The effect of exercise on large artery haemodynamics in healthy young men

J. E. Sharman[*†], C. M. McEniery[‡], R. I. Campbell[§], J. S. Coombes[†], I. B. Wilkinson[‡] and J. R. Cockcroft[§]

[*]The University of Queensland and [†]School of Human Movement Studies, Princess Alexandra Hospital, Brisbane, 4102, Australia, [‡]University of Cambridge, Addenbrooke's Hospital, Box110, Cambridge, CB2 2QQ, UK, [§]University of Wales College of Medicine, University Hospital, Cardiff, CF4 4XN, UK

Abstract

Background Brachial blood pressure predicts cardiovascular outcome at rest and during exercise. However, because of pulse pressure amplification, there is a marked difference between brachial pressure and central (aortic) pressure. Although central pressure is likely to have greater clinical importance, very little data exist regarding the central haemodynamic response to exercise. The aim of the present study was to determine the central and peripheral haemodynamic response to incremental aerobic exercise.

Materials and methods Twelve healthy men aged 31 ± 1 years (mean ± SEM) exercised at 50%, 60%, 70% and 80% of their maximal heart rate (HRmax) on a bicycle ergometer. Central blood pressure and estimated aortic pulse wave velocity, assessed by timing of the reflected wave (T_R), were obtained noninvasively using pulse wave analysis. Pulse pressure amplification was defined as the ratio of peripheral to central pulse pressure and, to assess the influence of wave reflection on amplification, the ratio of peripheral pulse pressure to nonaugmented central pulse pressure (PPP : CDBP-P_1) was also calculated.

Results During exercise, there was a significant, intensity-related, increase in mean arterial pressure and heart rate ($P < 0.001$). There was also a significant increase in pulse pressure amplification and in PPP : CDBP-P_1 ($P < 0.001$), but both were independent of exercise intensity. Estimated aortic pulse wave velocity increased during exercise ($P < 0.001$), indicating increased aortic stiffness. There was also a positive association between aortic pulse wave velocity and mean arterial pressure ($r = 0.54$; $P < 0.001$).

Conclusions Exercise significantly increases pulse pressure amplification and estimated aortic stiffness.

Keywords Aerobic exercise, arterial stiffness, blood pressure.
Eur J Clin Invest 2005; 35 (12): 738–744

The University of Queensland Department of Medicine (J. E. Sharman) and School of Human Movement Studies, Princess Alexandra Hospital, Brisbane, 4102, Australia (J. E. Sharman, J. S. Coombes), Clinical Pharmacology Unit, University of Cambridge, Addenbrooke's Hospital, Box110, Cambridge, CB2 2QQ, UK (C. M. McEniery, I. B. Wilkinson), Department of Cardiology, University of Wales College of Medicine, University Hospital, Cardiff, CF4 4XN, UK (R. I. Campbell, J. R. Cockcroft).

Correspondence to: James E. Sharman, PhD, The University of Queensland, Department of Medicine, Princess Alexandra Hospital, Brisbane, 4102, Australia.
Tel.: +61 (0)7 3240 6438; fax: +61 (0)7 3240 5399;
e-mail: jsharman@soms.uq.edu.au

Received 6 July 2005; accepted 11 October 2005

Introduction

High peripheral blood pressure is a well-established risk factor for future cardiovascular events [1]. An exaggerated systolic blood pressure response to low-intensity exercise is also a strong predictor of cardiovascular mortality in otherwise healthy middle-aged men [2,3]. Traditionally, blood pressure is measured by cuff sphygmomanometry at the brachial artery. However, there is variation in blood pressure throughout the arterial tree, with systolic blood pressure increasing towards the periphery, while diastolic and mean arterial pressures remain relatively constant. The overall effect is the amplification of pulse pressure from the aorta to the brachial artery. Therefore, blood pressure obtained peripherally is not representative of central blood

pressure [4]. Indeed, during exercise, aortic systolic blood pressure may be overestimated by as much as 80 mmHg if only brachial systolic blood pressure is considered [5].

The variation in pulse pressure throughout the arterial tree is likely to be clinically important because the heart, coronary and carotid arteries are influenced by central, not peripheral blood pressure. Indeed, it is central blood pressure that determines left ventricular workload [6] and correlates with carotid artery intima-media thickness [7], both of which are independent predictors of mortality. Moreover, central blood pressure is a stronger predictor of all-cause mortality in high-risk patients with cardiovascular disease than peripheral blood pressure [8]. However, the difference between central and peripheral pressure varies with a number of factors, including age [9], gender and heart rate [10].

