

Exercise reduces arterial pressure augmentation through vasodilation of muscular arteries in humans

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Submitted 9 October 2007; accepted in final form 12 February 2008

Munir S, Jiang B, Guilcher A, Brett S, Redwood S, Marber M, Chowienczyk P. Exercise reduces arterial pressure augmentation through vasodilation of muscular arteries in humans. *Am J Physiol Heart Circ Physiol* 294: H1645–H1650, 2008. First published February 22, 2008; doi:10.1152/ajpheart.01171.2007.—Exercise markedly influences pulse wave morphology, but the mechanism is unknown. We investigated whether effects of exercise on the arterial pulse result from alterations in stroke volume or pulse wave velocity (PWV)/large artery stiffness or reduction of pressure wave reflection. Healthy subjects ($n = 25$) performed bicycle ergometry, with workload increasing from 25 to 150 W for 12 min. Digital arterial pressure waveforms were recorded using a servo-controlled finger cuff. Radial arterial pressure waveforms and carotid-femoral PWV were determined by applanation tonometry. Stroke volume was measured by echocardiography, and brachial and femoral artery blood flows and diameters were measured by ultrasound. Digital waveforms were recorded continuously. Other measurements were made before and after exercise. Exercise markedly reduced late systolic and diastolic augmentation of the peripheral pressure pulse. At 15 min into recovery, stroke volume and PWV were similar to baseline values, but changes in pulse wave morphology persisted. Late systolic augmentation index (radial pulse) was reduced from $54 \pm 3.9\%$ at baseline to $42 \pm 3.7\%$ ($P < 0.01$), and diastolic augmentation index (radial pulse) was reduced from $37 \pm 1.8\%$ to $25 \pm 2.9\%$ ($P < 0.001$). These changes were accompanied by an increase in femoral blood flow (from 409 ± 44 to 773 ± 48 ml/min, $P < 0.05$) and an increase in femoral artery diameter (from 8.2 ± 0.4 to 8.6 ± 0.4 mm, $P < 0.05$). In conclusion, exercise dilates muscular arteries and reduces arterial pressure augmentation, an effect that will enhance ventricular-vascular coupling and reduce load on the left ventricle.

central blood pressure; pulse wave; nitroglycerin; pulse wave velocity

ARTERIAL PRESSURE DURING SYSTOLE is largely dependent on the function of large elastic and muscular arteries. The importance of muscular arteries is exemplified by nitroglycerin (NTG), a powerful dilator of such arteries (15). NTG has a characteristic effect on the pulse waveform: it reduces augmentation (Fig. 1) in the central and peripheral pulse waveforms and reduces central systolic pressure and central pulse pressure to a greater degree than peripheral pressure. These effects are thought to be due to reduction of pressure wave reflection from peripheral to central arteries by vasodilation of muscular arteries (10, 23, 34). The reduction in central systolic blood pressure cannot be determined simply by measurement of peripheral blood pressure but can be detected from changes in the peripheral pulse waveform (8), particularly reduction in peripheral systolic

augmentation index (AI), which approximates the ratio of central to peripheral pulse pressure (18). Exercise induces changes in pulse wave morphology, which are qualitatively similar to those mediated by NTG, and could have important implications for ventricular vascular coupling (19).

The purpose of the present study was to determine whether effects of exercise on peripheral pulse wave morphology are mediated by a mechanism similar to that of NTG, i.e., vasodilation of muscular arteries, or whether they are accounted for by changes in heart rate, stroke volume, or pulse wave velocity (PWV) in central arteries. To accomplish this, we measured peripheral pulse waveforms at rest and during and after exercise and measured stroke volume, large artery diameter, blood flow, and PWV at rest and after exercise. We compared changes in the pulse wave induced by exercise with those induced by NTG.

