

## Arterial distensibility: acute changes following dynamic exercise in normal subjects

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Submitted 25 June 2002; accepted in final form 11 November 2002

**Naka, Katerina K, Ann C Tweddel, Dimitris Parthimos, Andrew Henderson, Jonathan Goodfellow, and Michael P Frenneaux.** Arterial distensibility: acute changes following dynamic exercise in normal subjects. *Am J Physiol Heart Circ Physiol* 284: H970–H978, 2003. First published November 14, 2002; 10.1152/ajpheart.00529.2002.—The time course of acute changes in large artery distensibility immediately and for 60 min following maximum treadmill exercise in normal subjects was characterized by simultaneously measuring upper and lower limb pulse wave velocity (PWV). A new oscillometric technique was used, which has proven to be sensitive to changes in distensibility induced by acute changes in vascular tone independently of blood pressure. The observed changes in PWV are attributable to changes in vascular tone corresponding to recovery from a systemic net constrictor response and a local net dilator response to exercise with persisting postexercise vasodilatation. They are inadequately explained by associated changes in blood pressure and cannot be attributed to changes in heart rate or viscosity. Modeled as a system of  $n$  coupled linear differential equations, the minimum (and adequate) order required to reproduce these patterns was  $n = 1$  for the upper and  $n = 2$  for the exercising lower limb. The economy of the solution suggests entrainment among the multiple interactive mechanisms governing vasomotor control.

exercise physiology; large arteries; pulse wave velocity; vascular responses

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LARGE ARTERY DISTENSIBILITY is physiologically important for circulatory efficiency. It reduces impedance to systolic ejection and cardiac work, slows pulse wave velocity so that the return of reflected pressure waves is delayed until after aortic valve closure, and favors coronary perfusion during diastole. Conversely, arterial stiffening (as with aging, atherosclerosis, hypertension, and heart failure) is functionally disadvantageous, particularly in the presence of cardiac dysfunction, high blood pressure, or coronary artery disease and carries an adverse prognosis (5). The chronic effects of aging and disease on resting disten-

sibility, attributed generally to structural changes in the arterial wall, have attracted increasing clinical interest in recent years (3, 10, 11, 14, 22, 23, 28, 33, 36). Distensibility of large arteries, however, is determined not only by the passive properties of structural components but also by changes in vascular tone (4, 19, 34), effects that have been less well documented.

Pulsatile distensibility can be measured by relating luminal diameter and transmural pressure or by pulse wave velocity (PWV) to which it is inversely related (3, 4, 7). Goodfellow et al. (16) and Ramsey et al. (34) have shown, for example, that distensibility measured by PWV is acutely increased during a hyperemia-induced increase in flow in normal subjects but not in patients with heart failure or diabetes where flow-related endothelium-mediated vasodilatation is impaired.

Resting arterial distensibility is greater in athletes (6, 20) and has been shown to be increased 4 wk after a period of exercise training (9) and when first measured 30 min after a single episode of submaximal cycling exercise (19). Exercise is an integral part of normal life, yet the acute effects of exercise on this physiologically important variable of large artery distensibility have otherwise been studied little.

In the present study, we have characterized the immediate effects of maximum symptom-limited exercise on large artery distensibility in healthy young subjects. PWV immediately and for 60 min following maximal exercise was measured over both upper and lower limb arteries, as representative of large arteries supplying nonexercising and exercising muscles, respectively, using a newly developed computerized technique of oscillometry to identify wave timing. The method was validated in that acute changes in vascular tone induce the appropriate changes in PWV (29). The findings extend knowledge of the immediate effects of exercise on arterial distensibility in normal subjects. The data have been modeled to provide a quantitative reference against which to compare the effects of exercise in other conditions.

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## METHODS

### Subjects

The subjects studied were normal, adult volunteers of average "sedentary" fitness for their age of  $<45$  yr ( $31 \pm 6$  yr, means  $\pm$  SD) (see Table 1; of the total of 50 subjects studied by these methods, 25 participated in the exercise study). None smoked, was hypertensive (blood pressure  $>140/80$  mmHg), diabetic, hyperlipidemic (fasting serum cholesterol or triglycerides  $>6.0$  and  $>2.0$  mmol/l, respectively), or obese (body mass index  $>30$  kg/m<sup>2</sup>), and none was taking medication. Physical examination was normal in all cases. All gave written informed consent to the study, which was approved by the local ethics committee.