Some early studies have examined pressure waveform changes in healthy men during supine cycling or treadmill running using invasive recordings [5,11,12], but there is no data on the central haemodynamic response to upright cycling in this population. Nor is there information on the effect of this mode of exercise on parameters now known to be predictive of mortality, such as augmentation index. We hypothesized that exercise would not only alter pulse pressure amplification but also augmentation index, because of changes in wave reflection. The aim of this study was to test this hypothesis in a cohort of healthy young individuals using pulse wave analysis to assess central haemodynamics noninvasively.

Methods

Subjects

Twelve healthy young men (age 31 ± 1 years) were recruited for the study. Subjects were either sedentary or recreationally active, and none were participating in regular exercise training for competition. Cigarette smokers, and subjects with hypercholesterolaemia (total cholesterol > 6·0 mmol L^{-1}), hypertension (> 140/90 mmHg) or a history of cardiovascular disease or diabetes and those individuals receiving medication were excluded. The local research ethics committee approved procedures and participants gave their written informed consent. The study was performed according to the Declaration of Helsinki.

Peripheral blood pressure

Peripheral systolic and diastolic blood pressures were measured at the right arm using an electrocardiogram gated ascultatory device (Accutracker II, SunTech II SunTech Medical Instruments, Raleigh, USA), which has been validated for use during exercise [13,14]. All readings were taken with the subject's arm relaxed and supported with the cuff at the level of the heart.

Central haemodynamics

Peripheral pressure waveforms were obtained from the radial artery of the left arm using servo-controlled applanation tonometry (Colin CBM-7000; Colin Corp., Komaki City, Japan). Pulse wave analysis (SphygmoCor 7·01; AtCor Medical, Sydney, Australia) was then used to derive a central (ascending aortic) pressure waveform from the peripheral (radial) pressure waveform using a validated transfer function [15–17]. A typically derived central-pressure waveform from a middle-aged person is depicted in Fig. 1. Augmentation index (AIx), a measure of systemic arterial stiffness [18], was calculated as the difference between the second (P_2) and first (P_1) peaks expressed as a percentage of the pulse pressure (PP). Timing of the reflected pressure wave (T_R) was determined by the method of Murgo et al. [19] as the time between the foot of the pressure wave (T_F) and the inflection point (P_i). The T_R denotes the round-trip travel time of the pulse wave to peripheral reflecting sites and its return to the heart. It has been shown to correlate strongly with aortic pulse wave velocity [20,21] and is an indicator of aortic stiffness. The area under the aortic systolic (tension time index; TTI) and diastolic (diastolic time index; DTI) portions of the pressure wave was determined by the area under the waveform during systole and diastole, respectively. The TTI relates to myocardial oxygen demand and DTI to coronary perfusion [22]. Pulse pressure amplification was calculated as the ratio of the peripheral pulse pressure to central pulse pressure (PPP : CPP) [9]. The nonaugmented pulse pressure amplification was calculated as the ratio of the peripheral pulse pressure to nonaugmented central pulse pressure (PPP : CDBP – P_1).

In a separate study, we prospectively tested the validity of the generalized transfer function at rest and during aerobic exercise in six patients aged 53 ± 7 years (three men) undergoing diagnostic coronary angiograms via femoral ($n = 4$)
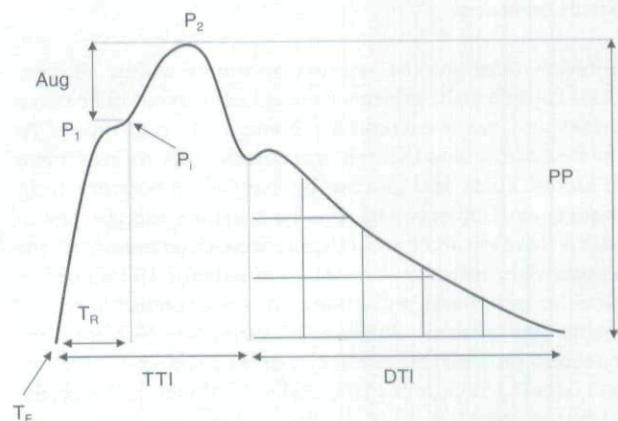

Figure 1 Typical resting ascending aortic waveform in a healthy middle-aged man. Two systolic peaks are labelled P_1 and P_2. The area under the curve (AUC) during systole is the tension time index (TTI), and AUC during diastole is diastolic time index (DTI). T_R is defined as the time between the foot of the wave (T_F) and the inflection point (P_i).

