times 0.6]$. This exercise intensity approximates light to moderate activity. As expected, the younger men had lower augmentation index and higher pulse pressure amplification during exercise compared with healthy older men. This finding was later confirmed by Casey et al.[30] who emphasised that, while exercise central BP was different between older and younger men, the magnitude of the central haemodynamic change from baseline was similar. Conversely, we found men with hypercholesterolaemia to have higher augmentation index and blunted pulse pressure amplification compared with age-matched healthy counterparts during light exercise.[29] This occurred in spite of baseline haemodynamics and brachial SBP during exercise being similar to controls. Clearly, the exercise central haemodynamic response associated with hypercholesterolaemia represented a deficient ventricular–vascular relationship with increased myocardial afterload.

Taken altogether, light exercise central haemodynamics provides BP information that is additive to the same measures obtained under resting conditions (see example in Fig. 3). But what may be the practical application of these observations? The current ''gold standard'' method for determining BP control is 24 ABPM because parameters from this technique (i.e. daytime or 24-h SBP) correlate more strongly with target organ damage than either clinic or home BP measures.[31] Importantly, 24 ABPM daytime SBP is recorded during physical activity in which heart rates may be similar to those in which pulse pressure amplification is significantly altered from the resting state,[28–30] but the magnitude of amplification cannot be discerned with 24 ABPM. This raises the intriguing possibility that the light exercise central BP tonometry method, performed at an intensity similar to daily life, may be more useful than 24 ABPM for delineating risk related to BP.[32] Certainly, a 10–15-min gentle exercise test would be an attractive alternative to the imposition of 24 ABPM, and some preliminary data does appear to corroborate the above hypothesis,[33] but more studies are required.

Mechanisms of abnormal exercise central BP

Little is known on the factors that modulate central BP, augmentation index and pulse pressure amplification during exercise. Several aspects of arterial structure and function may be influential, including large central artery stiffness (e.g. aortic pulse wave velocity),[34] muscular large artery function (e.g. femoral dilatation),[35] peripheral vasodilatory capacity (e.g. limb endothelial function),[36] blood rheology (e.g. viscosity),[37] vasoreactive metabolites (e.g. adenosine), neurovascular regulation (e.g. autonomic function) or disease specific metabolic irregularities (e.g. insulin resistance).[38] It is unknown whether one of these factors may dominate over another, or an interplay of several may combine to affect the exercise central haemodynamic milieu. Adding further complexity is recent data showing that modulatory variables under resting conditions (i.e. nitric oxide)[39] appear to have a negligible effect during exercise.[40] It is also possible that the pathophysiology underlying an exaggerated brachial BP during maximal exercise is not the same as that accounting for raised central BP during light activity. Additional work is needed to address the various deficits in the literature.

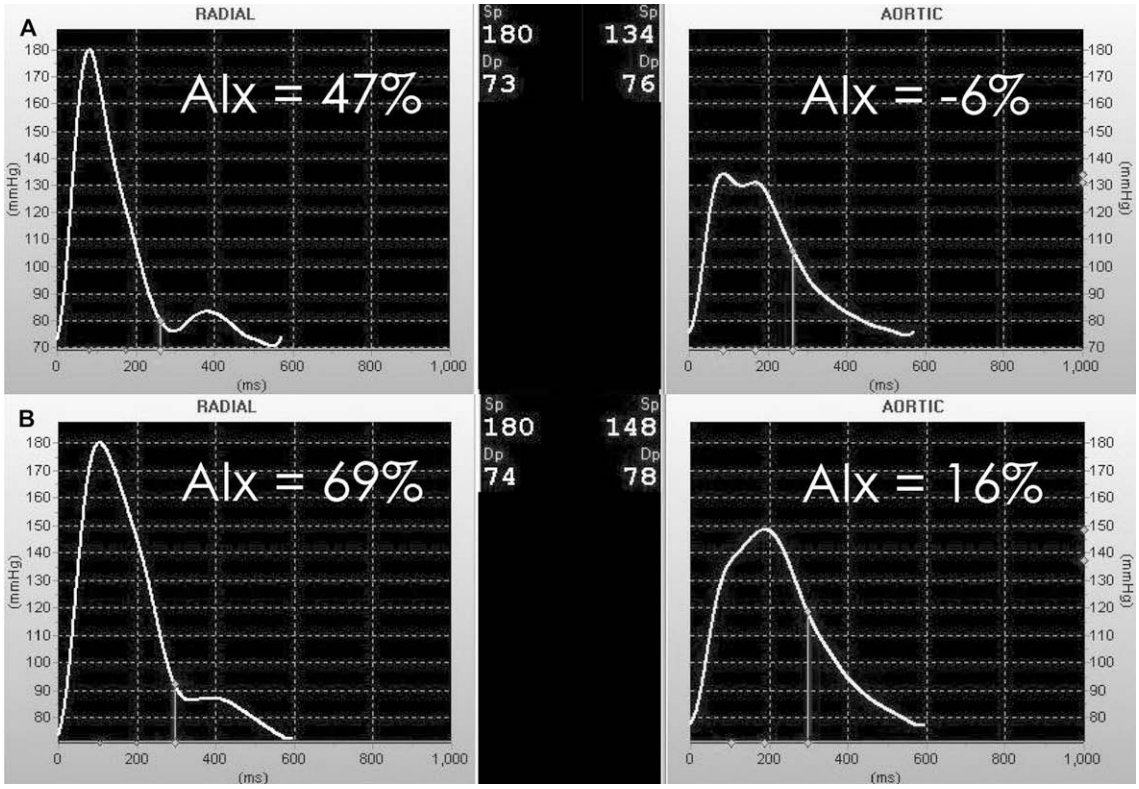

Figure 3 Example radial (left panel) and synthesised aortic (right panel) pressure waveforms during light exercise (60% intensity; heart rates 105 bpm [A] and 102 bpm [B]) in two middle-aged normotensive (at rest) men with the same brachial systolic blood pressure (180 mm Hg) but different exercise central systolic blood pressure (134 versus 148 mm Hg) and augmentation index (AIx). Data were recorded using servo-controlled radial tonometry (Colin CBM-7000; Colin Corp., Komaki-City, Japan) with central blood pressure estimated by generalised transfer function and brachial blood pressure measured by mercury sphygmomanometer.

Summary and future directions

Exaggerated exercise BP appears to be a signal of vascular irregularities which predisposes seemingly normotensive individuals to increased risk for cardiovascular events. While the area of exercise pressure waveform analysis is in its infancy, the technique provides clinically informative estimates of central systolic loading that are different to the resting state and unattainable with traditional upper arm BP measures. More work is required to determine the medical consequences of raised exercise central BP, particularly during light activity, which is an area that seems to hold special promise. Investigation is also needed to determine physiological mechanisms controlling exercise central haemodynamics, as well as to establish normative values and identify patient populations that may be especially vulnerable to an abnormal central BP reaction to exercise. Finally, the exercise central BP response to therapy (both pharmacological and lifestyle modification) in higher risk patient populations, such as those with type 2 diabetes, may be a fruitful area of inquiry.

Conflict of interest

Dr. Sharman has research collaborations with AtCor Medical, the manufacturers of the SphygmoCor device.

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