METHODS

Subjects ($n = 25$) were nonsmoking healthy volunteers aged 19–33 yr recruited from the local community. They were recreationally active, but none were amateur or professional athletes. They had no history of cardiovascular disease and were taking no regular prescribed medication. The study was approved by St. Thomas' Hospital research ethics committee, and all subjects gave written informed consent. Exercise studies were performed in the morning in a quiet temperature-controlled vascular laboratory. Subjects were instructed to avoid caffeine and exercise other than walking on the morning of the study. Baseline measurements of brachial blood pressure, radial and digital pulse waveforms, PWV, stroke volume, brachial and femoral artery diameter, and blood flows were determined with subjects in the semisupine position. Subjects then performed a period of supervised exercise on a magnetically braked bicycle ergometer (Seca Cardiotest 100, Cardiokinetis, Salford, UK). Workload commenced at 25 W and was increased by 25 W at 2-min intervals to a maximum of 12 min (with peak workload of 150 W) or until exhaustion. Exercise was not interrupted during acquisition of digital artery waveforms (see below). Immediately after exercise, subjects returned to a semirecumbent posture, and hemodynamic and arterial measurements were obtained immediately after exercise (blood pressure and pulse wave measurements at 1 min after exercise and PWV 1–3 min after exercise) and at 15, 30, and 60 min into recovery.

Hemodynamic and arterial measurements. Brachial systolic and diastolic blood pressure was measured at rest and after exercise by an automated oscillometric method (model 705CP, Omron). Mean arterial pressure (MAP) was derived from the radial artery waveform (see below) calibrated with oscillometric values of systolic and diastolic pressure. The digital arterial waveform was continuously recorded

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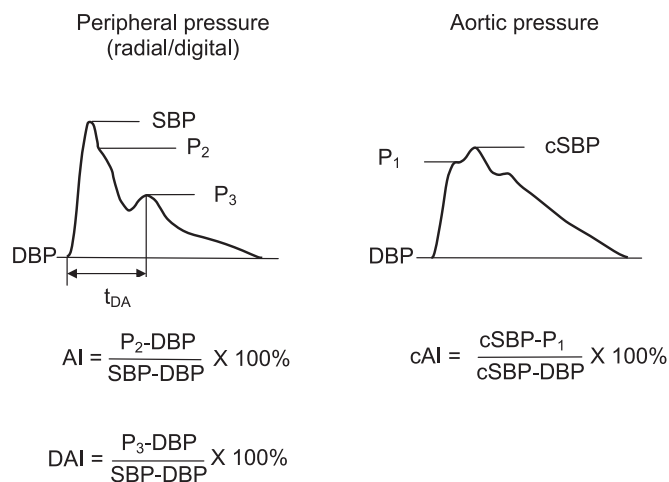


Fig. 1. Typical aortic and peripheral (radial) pressure pulse waveforms. Peripheral systolic pressure differs from aortic systolic pressure (peripheral usually greater than aortic) as a result of propagation and pressure wave reflection in the upper limb. Pressure wave reflection within the systemic circulation is thought to influence the morphology of the aortic and peripheral pulse. Measures of morphology include peripheral augmentation index (AI, defined from the peripheral pulse wave as shown) and central augmentation index (cAI, defined from the aortic pulse wave). Changes in the diastolic portion of the peripheral waveform were also quantified using diastolic augmentation index (DAI) and time of diastolic augmentation (t_{DA}) defined as shown. SBP and DBP, systolic and diastolic blood pressure.

using a servo-controlled finger pressure cuff (Finometer, Finapres Medical Systems). Waveform data were sampled at 100 Hz and stored on disk for subsequent analysis using in-house software. Radial artery pressure waveforms were acquired via applanation tonometry (SphygmoCor, Atcor) at rest and after exercise. Digital artery waveforms are closely related to radial artery waveforms (17) and, with use of the Finometer, can be obtained continuously during exercise (in contrast to the SphygmoCor system, which cannot be used during exercise). The primary measures of pressure augmentation were AI (the difference between pressure at the point of late systolic augmentation and diastolic pressure expressed as a percentage of pulse pressure; Fig. 1) and diastolic AI (DAI, the difference between peak pressure in early diastole and diastolic pressure expressed as a percentage of pulse pressure; Fig. 1). Because AI and DAI are ratios of pressures, they are not dependent on calibration of the arterial pressure waveforms. AI and DAI were calculated from the radial and digital waveforms. The within-subject standard deviation of repeated measures of AI and DAI in our laboratory ranges from 8 to 12%.