or brachial ($n = 2$) approach. Following the angiographic procedure, a micromanometer-tipped 6F Millar catheter (Millar Instruments, Houston, USA) was placed in the ascending aorta to record aortic pressure waveforms. Simultaneous radial pressure waveforms were recorded as described previously, at rest and following one- or two-legged supine exercise on a portable cycle ergometer. Offline analysis of the direct and synthesized central pressure signals was performed using the SPHYGMOCOR 7·01 software. There was excellent agreement between measures with a mean difference (± SD) for central systolic blood pressure and central pulse pressure of $1·8 \pm 1·1$ mmHg at rest, and $-0·8 \pm 1·6$ mmHg at peak exercise. During exercise, heart rate and mean arterial pressure were increased from resting values by 13 ± 9 beats min^{-1} and 12 ± 8 mmHg (mean ± SD), respectively. There was significant disparity between the radial and measured aortic pulse pressures at rest (68 ± 16 mmHg vs. 53 ± 13 mmHg, respectively) and during exercise (82 ± 8 mmHg vs. 64 ± 7 mmHg; $P < 0·01$ for both). Thus, although the transfer function has previously been validated, we showed good agreement during exercise.

Cardiorespiratory fitness

Maximal oxygen consumption (VO$_2$max) and heart rate at VO$_2$max (HRmax) were determined on an ergometric stationary bicycle (874E; Monark Exercise AB, Varberg, Sweden). The incremental test commenced at an initial workload of 60 W, which was increased thereafter by 30 W every 3 min until 180 W, then by 20 W per minute until volitional fatigue. Heart rate was recorded from a 12-lead ECG at rest and at the end of each workload. Expired air was analysed every 30 s during exercise using Pulmolab model Ex 670 mass spectrometry gas analysis (Morgan Medical Ltd, Kent, UK).

Study protocol

Subjects were studied on two occasions within 14 days. Prior to each visit, subjects were asked to avoid caffeinated drinks and heavy exercise for 3 and 24 h, respectively. At the first visit, a blood sample was obtained (for measurement of serum lipids and glucose by standard laboratory techniques) and subjects performed a maximal exercise test in which their VO$_2$max and HRmax were determined. At the second visit, subjects were seated quietly for 15 min before baseline peripheral and central haemodynamic measurements were taken simultaneously in triplicate. Subjects then exercised on a bicycle ergometer at 50 r.p.m and at a heart rate equal to 50%, 60%, 70% and 80% of their HRmax (the cycling protocol avoided the 'beat' phenomenon that may occur during running as described by Palatini *et al.* [23]). Resistance on the bicycle was adjusted in order for each subject to maintain a steady state heart rate for a minimum of 4 min at each exercise intensity. The average of two simultaneously recorded measures of peripheral and central haemodynamics, during each exercise workload, was taken

Table 1 Baseline clinical characteristics of study participants ($n = 12$)

Variable	Mean ± SEM
Age (years)	31 ± 1
BMI (kg m^{-2})	$24·3 \pm 0·9$
Waist : hip ratio	$0·87 \pm 0·01$
VO$_2$max (mL kg^{-1} min^{-1})	$51·2 \pm 1·1$
Total cholesterol (mmol L^{-1})	$4·6 \pm 0·2$
HDL cholesterol (mmol L^{-1})	$1·3 \pm 0·1$
LDL cholesterol (mmol L^{-1})	$2·7 \pm 0·2$
VLDL cholesterol (mmol L^{-1})	$0·7 \pm 0·1$
Triglycerides (mmol L^{-1})	$1·4 \pm 0·2$
Glucose (mmol L^{-1})	$5·3 \pm 0·1$

BMI, body mass index; VO$_2$max, maximal oxygen consumption.

for later analysis. In the postexercise period, readings were taken at 2-min intervals for 10 min.

Data analysis

Data are presented as means ± SEM and were analysed as change from baseline using one-way analysis of variance (ANOVA) with Bonferroni's post hoc test. Comparisons between variables during exercise were analysed by repeated measures ANOVA. Paired Student's *t*-tests were used as indicated and $P < 0·05$ considered significant. Pearson product moment coefficient of correlation (r) was used to determine relationships between variables within the data pooled from resting and exercise conditions.

Results

The baseline characteristics of subjects are presented in Table 1, and the effect of increasing exercise intensity on haemodynamics is presented in Table 2. Compared to the baseline, all haemodynamic parameters, except peripheral diastolic blood pressure, changed significantly with exercise ($P < 0·05$). Central diastolic blood pressure was significantly higher than peripheral diastolic blood pressure at each intensity of exercise ($P < 0·001$ for all comparisons; Table 2), but there was no significant difference in the effect of exercise on the two parameters ($P = 0·3$). There was a significant reduction in T$_R$ with exercise ($P < 0·001$), indicating an increase in estimated aortic pulse wave velocity. When the baseline and exercise data were pooled, mean arterial pressure was negatively associated with T$_R$ ($r = -0·54$; $P < 0·001$) and positively associated with TTI ($r = 0·61$; $P < 0·001$).