### Measurements

**Pulse wave velocity.** PWV was measured simultaneously and noninvasively in the arm and the leg by oscillometry (time resolution  $\pm 2$  ms; QVL SciMed (Bristol, UK). The right arm and leg were used for all the exercise studies. All measurements were made by the same operator (K. K. Naka). Nonocclusive cuffs were placed over the brachial and radial arteries and at the mid thigh and ankle, connected by "non-compliant" tubing to pressure transducers and inflated to 65–70 mmHg for measurement of pulse waves. Pulse pressure waveforms caused by the volume displacement of the traveling pulse wave were obtained from each of the four cuffs. A computer program was developed to characterize the waveform with respect to time at 30, 40, and 50% of peak pressure along its ascending limb and measure the transit time of normal pulse waves between the pairs of upper limb and of lower limb cuffs. It was designed to discard ectopic beats and abnormal waveforms. Transit times between the proximal and distal sites of the upper and lower limb pairs of cuffs were measured as the average of the time delays between each of the three time points in each pulse and are given as the average of the transit times in 10 consecutive beats. PWV was derived as the distance between the proximal edges of each pair of cuffs divided by the transit time. Each recording of PWV took  $\sim 15$  s. Measurements were made every minute throughout each study.

Reproducibility of resting supine PWV was assessed by within-subject coefficients of variation over 10 and 60 min of consecutive measurements and of measurements repeated 7 days apart.

**Heart rate and blood pressure.** Heart rate and blood pressure (BP) were measured continuously throughout each study by digital plethysmography (Finapres; Ohmeda, UK) (18) using the index finger of the free arm. Data were converted to digital form (500 samples/s) and stored for off-line

analysis (Acknowledge III, Biopac Systems; Santa Barbara, CA) and are presented as the averages over successive 5-min periods. BP was measured also by manual sphygmomanometry in the brachial and popliteal arteries, before and at specific times after exercise, with subjects resting supine.

**Hematocrit and plasma viscosity.** Hematocrit and plasma viscosity were measured in blood samples drawn from non-occluded veins into EDTA-containing vacutainer tubes, taken before exercise, and immediately, 20 and 60 min after maximum treadmill exercise. Plasma viscosity was measured using a Coulter Viscometer II (Coulter Electronics) and expressed as cP.

### Exercise Protocol

All subjects attended in a fasted state and at the same time on the morning of each study, having avoided formal and strenuous exercise for 48 h and caffeine-containing beverages for 12 h. All interventions and measurements were preceded by a preliminary period of  $>15$  min supine rest in a quiet, darkened, temperature-controlled room at 22°C. All measurements were performed with subjects resting supine.

**Treadmill exercise.** The effects of maximal symptom-limited treadmill exercise, performed according to the Bruce Protocol (Marquette Electronics; Milwaukee, WI), were measured in 25 subjects. Analysis of expired carbon dioxide and oxygen (Pulmolab Ex 670, Morgan Medical; Kent, UK) confirmed the achievement of a respiratory exchange ratio of  $>1.1$  in all subjects. Upper and lower limb PWV was recorded at 1-min intervals throughout the study, resting supine for 10 min before exercise, restarting "immediately" after exercise (as soon as was practically possible, i.e., 3 min after the end of exercise), and continuing for 60 min. Reproducibility of the pattern of changes after exercise was confirmed.

**Modeling of postexercise PWV.** The pattern of changes in upper and lower limb PWV was modeled by a system of coupled linear differential equations (see RESULTS) whose coefficients were determined by least squares fit to the individual PWV time series data (normalized as a percentage of the baseline PWV in each case), using SigmaStat (Jandel Scientific) (13) ( $n = 22$  after exclusion of 3 of the 25 subjects shown in Fig. 1 because anomalies in their individually plotted PWV data-time series prevented their individual modeling).

**Statistics.** Data are given as means  $\pm$  SD. Paired *t*-test or repeated measures analysis of variance with paired *t*-test and Bonferroni's correction (SPSS 10.0 for Windows) were used to compare results, as detailed in each case (see figure legends).

## RESULTS

### Resting Preexercise

PWV in normal subjects resting supine (averaged over 10 measurements at 1-min intervals in each case) was slightly but significantly higher in the lower limb ( $8.0 \pm 1.2$  m/s) than in the upper limb ( $7.3 \pm 0.9$  m/s) ( $n = 50$ ,  $P < 0.0005$ ) (Table 1).

**Reproducibility.** The within-subject coefficients of variation of PWV were 1) 3.6% for the upper limb and 2.2% for the lower limb, measured for 10 consecutive measurements at 1-min intervals ( $n = 16$  subjects); 2) 4.9% for the upper limb and 2.1% for the lower limb, for six consecutive 10-min-averaged levels of measurements over 60 min ( $n = 6$ ); and 3) 5.4% for the upper limb and 5.6% for the lower limb, for 10-min-averaged

Table 1. Subject characteristics

<i>n</i>	50
Age, years (range)	30.7 (5.8) (18–45)
Men:women	46:4
BMI, kg/m <sup>2</sup>	24.5 (3.5)
Total cholesterol, mmol/l	4.7 (0.7)
Triglycerides, mmol/l	1.0 (0.4)
BP, mmHg	123 (12)/71 (9)
Heart rate, beats/min	60 (8)
UL PWV, m/s	7.3 (0.9)
LL PWV, m/s	8.0 (1.2)*

Values are means  $\pm$  SD. BMI, body mass index; BP, blood pressure; UL/LL PWV, upper limb/lower limb pulse wave velocity. \* $P < 0.0005$  cf. UL PWV (paired *t*-test).