AI has previously been shown to change, in parallel with central aortic AI (cAI), the difference between peak aortic systolic pressure and the first systolic shoulder of the aortic pulse wave (Fig. 1) and to closely approximate the ratio of central to peripheral pulse pressure (18). To verify that this relationship remains during exercise, we simultaneously measured AI from the carotid artery (a close surrogate of cAI) by carotid tonometry and AI derived from the digital artery at rest and immediately after exercise in a subset of 10 subjects. Carotid tonometry immediately after exercise was performed with the subjects in the semisupine position, with the head supported (rehabilitation trainer 881E, Monark), which limited the maximum workload to 100 W. The radial-to-aortic transfer function in the SphygmoCor system [validated for use during low-workload exercise (25)] was also used to estimate central systolic blood pressure and cAI at rest and after exercise. Radial artery waveforms were calibrated from brachial systolic and diastolic blood pressure, and the radial-to-aortic transfer function incorporated in the SphygmoCor system was used to estimate central systolic blood pressure and cAI.

Carotid-femoral PWV was measured by ECG-referenced carotid-femoral arterial tonometry using the SphygmoCor system. Path length

over the carotid-to-femoral region was estimated from the distance between the sternal notch and femoral artery at the site of applanation. The points of applanation on the carotid and femoral arteries were kept constant throughout the study. Apart from measurements immediately after exercise, all blood pressure, waveform, and PWV measurements were means of three consecutive readings centered over the time points defined above.

Stroke volume and brachial and femoral artery diameters were determined at rest and after exercise by transthoracic echocardiography (Accuson 128XP with 4-MHz probe) and duplex ultrasound (Accuson 128XP with 7-MHz vascular probe), respectively. Aortic outflow tract diameter was measured, and stroke volume was calculated from aortic outflow tract cross-sectional area and velocity-time