Pulse pressure amplification increased significantly at all levels of exercise compared to the baseline ($P < 0·001$; Fig. 2) and was positively associated with heart rate ($r = 0·60$; $P < 0·001$) when the resting and exercise data were pooled. The peripheral pulse pressure increased significantly more than the central pulse pressure ($P < 0·001$) and peripheral

Table 2 Effect of increasing intensity of exercise on central and peripheral haemodynamics in healthy men

	HR (beats min⁻¹)	AIx (%)	Aug (mmHg)	MAP (mmHg)	T_R (ms)	PSBP (mmHg)	PDBP (mmHg)	PPP (mmHg)	CSBP (mmHg)	CDBP (mmHg)	CPP (mmHg)
Baseline	62 ± 3	7 ± 3	3 ± 1	86 ± 2	156 ± 3	121 ± 3	69 ± 2	52 ± 3	104 ± 2	70 ± 2†	34 ± 2
% maximum HR											
50	92 ± 2*	−3 ± 4	−1 ± 2	90 ± 2	139 ± 2*	138 ± 2*	68 ± 2	70 ± 3*	111 ± 2	71 ± 2†	40 ± 1
60	111 ± 2*	−9 ± 4*	−4 ± 2	97 ± 3	134 ± 1*	154 ± 3*	72 ± 3	82 ± 4*	121 ± 3*	77 ± 3†	44 ± 2*
70	130 ± 3*	−14 ± 4*	−7 ± 2	103 ± 3*	130 ± 1*	167 ± 4*	76 ± 4	91 ± 5*	130 ± 3*	80 ± 4†	49 ± 3*
80	147 ± 3*	−18 ± 3*	−10 ± 2	108 ± 4*	128 ± 1*	175 ± 5*	79 ± 4	96 ± 6*	136 ± 4*	84 ± 4*†	52 ± 3*
Significance	< 0·001	< 0·001	< 0·001	< 0·001	< 0·001	< 0·001	0·08	< 0·001	< 0·001	0·007	< 0·001

HR, heart rate; AIx, augmentation index; Aug, augmented pressure; MAP, mean arterial pressure; T_R, estimated aortic pulse wave velocity; PSBP, peripheral systolic blood pressure; PDBP, peripheral diastolic blood pressure; PPP, peripheral pulse pressure; CSBP, central systolic blood pressure; CDBP, central diastolic blood pressure; CPP, central pulse pressure. All values are mean ± SEM. Data were analysed by one way ANOVA and post hoc multiple comparisons adjusted using Bonferroni's tests. Significant differences compared to baseline are indicated by *$P < 0.05$. Significant difference from PDBP is indicated by †$P < 0.001$. Sample $n = 12$.
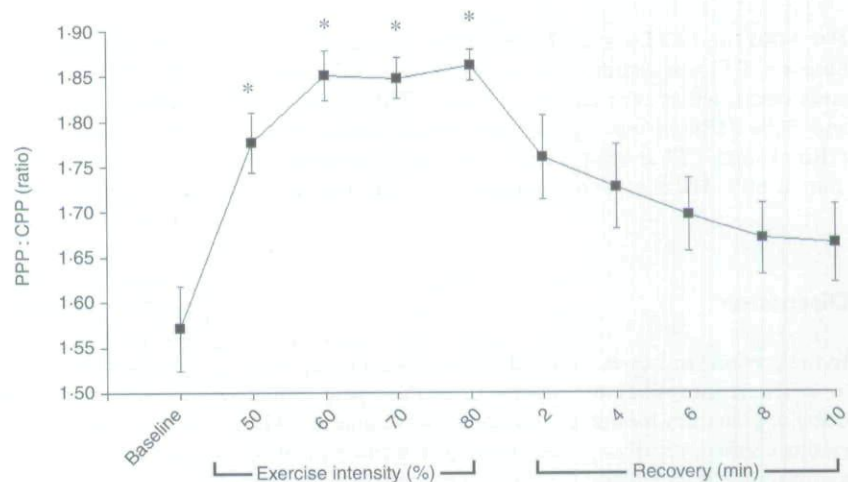