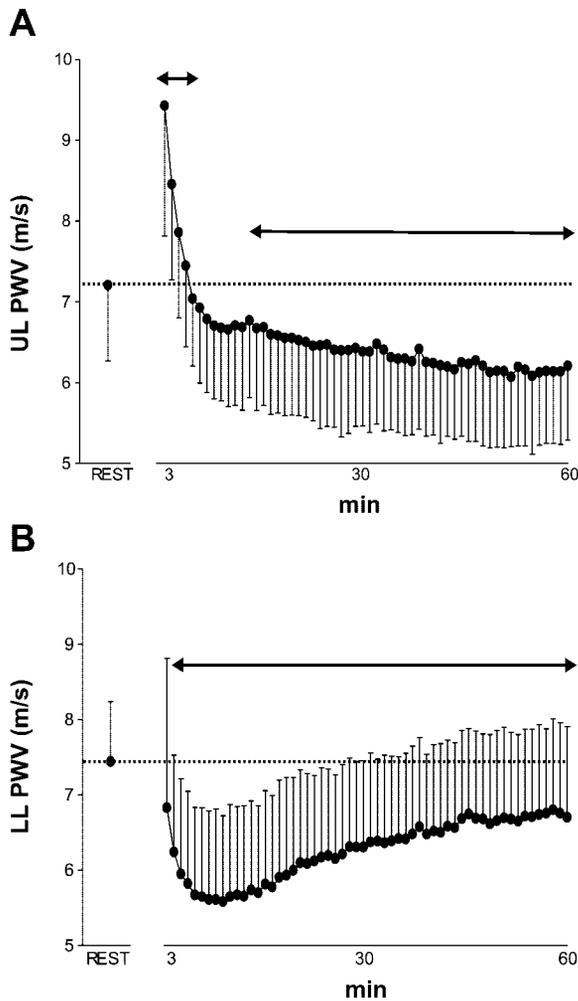


Fig. 1. Changes in upper limb pulse wave velocity (UL PWV, *A*) and lower limb PWV (LL PWV, *B*) after maximum treadmill exercise. Values are means  $\pm$  SD;  $n = 25$ . Horizontal arrowed bars indicate individual data points significantly different from the 10-min averaged preexercise resting data ( $P < 0.05$ ) (repeated-measures analysis of variance and paired  $t$ -test with Bonferroni's correction).

levels of measurements repeated four times at 7-day intervals ( $n = 8$ ).

#### Exercise

Maximum treadmill exercise duration was  $14.5 \pm 2.6$  min, representing  $16.5 \pm 2.4$  metabolic equivalents, with peak  $\dot{V}O_2$  ( $\dot{V}O_{2\max}$ ) of  $3.3 \pm 0.9$  l/min ( $43.0 \pm 10.4$  ml $\cdot$ kg $^{-1}\cdot$ min $^{-1}$ ),  $106\% \pm 27\%$  of the predicted for age and sex  $\dot{V}O_{2\max}$ , and respiratory exchange ratio ( $\dot{V}CO_2/\dot{V}O_2$ )  $> 1.1$  in all subjects, maximal heart rate  $191 \pm 9$  beats/min, peak systolic blood pressure  $209 \pm 20$  mmHg, and rate-pressure product  $39,900 \pm 4,700$  mmHg/min ( $n = 25$ ).

#### After Exercise

**Upper and lower limb PWV.** The upper and lower PWVs were measured in the resting supine position for 60 min after exercise at 1-min intervals, as during the preexercise resting state (Fig. 1). "Immediately" (3

min) after exercise, upper limb PWV was  $\sim 35\%$  higher than preexercise baseline, declining to  $\sim 6\%$  below baseline by 10 min and toward a near steady level  $\sim 10\%$  below baseline by 60 min. PWV in the lower limb showed a similar early decrease but from an initial postexercise level, which did not differ from its preexercise level, to a nadir  $\sim 23\%$  below baseline at 10 min, after which it increased to a near steady level, which as in the upper limb was  $\sim 10\%$  below baseline by 60 min.

**Blood pressure.** BP was measured continuously by digital plethysmography (Fig. 2*A*). Before exercise, BP was averaged over 10 min. After exercise, it was averaged over the initial 3- to 5-min period and over subsequent 5-min periods for 60 min. Systolic BP in the initial 3- to 5-min period was the same as preexercise, after which it remained steady at a significantly lower level (minus  $\sim 10\%$ ) than preexercise. Diastolic and mean BP remained steady throughout the 3- to 60-min period at a slightly but not significantly lower level than preexercise.