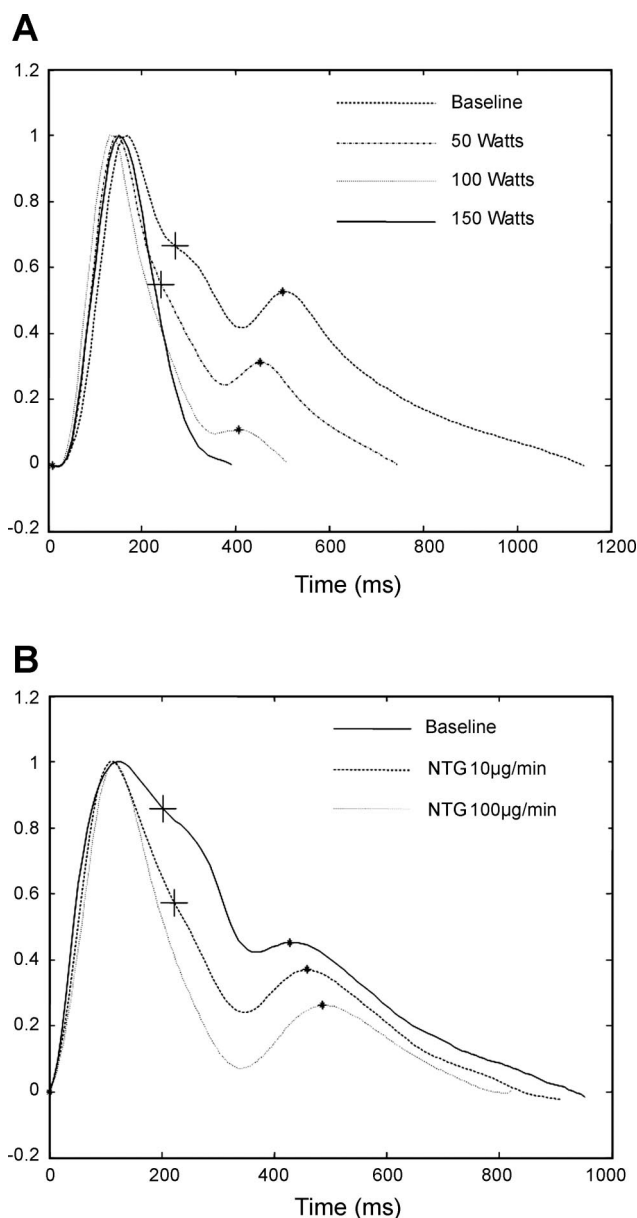


Fig. 2. A: typical digital pressure pulse waveforms obtained by Finapres at baseline and during exercise. Waveforms are ensemble averages of ~10 cardiac cycles and are shown normalized to the same diastolic and systolic pressures to demonstrate the change in morphology. Exercise was accompanied by reduction or abolition of late systolic augmentation (+) and diastolic augmentation (♦). B: similar changes in pulse wave morphology in response to nitroglycerin (NTG) infusion at rest, in the absence of any change in heart rate.

integral of the Doppler-derived aortic velocity measurements. Cardiac output and total peripheral resistance were calculated from stroke volume, heart rate, and MAP (derived from the SphygmoCor system by integration of the radial pressure waveform). Wall tracking software (Medical Imaging Applications) was used to measure brachial and femoral artery diameters in diastole. Blood flow was obtained from arterial diameter and mean velocity, computed from the velocity-time integral (with incorporation of any reverse flow during diastole). Echocardiographic and ultrasound measurements were performed by a second operator, so that they could be obtained at the same time point as PWV measurements.

To compare exercise- with NTG-induced changes in the pulse waveform, we analyzed data previously obtained during NTG infusion (27). Eight healthy subjects were infused intravenously with a cumulative dose of NTG (10, 30, and 100 $\mu\text{g}/\text{min}$, each dose for 15 min) that produces a change in large artery (brachial, femoral, and carotid) diameter of 5–20% (1, 27). Blood pressures, radial artery waveforms, and PWV were obtained as described above at baseline and during the last 5 min of each NTG dose.

Statistics. Results were compared by analysis of variance (for repeated measures where appropriate). When this showed an overall change, values at individual time points were compared by Student's paired *t*-test. Results are summarized as means \pm SE. Heart rate was incorporated as a covariate in the analysis for comparison of changes in AI. All tests were two-sided, and $P < 0.05$ was taken as significant.

RESULTS

The majority (21 of 25) of the subjects completed the 12-min exercise protocol; the remaining subjects completed 10 min of the protocol. Exercise was associated with a marked change in morphology of the radial and digital pressure pulse waveforms comprising a relative reduction in late systolic augmentation and diastolic augmentation and, hence, AI and DAI (Fig. 2). At higher workloads (and in 2 of 25 subjects early in recovery), systolic and/or diastolic augmentation was undetectable. The reduction in AI and DAI persisted for 60 min into recovery and was present even when heart rate had returned to baseline (Table 1). Correction for change in heart rate in the recovery

period did not explain differences in AI and DAI, and there was no significant correlation between changes in AI and changes in heart rate. The SphygmoCor software did not detect AI reliably immediately after exercise (when values obtained from the digital artery were used); however, at rest and at other time points in recovery, AI and DAI values obtained from the radial and digital waveforms were comparable (Table 1). The time to the point of maximal diastolic augmentation (t_{DA}) was reduced during and immediately after exercise, but not by as much as the reduction in pulse period; at later stages in recovery, t_{DA} remained similar to baseline, despite a reduction in DAI (Table 1). Estimated central systolic blood pressure and pulse pressure were lower than brachial blood pressure at rest and after exercise, with a tendency for the difference to be greater after exercise. There was also a reduction in estimated aortic AI that paralleled the reduction in digital/radial AI. Measurements of AI derived from the carotid and digital arteries produced a similar change in carotid and digital AI [of 12.2 ± 2.2 and $13.3 \pm 4.3\%$, respectively, each $P < 0.05$, $P =$ not significant (NS) for difference].

Carotid-femoral PWV remained similar to baseline at all time points after exercise (Table 1). At 15 min after exercise, when echocardiographic and ultrasound measurements were made, cardiac output was significantly higher and peripheral vascular resistance was significantly lower than at baseline, but stroke volume was unchanged compared with baseline (Table 2). Brachial artery blood flow was lower than at baseline, and brachial artery diameter was similar to baseline. Femoral blood flow was approximately twice that at baseline (Table 2). This increase in femoral blood flow was associated with a significant increase in femoral artery diameter (Table 2). The change from baseline in femoral artery diameter was not significantly correlated with the change in AI or DAI.