Figure 2 Changes in pulse pressure amplification at baseline, during exercise and recovery ($n = 12$). Values are mean ± SEM and *$P < 0.001$ by ANOVA compared to baseline.
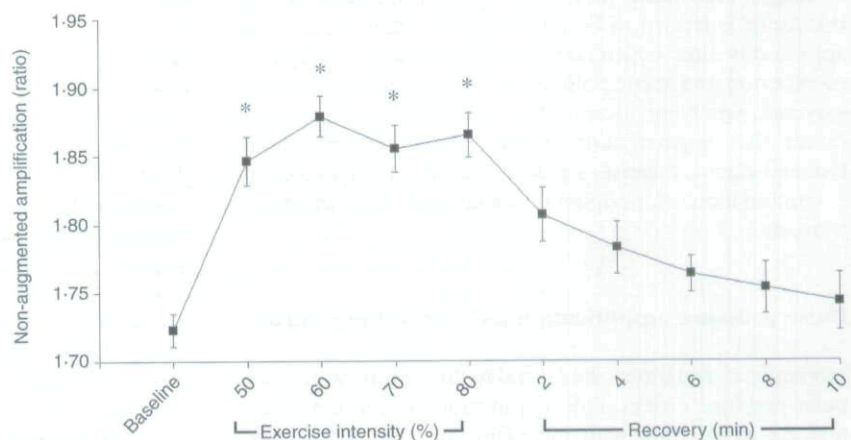

Figure 3 Changes in nonaugmented pulse pressure amplification (PPP : CDBP-P_1) at baseline, during exercise and recovery ($n = 12$). The ratio represents pulse pressure amplification without the influence of wave reflection. Values are mean ± SEM and significance by ANOVA compared to the baseline is indicated by *$P < 0.001$.

systolic increased more than central systolic blood pressure ($P < 0.001$) during exercise. The nonaugmented pulse pressure amplification also increased significantly ($P < 0.001$) at all exercise intensities (Fig. 3). The increase in pulse pressure amplification was not dependent on the intensity of exercise, as there were no significant changes in amplification from 50% to 80% of HRmax ($P = 0.7$).

For the pooled resting and exercise data, heart rate was inversely correlated with AIx ($r = -0.64$; $P < 0.001$) and positively correlated with central pulse pressure ($r = 0.60$;
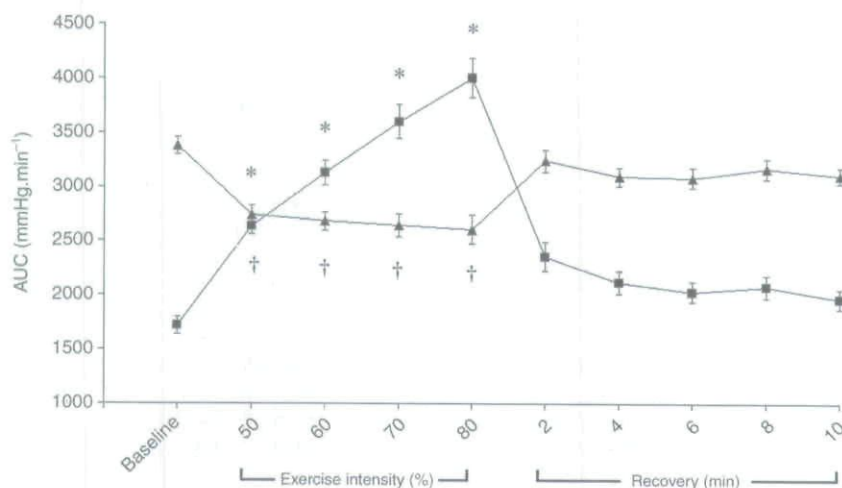
Figure 4 Changes in the area under the curve (AUC) of the central systolic (TTI; ■) and central diastolic (DTI; ▲) pressure waveform at baseline, during exercise and recovery ($n = 12$). Values are mean ± SEM and significant differences by ANOVA are indicated as $^*P < 0.001$ for TTI compared to the baseline and $^†P < 0.001$ for DTI compared to baseline.

$P < 0.001$) and TTI ($r = 0.87; P < 0.001$). Compared to the baseline, TTI was significantly increased and DTI significantly decreased at each exercise intensity. The TTI at 70% and 80% HRmax was significantly greater than at 50% HRmax, and TTI at 80% HRmax was significantly greater than at 60% HRmax. These data are shown in Fig. 4.

Discussion

In the present study, we evaluated haemodynamic responses to different intensities of exercise in healthy young men, using applanation tonometry and pulse wave analysis. Our results confirm previous work, showing that pulse pressure amplification is increased by exercise. The main novel finding of the current study was that exercise significantly increased nonaugmented pulse pressure amplification, even though this index is known to be unaffected by other factors that appreciably alter ventricular–vascular interaction. Furthermore, estimated aortic pulse wave velocity increased during exercise, signifying increased aortic stiffness. Finally, we found that augmentation index (AIx) was significantly reduced during exercise, an effect that was likely caused by a combination of peripheral vasodilation and increased heart rate.