In 11 of the subjects, BP was measured in the brachial and popliteal arteries by sphygmomanometry, as

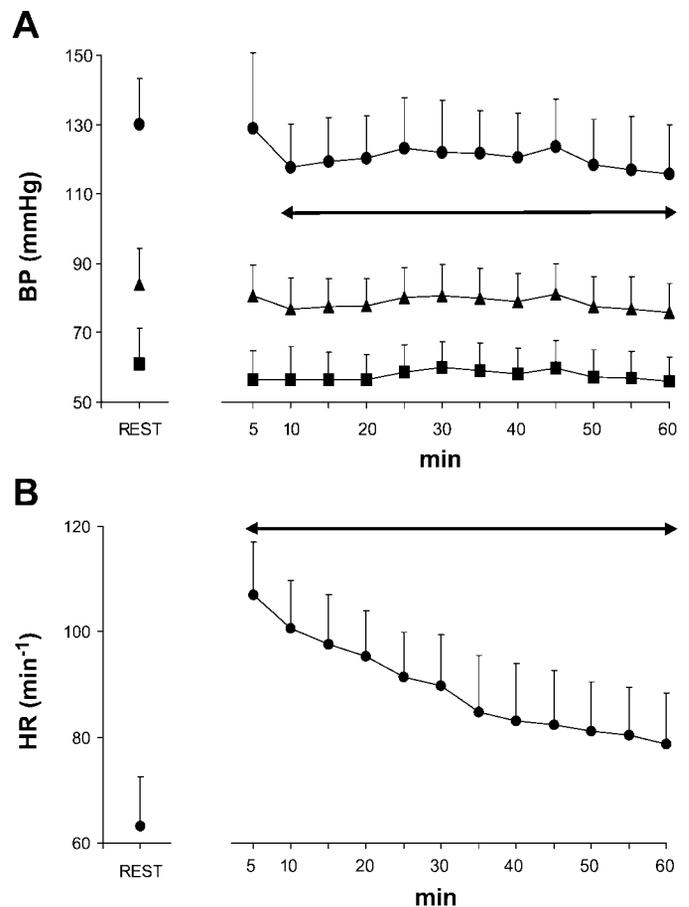


Fig. 2. Associated effects on blood pressure (BP; *A*) and heart rate (HR; *B*). Measurements by digital plethysmography (Finapres) averaged over the initial 3–5 min and over subsequent consecutive 5-min periods (the end of each period corresponding to its time marker). Round, triangular, and square symbols represent systolic, mean, and diastolic pressure (mmHg), respectively. Conventions as in Fig. 1. Values are means  $\pm$  SD;  $n = 25$ .

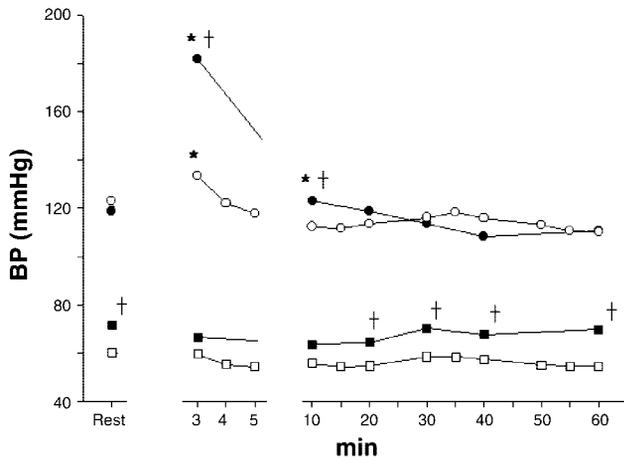


Fig. 3. BP measurements by brachial artery sphygmomanometry and by digital plethysmography compared. Subgroup of subjects are shown in Figs. 1 and 2 ( $n = 11$ ). Brachial artery (solid symbols), digital artery (open symbols), systolic (circles), and diastolic (squares) pressure are shown. Measurements were made at rest preexercise and after exercise. Digital measurements were made at 3, 4, and 5 min (each averaged over 5 beats) and thereafter averaged over 5-min periods identified in the figure by the final minute of each period. Note change of time scale. Brachial artery measurements were made at the times shown. \* $P < 0.05$  cf. preexercise, † $P < 0.05$  cf. digital reading (repeated-measures analysis of variance and paired  $t$ -test with Bonferroni's correction).