Pulse wave changes in response to NTG are summarized in Table 3. NTG induced qualitatively similar changes in the pulse waveform to exercise (Fig. 2), with a reduction in AI and

Table 1. Peripheral blood pressure and measures of pulse contour and PWV before and after exercise

Measurement	Preexercise	Postexercise			
		1–3 min ^a	15 min	30 min	60 min
Heart rate, min^{-1}	69 ± 2.2	105 ± 4.4^c	80 ± 2.7^c	74 ± 2.4^c	73 ± 2.6
Brachial blood pressures, mmHg					
SBP	117 ± 2.2	138 ± 3.9^c	117 ± 2.7	116 ± 2.4	110 ± 2.5
DBP	66 ± 1.7	64 ± 1.4	69 ± 2.0	69 ± 2.2	66 ± 1.2
MAP	84 ± 1.5	88 ± 2.4^c	80 ± 1.6^c	81 ± 1.3	79 ± 1.0^d
PP	50 ± 2.5	74 ± 3.4^c	48 ± 2.8	47 ± 2.8	44 ± 2.3^c
Peripheral augmentation					
AI, %					
Radial ^b	54 ± 3.9		42 ± 3.7^d	47 ± 3.6^d	45 ± 3.5^e
Finger	51 ± 3.8	19 ± 4.0^c	45 ± 2.3	45 ± 3.1^c	47 ± 1.7^c
DAI, %					
Radial	37 ± 1.8	11 ± 1.5^c	25 ± 2.9^c	29 ± 1.9^d	31 ± 2.8^c
Finger	37 ± 1.7	8.5 ± 1.4^c	25 ± 2.9^c	30 ± 1.8^e	30 ± 1.5^e
t_{DA} (finger), ms	480 ± 20	369 ± 13^c	464 ± 9	487 ± 16	478 ± 21
Estimated central pressures and augmentation					
SBP, mmHg	104 ± 2.1	120 ± 2.8^c	100 ± 2.0	100 ± 2.0	96 ± 1.4^d
PP, mmHg	35 ± 1.6	51 ± 2.4^c	32 ± 2.0	31 ± 1.6	29 ± 1.4^d
AI (aorta), %	6.2 ± 2.0	3.3 ± 1.8	1.0 ± 1.6^c	1.2 ± 1.8^d	2.9 ± 2.1^c
PWV, m/s	7.1 ± 0.2^a	7.4 ± 0.2	7.1 ± 0.2	7.0 ± 0.2	7.1 ± 0.2

Values are means \pm SE. SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean blood pressure; PP, pulse pressure; AI, augmentation index; DI, diastolic augmentation index; PWV, pulse wave velocity. ^aBlood pressure and pulse wave were measured 1 min after exercise; PWV was measured 1–3 min after exercise. ^bSphygmoCor values for radial AI could not be obtained during or immediately after exercise. ^c $P < 0.05$; ^d $P < 0.01$; ^e $P < 0.001$ vs. preexercise.

Table 2. Stroke volume and femoral and brachial artery diameter and flow before and 15 min after exercise

	Preexercise	Postexercise
Heart rate, min ⁻¹	69±2.2	80±2.7†
Stroke volume, ml	84.1±4.5	87.3±6.2
Cardiac output, l/min	5.5±0.3	6.5±0.3*
PVR, mmHg·l ⁻¹ ·min	16.0±1.1	13.1±0.5*
Diameter, mm		
Femoral artery	8.2±0.4	8.6±0.4*
Brachial artery	3.8±0.2	3.8±0.2
Flow, ml/min		
Femoral	409±44	773±48*
Brachial	143±25	85.7±14.6*

Values are means ± SE. PVR; peripheral vascular resistance. **P* < 0.05; †*P* < 0.001 vs. preexercise.

DAI. At lower doses, NTG induced a marked reduction in AI and DAI without a significant change in heart rate. There was also no significant change in carotid-femoral PWV.