Pulse pressure amplification and central pressures

Normally, moving from the central to the peripheral arteries, pulse pressure widens. This amplification of pulse pressure may be augmented with increasing heart rate [10] and postural changes [11], and reduced with increasing age [9], certain vasoactive drugs [24] and hypercholesterolemia [25]. The findings of the present study are in agreement with previous work, showing that amplification of the pulse pressure is increased during exercise [5,11]. This effect has previously been attributed to peripheral systolic blood pressure increasing significantly more than central systolic blood

pressure [5], which was also observed in the current study ($P < 0.001$). This may be the result, in part, of the increase in heart rate observed during exercise. An increase in heart rate will shorten the absolute duration of systole, forcing the reflected wave into diastole. Because the reflected wave contributes more to central rather than peripheral systolic pressure, the net effect will be to attenuate any rise in central systolic pressure, thus increasing the difference between central and peripheral systolic pressures. Indeed, we have previously demonstrated such an effect of heart rate per se on pulse pressure amplification [26]. Conversely, the observed rise in mean arterial pressure is unlikely to explain the increase in amplification during exercise because we have previously demonstrated a negative association between distending pressure and amplification [27].

In order to further investigate the effect of exercise on pulse pressure amplification, the amplification properties of the brachiocephalic system itself were assessed by measuring the nonaugmented pulse pressure amplification ratio. This removes the influence of wave reflection during systole, thus enabling a true assessment of pressure amplification. We found that exercise significantly increases this ratio, but not in a manner that is dependent on the intensity of exercise. Therefore, the stimulus of exercise alters the transmission characteristics of the arterial system from the aorta to the brachial artery. This is of particular interest since nonaugmented amplification is unaffected by gender, age, heart rate and vasoactive drugs [10,24,26,27]. This effect may be the result of a change in the profile of the forward going wave, or preferential stiffening of the brachial artery. Indeed, a recent study showed a 35% increase from resting values in brachial pulse wave velocity following maximal exercise [28].

To examine further changes in the central (aortic) pressure waveform that occurred throughout the study, we analysed the area under the central systolic (TTI) and diastolic (DTI) pressure waveforms, enabling assessment of the subendocardial viability ratio. The TTI significantly increased in an intensity-dependent manner with exercise, whereas DTI significantly decreased at the onset of exercise and did not change thereafter with heightened exercise intensity (Fig. 4).

This effect resulted in a stepwise significant reduction in the subendocardial viability ratio as exercise intensity increased. Because the TTI is associated with oxygen consumption and DTI relates to the pressure and time for coronary artery perfusion [22], the significantly reduced time for coronary perfusion, coupled with increased oxygen demand, may contribute to myocardial ischemia with increased exercise intensity. Whether the exercise oxygen demand–supply relationship may differ in other subject populations is unknown, although there is recent evidence to suggest that subendocardial perfusion capacity is improved in endurance athletes, at least under resting conditions [29].

Arterial stiffness

In order to assess arterial stiffness, estimated aortic pulse wave velocity (T_R) and AIx were calculated from the central pressure waveform. Exercise caused a significant fall in AIx, whereas estimated aortic pulse wave velocity and mean arterial pressure increased, suggesting that, overall, exercise caused an acute increase in arterial stiffness. The fall in AIx during exercise is most likely related to the significant increase in heart rate, because there is an inverse relationship between these two parameters [26,30], which exists independently of arterial stiffness [10,31]. Moreover, vasodilatation of muscular arteries in the leg during exercise (potentially via endothelium-dependent mechanisms) was probably a major contributor to reduced wave reflection and thus a fall in AIx. Our findings are consistent with those of others, who found input impedance (a measure of reflection intensity directly related to AIx) to decrease with exercise [12,32].

In the present study, as exercise intensity increased there was a graded increase in mean arterial pressure, which was significantly correlated to T_R ($r = -0.54$; $P < 0.001$). Hence, the increase in estimated aortic pulse wave velocity might have been secondary to an increase in mean arterial pressure, a key determinant of arterial stiffness. The increase in heart rate is unlikely to have contributed to the observed changes in estimated aortic pulse wave velocity, as previous data indicate that when heart rate is incrementally raised with cardiac pacing, there is no change in T_R or mean arterial pressure [10]. The relationship between these two variables has relevance because, as mean pressure increases, there is a change in the type of fibres that sustain vessel-wall stresses. At low mean pressures the more compliant elastin fibres predominate, but collagen fibres are progressively recruited with mounting pressure [33], effectively 'stiffening' the large central elastic arteries, resulting in increased pulse wave velocity. Thus, in the present study, as has been suggested previously [12], it is likely that exercise acutely altered aortic stiffness.