well as in the finger by digital plethysmography at the times shown, which in this study included separate digital readings at 3, 4, and 5 min (Fig. 3). Resting systolic BP was slightly but not significantly lower in the brachial than the finger artery ( $119 \pm 11$  cf.  $123 \pm 10$  mmHg), whereas diastolic BP was significantly (+17%) higher ( $72 \pm 10$  cf.  $60 \pm 11$  mmHg,  $P < 0.005$ ). At 3 and 10 min after exercise, systolic BP was significantly higher (+37% and +10%, respectively) in the brachial than the finger artery, after which the two measurements reverted to their preexercise relationship. Brachial artery pressure thus exceeded finger pressure only when systolic pressure was acutely elevated. Diastolic BP remained slightly higher in the brachial than the finger measurements. Brachial systolic BP was significantly higher than preexercise at 3 and 10 min after exercise [+53% at 3 min, when it was also slightly raised (+8%) at the finger]. Popliteal BP, measured by sphygmomanometry at 3, 10, 20, 40, and 60 min after exercise, showed similar but less marked changes relative to basal levels, 147/58 at 3 min cf. 123/69 mmHg preexercise, and 109 to 113/63 to 71 mmHg in the later postexercise readings; systolic pressure was thus 20% higher at 3 min than preexercise ( $P < 0.05$ ) and ~9% lower (not significant) on subsequent readings, whereas mean and diastolic pressures remained similar to preexercise levels.

Heart rate was initially 60% higher than preexercise and declined steadily thereafter to a rate still 25% above baseline by 60 min (Fig. 2B).

**Reproducibility of exercise data.** This was confirmed in five subjects in whom the protocol was repeated 10 days apart. PWV data are shown in Fig. 4. Exercise parameters did not differ between the two tests: peak

levels for heart rate were  $176 \pm 16$  and  $176 \pm 20$  beats/min, respectively; for systolic blood pressure were  $209 \pm 25$  and  $226 \pm 21$  mmHg, respectively; for rate-pressure product were  $36,200 \pm 2,900$  and  $38,300 \pm 3,200$  mmHg/min, respectively; and for  $\dot{V}O_2$  were  $2.7 \pm 0.7$  and  $2.5 \pm 0.6$  l/min, respectively.

Plasma viscosity increased by 12% from  $1.57 \pm 0.4$  cP before exercise to  $1.76 \pm 0.07$  cP immediately after exercise ( $n = 7$ ,  $P < 0.01$ ), returning to near baseline levels by 20 min, i.e.,  $1.62 \pm 0.05$  cP at 20 min and  $1.56 \pm 0.04$  cP at 60 min after exercise. Hematocrit increased by 14% from  $40.4 \pm 1.7\%$  before exercise to  $46.0 \pm 2.3\%$  immediately after exercise ( $n = 15$ ,  $P < 0.01$ ), returning to preexercise levels by 20 min, i.e.,  $41.3 \pm 2.0\%$  at 20 min and  $39.9 \pm 1.9\%$  at 60 min after exercise. From these data, blood viscosity may be estimated to have increased by ~12% immediately after exercise and to have returned to normal when then measured 20 min after exercise.

#### Modeling of Postexercise Changes in PWV

As a first approach to characterizing what are likely to reflect multiple contributory mechanisms, the dynamic patterns of PWV after treadmill exercise were described by a linear  $n$ -dimensional mathematical model (whose general solution could be oscillatory or exponential, an exponential solution being employed in the absence of any evidence of oscillatory pattern) (Fig. 5). The most general form would be  $d\bar{x}/dt = f(\bar{x})$ , where

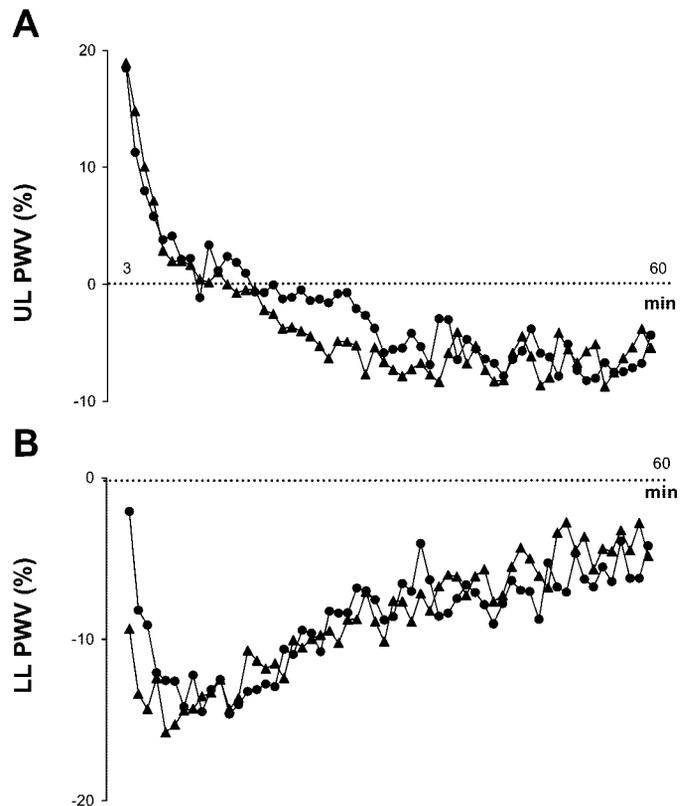


Fig. 4. Reproducibility of upper limb (A) and lower limb (B) PWV changes after maximum treadmill exercise repeated 10 days apart. Values are means;  $n = 5$ .