DISCUSSION

Although cardiac function during exercise has been studied extensively, relatively little is known about the influence of exercise on ventricular vascular coupling and pulse wave morphology. The main finding of the present study is that exercise induces marked changes in the morphology of the radial and digital pulse wave similar to changes induced by nitrovasodilators, comprising a reduction in late systolic and early diastolic pressure augmentation. These changes increase with increasing intensity of exercise and persist for up to 60 min into recovery. In principle, such changes could be due to altered heart rate/ventricular ejection characteristics, large artery stiffness/PWV, or change in tone of muscular arteries influencing pressure wave reflection (21). However, changes in waveform morphology were present in recovery when stroke volume and carotid-femoral PWV values were similar to those at baseline. Although small but significant differences in heart rate persisted for up to 30 min into recovery, changes in augmentation persisted for up to 60 min.

At 15 min into recovery, changes in augmentation were not correlated with heart rate but were accompanied by dilation of

the femoral arteries. Changes in augmentation were not correlated with changes in femoral artery diameter, but the absolute changes (~400 μm) were relatively small in comparison with the resolution of the scanner (~100 μm) and subject to within-subject variability of ~30%. Reflection depends on impedance, which is related to high-order powers of diameter, which will amplify within-subject variability in diameter and limit any correlation with measured change in diameter. Furthermore, we did not measure femoral artery diameter at 60 min into recovery, and we cannot exclude the possibility that another mechanism might be responsible for or contribute to the reduction in augmentation during/after exercise. Nevertheless, the similarity of exercise- to NTG-induced changes in AI strongly suggests that vasodilation of muscular arteries with a reduction in pressure wave reflection from the lower body is an independent mechanism underlying exercise-induced changes in pulse waveform morphology. Relaxation of vascular smooth muscle in muscular arteries leads to vasodilation and a reduction in PWV (2, 12). The present findings are, therefore, consistent with the decrease in PWV after exercise in muscular arteries of the exercising limb observed by a number of other investigators (7, 11, 20, 29). Although aortic PWV (closely related to carotid-femoral PWV) is probably more important than lower limb PWV in determining the timing of reflections and, hence, augmentation, a decrease in lower limb PWV could also contribute to a reduction in pressure augmentation.

The most obvious implications of the exercise-induced change in the arterial pulse relate to loading on the left ventricle. Central aortic systolic pressure is usually estimated using a radial-aortic transfer function, such as that incorporated into the SphygmoCor system. This transfer function has been validated to reliably estimate central systolic blood pressure (and pulse pressure) at low workloads (25) but has not been validated at higher heart rates/workloads (approx >100 beats/min). Transfer functions do change during exercise (28), and the technique may have limitations with respect to precise estimation of central pressure at high heart rates/workloads. Limitations on the accuracy of estimation of central pressure may also be imposed by calibration of peripheral arterial waveforms by brachial cuff pressure (22) and by brachial-to-radial amplification (30). In the present study, we used mea-

Table 3. Peripheral blood pressure and measures of pulse contour and PWV at baseline and during NTG infusion

	Baseline	NTG		
		10 μg/min	30 μg/min	100 μg/min
Heart rate, min ⁻¹	63.6±4.5	64.5±3.8	64.3±4.1	68.8±4.7†
Brachial blood pressures, mmHg				
SBP	109.5±3.6	108.2±3.2	105.4±3.3†	102.2±3.1†
DBP	68.2±2.1	61.4±1.9‡	59.6±1.8‡	57.2±2.5‡
MAP	82.0±2.4	77.0±2.2‡	74.9±2.0‡	72.2±2.5‡
PP	41.3±2.8	46.8±2.3†	45.7±3.0*	45.1±2.1
Peripheral augmentation				
AI (radial), %	60.1±6.2	37.4±3.7‡	36.9±5.3†	33.7±3.9‡
DAI (radial), %	41.2±2.5	33.3±2.0†	32.1±1.4†	28.1±2.1‡
t _{DA} (radial), ms	418±4.8	450±5.8‡	452±6.5‡	459±7.8‡
Estimated central pressures and augmentation				
SBP, mmHg	92.9±4.5	78.7±2.7‡	76.8±3.5‡	72.4±3.2‡
PP, mmHg	24.7±3.0	17.2±1.5‡	17.2±3.9*	15.2±2.0‡
AI (aorta), %	16.2±4.6	1.1±3.4†	-4.4±2.7‡	-6.9±3.1‡
PWV, m/s	8.9±0.36	8.7±0.37	8.6±0.47	8.4±0.39