Study significance

The present study describes a significant discrepancy between the central and peripheral blood pressure response to exercise in healthy young men. Such findings highlight the need to assess the predictive value of central compared to peripheral blood pressure changes during exercise, as it is likely that central blood pressure changes will more powerfully predict future cardiovascular risk. Central haemodynamics determines left ventricular workload [6] and remodelling [34], and also predict cardiovascular mortality [8]. Notwithstanding the known cardioprotective effect of regular aerobic exercise, an excessive rise in central pressures, particularly in response to low-level exercise such as that associated with activities of daily living, may increase cardiovascular risk.

Summary

Using noninvasive methods, we have examined the central and peripheral haemodynamic responses to different exercise intensities in healthy young men. During exercise, there was a significant difference between the peripheral (brachial artery) and central (aorta) blood pressure responses, such that exercise significantly enhanced central to peripheral pulse pressure amplification. Exercise also increased estimated aortic pulse wave velocity, indicating increased aortic stiffness, although this effect was probably secondary to an increase in mean arterial pressure. We conclude that exercise acutely changes the biophysical properties of the large central arteries resulting in arterial stiffening. Furthermore, we suggest that determining the central and peripheral haemodynamic reaction to exercise may more accurately predict cardiovascular risk rather than peripheral measures alone.

Grants

Acknowledgements

References

1 Stamler J. Blood pressure and high blood pressure. Aspects of risk. *Hypertension* 1991;18:I95–107.

2 Mundal R, Kjeldsen SE, Sandvik L, Erikssen G, Thaulow E, Erikssen J. Exercise blood pressure predicts mortality from myocardial infarction. *Hypertension* 1996;**27**:324–9.

3 Kurl S, Laukkanen JA, Rauramaa R, Lakka TA, Sivenius J, Salonen JT. Systolic blood pressure response to exercise stress test and risk of stroke. *Stroke* 2001;**32**:2036–41.

4 Pauca AL, Wallenhaupt SL, Kon ND, Tucker WY. Does radial artery pressure accurately reflect aortic pressure? *Chest* 1992;**102**:1193–8.

5 Rowell LB, Brengelmann GL, Blackmon JR, Bruce RA, Murray JA. Disparities between aortic and peripheral pulse pressures induced by upright exercise and vasomotor changes in man. *Circulation* 1968;**37**:954–64.

6 Westerhof N, O'Rourke MF. Haemodynamic basis for the development of left ventricular failure in systolic hypertension and for its logical therapy. *J Hypertens* 1995;**13**:943–52.

7 Boutouyrie P, Bussy C, Lacolley P, Girerd X, Laloux B, Laurent S. Association between local pulse pressure, mean blood pressure, and large-artery remodelling. *Circulation* 1999;**100**:1387–93.

8 Safar ME, Blacher J, Pannier B, Guerin AP, Marchais SJ, Guyonvarc'h PM *et al.* Central pulse pressure and mortality in end-stage renal disease. *Hypertension* 2002;**39**:735–8.

9 Nichols WW, O'Rourke MF. *McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles.* 1998. London: Edward Arnold.

10 Wilkinson IB, Mohammad NH, Tyrrell S, Hall IR, Webb DJ, Paul VE *et al.* Heart rate dependency of pulse pressure amplification and arterial stiffness. *Am J Hypertens* 2002;**15**:24–30.

11 Kroeker EJ, Wood EH. Comparison of simultaneously recorded central and peripheral arterial pressure pulses during rest, exercise and tilted position in man. *Circ Res* 1955;**3**:623–32.

12 Murgo JP, Westerhof N, Giolma JP, Altobelli SA. Effects of exercise on aortic input impedance and pressure wave forms in normal humans. *Circ Res* 1981;**48**:334–43.

13 White WB, Lund-Johansen P, Omvik P. Assessment of four ambulatory blood pressure monitors and measurements by clinicians versus intraarterial blood pressure at rest and during exercise. *Am J Cardiol* 1990;**65**:60–6.

14 Taylor R, Chidley K, Goodwin J, Broeders M, Kirby B. Accutracker II (version 30/23) ambulatory blood pressure monitor: clinical validation using the British Hypertension Society and Association for the Advancement of Medical Instrumentation standards. *J Hypertens* 1993;**11**:1275–82.