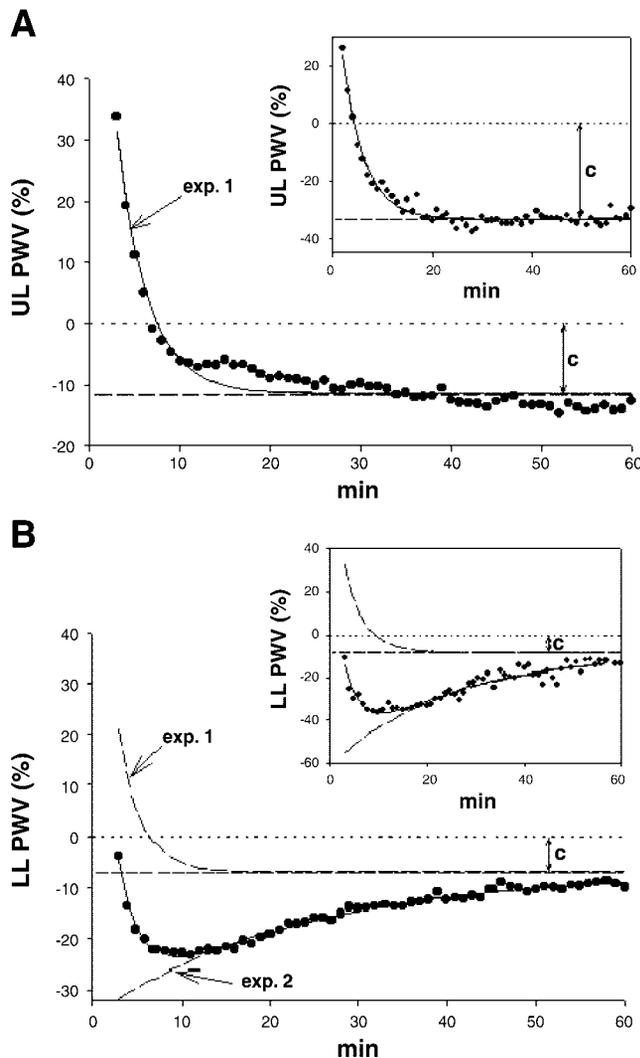


Fig. 5. Changes in PWV after maximum treadmill exercise modelled in terms of exponential functions. *A*: mean observed upper limb PWV data points (closed circles) as in Fig. 1 ( $n = 22$ ) and the least-squares error fit according to Eq. 2a (continuous line). The single exponential term (*exponential 1*) has been translated vertically by an offset  $c$ . *Inset* in *A* presents the findings in a representative individual. *B*: mean observed lower limb PWV data points, as above, and the least-squares error fit according to Eq. 2b (continuous line), i.e., algebraic sum of *exponential 1* and *exponential 2* (dashed lines), with intercepts  $b_1$  and  $b_2$  at zero time (the end of exercise) and decay slopes  $s_1$  and  $s_2$  and an offset  $c$  from the preexercise baseline.  $s_1$  and  $s_2$  are both positive, i.e., both exponentials are decaying.  $b_1$  is positive and  $b_2$  is negative, i.e., the two exponentials (*exponential 1* and *exponential 2*), vertically translated by the offset, start at positive and negative values, respectively, and decay to their shared asymptote at offset  $c$ . *Inset* in *B*: a representative individual (see also legend to Table 2; note that the excellence of the fit permitted data to be compared statistically using the means of the coefficients without taking account of the small variance).

$\bar{x}$  is a vector  $\{x_1, x_2, \dots, x_n\}$  of the  $n$  interdependent dominant control parameters, and  $f(\cdot)$  is the function that describes the rates of change of  $x_i$ . Because the dynamics of PWV appeared to be composed of exponentially decaying time series, a linear coupling was assumed as a first approximation and thus a model of the form:  $d\bar{x}/dt = F\bar{x} + g$ , where  $F$  is an  $n \times n$  matrix and

$g$  a vector of length  $n$ . The general solution of this equation would be of the form

$$X_i(t) = c_i + \sum_{k=1}^n b_{ik} e^{-s_k t} \quad (1)$$

where  $c_i$  and  $b_{ik}$  are constants and  $-s_k$  values ( $k = 1$  to  $n$ ) are the eigenvalues of the system. For real  $s_k > 0$ ,  $x(t)$  is a linear combination of exponentially decaying terms, in which  $s_k$  specifies the rate of decay in time, and  $c$  represents a constant offset from the zero reference point of the basal preexercise PWV. The minimal order  $n$  was sought for values of  $n$  up to  $n = 3$  exponentials for both the upper and the lower limb. In each case, the coefficients  $c$ ,  $b_k$ , and  $s_k$  were identified through least-squares error fitting of Eq. 1 to the experimentally derived PWV traces to determine the minimum number ( $n$ ) of exponentials that would adequately describe the pattern of changes in PWV, both in the upper and in the lower limb.