Values are means ± SE. NTG, nitroglycerin. **P* < 0.05; †*P* < 0.01; ‡*P* < 0.001 vs. baseline.

surements of augmentation obtained directly from the digital and radial arteries without the use of a transfer function, as well as transfer function estimates of central systolic pressure and cAI. Although the upper limb modifies the pulse waveform, vascular tone in the upper limb has only a minor influence on the peripheral pulse, in contrast to that in the systemic circulation (6). Changes in peripheral AI parallel changes in cAI (measured invasively) during pacing and after administration of vasodilators, interventions producing hemodynamic changes similar to those induced by exercise (18), and peripheral AI closely approximates the ratio of central to peripheral pulse pressure. In the present study, we observed parallel changes in carotid AI, a close surrogate of aortic AI, and peripheral AI. This confirms that reduction of radial/digital AI results from an exercise-induced change in the systemic circulation, rather than an artifact arising from change in the upper limb.

It is well established that exercise is associated with amplification of peripheral systolic blood pressure above central systolic blood pressure (13, 24, 26), which is expected on the basis of an increase in heart rate (31, 32). However, the present study suggests that peripheral vasodilation is an independent mechanism contributing to reduced AI and, therefore, a reduction in central relative to peripheral systolic blood pressure. Reduced pressure augmentation after exercise could be one mechanism contributing to the phenomenon of warm-up angina, whereby an initial period of exercise (even below the ischemic threshold) in patients with coronary heart disease limits subsequent angina (3).

Previous work on pulse wave analysis has focused on the systolic component of the waveform. However, it is thought that pressure wave reflection is responsible for the augmentation of diastolic pressure or "the diastolic tidal wave" (21). Indeed, if pressure wave reflection occurs from small muscular arteries proximal to resistance arteries but distal to conduit arteries, then calculations based on path length and PWV of reflected waves (expected to approximate that of forward waves) suggest that the majority of reflection would be expected to occur in diastole (6). In the present study, we observed a reduction in the diastolic wave in parallel with a reduction in late systolic augmentation, and at high levels of exercise the "diastolic wave" was virtually abolished. Although the time to the point of maximal diastolic augmentation was reduced during exercise (Fig. 1), it was not reduced to the same extent as the pulse period, and at later stages in recovery it remained similar to baseline, despite a reduction in DAI. This finding is consistent with formation of DAI by wave reflection. During exercise, reflected waves that arrive in diastole of the same cardiac cycle at low heart rates may arrive in systole of the next cycle when heart rate increases and the period of the pulse decreases. This would account for the disappearance of the diastolic wave as it becomes overridden by the systolic wave. Reduction of the "diastolic component" of the pressure wave is thus of importance; otherwise, by augmentation, it would lead to a greater rise in systolic blood pressure during exercise.

Our study did not identify the signaling pathway(s) through which vasodilation of muscular arteries occurs. Endothelium-derived mediators, such as nitric oxide (9), prostaglandins (33), and endothelin (16), may be involved, and under conditions associated with impaired endothelial vasomotor dysfunction (5), exercise-induced vasodilation may be impaired, with adverse consequences on ventricular-vascular coupling. Ana-

tomic or structural changes in the arterial tree, possibly associated with fetal programming, are also likely to influence regulation of pressure wave reflection during exercise (4, 14).

In conclusion, exercise leads to changes in the arterial pressure waveform that are likely to arise from dilation of muscular arteries supplying skeletal muscle and reduced pressure wave reflection. These changes are likely to form an important part of a functional adaptation to exercise that enhances ventricular-vascular coupling and reduces load on the left ventricle.

GRANTS

The authors acknowledge financial support from the Department of Health via the National Institute for Health Research comprehensive Biomedical Research Centre award to Guy's and St. Thomas' National Health Service Foundation Trust in partnership with King's College London. S. Munir was supported by British Heart Foundation Fellowship FS/04/059.

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