15 Soderstrom S, Nyberg G, O'Rourke MF, Sellgren J, Ponten J. Can a clinically useful aortic pressure wave be derived from a radial pressure wave? *Br J Anaesth* 2002;**88**:481–8.

16 Pauca AL, O'Rourke MF, Kon ND. Prospective evaluation of a method for estimating ascending aortic pressure from the radial artery pressure waveform. *Hypertension* 2001;**38**:932–7.

17 Karamanoglu M, O'Rourke MF, Avolio AP, Kelly RP. An analysis of the relationship between central aortic and peripheral upper limb pressure waves in man. *Eur Heart J* 1993;**14**:160–7.

18 Safar ME, London GM. Therapeutic studies and arterial stiffness in hypertension: recommendations of the European Society of Hypertension. The clinical committee of arterial structure and function. Working Group on Vascular Structure and Function of the European Society of Hypertension. *J Hypertens* 2000;**18**:1527–35.

19 Murgo JP, Westerhof N, Giolma JP, Altobelli SA. Aortic input impedance in normal man: relationship to pressure wave forms. *Circulation* 1980;**62**:105–16.

20 London G, Guerin A, Pannier B, Marchais S, Benetos A, Safar M. Increased systolic pressure in chronic uremia. Role of arterial wave reflections. *Hypertension* 1992;**20**:10–9.

21 Marchais SJ, Guerin AP, Pannier BM, Levy BI, Safar ME, London GM. Wave reflections and cardiac hypertrophy in chronic uremia. Influence of body size. *Hypertension* 1993;**22**:876–83.

22 Buckberg GD, Fixler DE, Archie JP, Hoffman JI. Experimental subendocardial ischemia in dogs with normal coronary arteries. *Circ Res* 1972;**30**:67–81.

23 Palatini P, Mos L, Mormino P, Di Marco A, Munari L, Fazio G *et al.* Blood pressure changes during running in humans: the 'beat' phenomenon. *J Appl Physiol* 1989;**67**:52–9.

24 Wilkinson IB, MacCallum H, Hupperetz PC, van Thoor CJ, Cockcroft JR, Webb DJ. Changes in the derived central pressure waveform and pulse pressure in response to angiotensin II and noradrenaline in man. *J Physiol* 2001;**530**:541–50.

25 Wilkinson IB, Prasad K, Hall IR, Thomas A, MacCallum H, Webb DJ *et al.* Increased central pulse pressure and augmentation index in subjects with hypercholesterolemia. *J Am Coll Cardiol* 2002;**39**:1005–11.

26 Wilkinson IB, MacCallum H, Flint L, Cockcroft JR, Newby DE, Webb DJ. The influence of heart rate on augmentation index and central arterial pressure in humans. *J Physiol* 2000;**525**:263–70.

27 Wilkinson IB, Franklin SS, Hall IR, Tyrrell S, Cockcroft JR. Pressure amplification explains why pulse pressure is unrelated to risk in young subjects. *Hypertension* 2001;**38**:1461–6.

28 Naka KK, Tweddel AC, Parthimos D, Henderson A, Goodfellow J, Frenneaux MP. Arterial distensibility: acute changes following dynamic exercise in normal subjects. *Am J Physiol Heart Circ Physiol* 2003;**284**:H970–8.

29 Edwards DG, Lang JT. Augmentation index and systolic load are lower in competitive endurance athletes. *Am J Hypertens* 2005;**18**:679–83.

30 Stefanadis C, Dernellis J, Vavuranakis M, Tsiamis E, Vlachopoulos C, Toutouzas K *et al.* Effects of ventricular pacing-induced tachycardia on aortic mechanics in man. *Cardiovasc Res* 1998;**39**:506–14.

31 Nichols WW, Conti CR, Walker WE, Milnor WR. Input impedance of the systemic circulation in man. *Circ Res* 1977;**40**:451–8.

32 Laskey WK, Kussmaul WG, Martin JL, Kleaveland JP, Hirshfeld JW Jr, Shroff S. Characteristics of vascular hydraulic load in patients with heart failure. *Circulation* 1985;**72**:61–71.

33 Armentano RL, Levenson J, Barra JG, Fischer EI, Breitbart GJ, Pichel RH *et al.* Assessment of elastin and collagen contribution to aortic elasticity in conscious dogs. *Am J Physiol* 1991;**260**:H1870–7.

34 Peterson LR, Rinder MR, Schechtman KB, Spina RJ, Glover KL, Villareal DT *et al.* Peak exercise stroke volume: associations with cardiac structure and diastolic function. *J Appl Physiol* 2003;**94**:1108–14.