It was observed that a first-order solution (i.e.,  $n = 1$ ) of the form

$$x(t) = c + b_1 \cdot e^{-s_1 t} \quad (2a)$$

successfully matched PWV in the upper limb ( $r = 0.97$  for modeling of mean data, 0.90 for mean of individually modeled data) (Fig. 5). When higher orders of  $n$  were used, the additional eigenvalues  $s_k$  ( $k = 2$  to  $n$ ) approached zero so that the corresponding term  $b_k \cdot e^{-s_k t}$  approximates to  $b_k$ , which is a clear indication of redundancy because it means that the term can be absorbed in the constant  $c$ . In contrast, in the lower limb a second-order expression (i.e.,  $n = 2$ )

$$x(t) = c + b_1 \cdot e^{-s_1 t} + b_2 \cdot e^{-s_2 t} \quad (2b)$$

was the minimum required adequately to approximate the PWV data-time series ( $r = 0.98$  and 0.90, for modeling of mean data and mean of individually modeled data, respectively), and higher orders of solution were likewise shown to be redundant. The model for the pattern of changes in PWV following exercise thus comprises just two exponential functions acting in opposite directions and together representing recovery from the consequences of the exercise: *exponential 1*, which describes a decrease in PWV (and is manifest in both the nonexercising and the exercising limbs) and *exponential 2* (shown to be negligible in the upper limb), which describes an increase in PWV. Table 2 shows the mean and SD values of the relevant coefficients derived from fitting Eqs. 2a and 2b to the individual subject PWV data-time series ( $n = 22$ ), as described above and in the legend to Table 2. When the PWV data-time series in the upper limb was fitted to a second-order equation of the form (Eq. 2b), the eigenvalue  $s_2$  was shown to be  $0.0012 \pm 0.0023$ , which confirms that the second exponential term can be approximated by a constant and is thus redundant. In the lower limb, however, *exponential 2* was prominent, adding algebraically to *exponential 1* by increasing PWV. The parametric values describing *exponential 1* were very closely matched in the upper and lower

Table 2. Coefficients of exponentials 1 and 2 describing time course of changes in upper and lower limb PWV following exercise

Coefficients	Upper Limb	Lower Limb
Offset		
$c$	-13.4(10.1)	-9.6(10.5)
<i>Exponential 1</i>		
$b_1$	127.5(78.9)	153.4(77.5)
$s_1$	0.33(0.15)	0.31(0.20)
<i>Exponential 2</i>		
$b_2$		-93.2(77.5)
$s_2$	[0.0012(0.0023)]†	0.08(0.04)*

These coefficients are derived from data shown in Fig. 1, normalized as percentage of basal levels, modeled by least-squares fit as described in RESULTS (means  $\pm$  SD,  $n = 22$ ). *Exponential 1* and *exponential 2* are characterized by their intercepts ( $b_1$  and  $b_2$ ) at zero time (i.e., end of exercise and start of the postexercise period), by their decay rate ( $s_1$  and  $s_2$ ), and by their asymptotic offset ( $c$ ) from the reference zero of basal preexercise PWV. In the upper limb, a single exponential (*Exp 1*) suffices, whereas in the lower limb, two exponentials (*Exp 1* and *Exp 2*) are needed to match the data (higher order solutions than 1 and 2 in the upper and lower limbs, respectively, were shown to be redundant, see text).  $s_1$  and  $s_2$  ( $\text{min}^{-1}$ ) are both positive values, indicating that both exponentials are decaying. *Exponential 1* monotonically decreases from its positive starting intercept ( $b_1 > 0$ ) and *exponential 2* monotonically increases from its negative starting intercept ( $b_2 < 0$ ). The constants ( $c$ ,  $b_1$ , and  $s_1$ ) describing *exponential 1* are very similar in the upper and the lower limbs, implying a similar underlying mechanism.  $c$  represents the asymptote of *exponential 1* in the upper limb and of the composite sum of *exponentials 1* and *2* in the lower limb. Offset ( $c$ ) from the preexercise baseline is similar in the upper and lower limbs, implying the existence of a third, common mechanism that dissipates much more slowly and whose characterization lies outside the time frame of a 60-min study. \* $P < 0.00005$  cf.  $s_1$ , † $P < 0.0000005$  cf.  $s_2$  for the LL, paired  $t$ -test, comparing the means of the coefficients derived from the fitted curve data (see legend to Fig 5).

limbs. Comparing *exponential 1* (as derived from either the upper or the lower limb) with *exponential 2* (in the lower limb),  $s_2$  was significantly less than  $s_1$ , suggesting that the biological mechanisms underlying the secondary increase in PWV (*exponential 2*) respond more slowly and over a longer time scale than the mechanisms underlying *exponential 1*. As illustrated in Fig. 5, the minimal models achieve a good fit to the PWV data-time series in both upper and lower limbs, both for mean data and for individual examples.

## DISCUSSION

In this study conducted in healthy young subjects, the acute effects of exercise on large artery distensibility were investigated by their influence on PWV, which is inversely related to distensibility. PWV was measured simultaneously in both the upper and the lower limb to distinguish systemic effects from directly exercise-related effects in the exercising limbs. Acute changes in PWV in these arteries may be considered generally representative of large artery responses throughout the vascular system, although quantitative differences in resting PWV between different large arteries have been reported (19).

## PWV as Measure of Acute Changes in Vascular Tone

PWV was measured with oscillometry by using a newly developed computerized technique to identify the pulse in time. Pulse transit times were measured between well-defined sites. PWV measured with this method in normal subjects has been shown to be sensitive to acute changes of vascular tone, independently of any associated change in blood pressure. PWV in the upper limb, for example, is decreased or increased  $\sim 10\%$  by local intra-arterial acetylcholine or  $N^G$ -methyl-L-arginine as echocardiographically measured arterial diameter is increased or decreased, respectively, whereas lower limb PWV, heart rate, and blood pressure are unchanged (21, 29, 34, and unpublished observations).

## Resting PWV

Resting PWV values were similar to those reported by others using different methods and different arteries (2, 3, 6, 19, 33). They were  $\sim 10\%$  faster in the lower than the upper limb.

## After Exercise

*PWV.* In the upper but not the lower limb, the “immediate” (3 min) postexercise PWV was higher than its preexercise basal level. PWV initially then decreased in both upper and lower limbs, PWV in the lower (exercising) limb exhibiting a biphasic response because it later increased to reach a level at 60 min, which was similar to that reached in the upper limb,  $\sim 10\%$  below basal level. These data provide evidence of the previously unreported pattern of changes in PWV immediately after maximum exercise. The difference between the patterns of recovery in the upper and lower limbs supports the possibility of discriminating between local and systemic consequences of exercise.

*Blood pressure.* From 5 to 60 min after exercise, blood pressure measured continuously by digital plethysmography (averaged over consecutive 5-min periods) remained steady, systolic pressure remaining significantly lower than preexercise after the first 5 min with diastolic and mean blood pressures remaining slightly but not significantly lower than preexercise. Brachial systolic pressure immediately after exercise, however, was considerably ( $\sim 50\%$ ) higher than preexercise. The previously reported tendency for digital plethysmography to give slightly higher systolic but slightly lower diastolic readings than brachial sphygmomanometry (17) was confirmed in the preexercise resting levels. In the earliest postexercise readings, however, systolic pressure was lower in the digital than the brachial measurements, coincident with high PWV as evidence of reduced large artery distensibility. The initially high brachial systolic pressure then declined rapidly to remain similar to the digital measurements from 5 to 60 min after exercise, during which time systolic, mean, and diastolic pressures remained constant.

*Heart rate.* Heart rate declined steadily toward, without reaching, preexercise levels by 60 min.

**Blood viscosity.** Blood viscosity was increased immediately after exercise but had returned to normal when next sampled 20 min after exercise.

These findings are consistent with and extend those of previous reports relating to postexercise changes. Most previous studies have not examined the very early changes. Supine systolic pressure has however similarly been reported to be transiently raised in the first few minutes after a maximal upright exercise protocol (31). It is also established that postexercise, predominantly systolic, hypotension may persist for many hours after exercise (12, 18, 19), attributable to decreased peripheral vascular resistance with increased cardiac output achieved by increased heart rate (12, 19, 31). Lower limb and aortofemoral PWV have, as in the present study, been reported to be reduced 30 min after submaximal exercise, returning to preexercise levels by 60 min (19).

#### *Potential Influence of Changes in Blood Pressure, Heart Rate, and Blood Viscosity on PWV*

PWV is inversely related to distensibility, being inversely proportional to the product of the square root of distensibility and blood viscosity (30). Distensibility of the arterial wall is related to its radius and is a nonlinear function of both structural elastic components in the artery wall and vascular tone as modulated by endothelial and other neurohumoral influences. An increase of intravascular diameter will stretch structural components along their steepening nonlinear compliance curve, thereby decreasing distensibility (and increasing PWV) to an extent that will depend on the arc traversed during pulsation of which mean pressure has been regarded an acceptable measure (19). Vasodilatation may thus both potentially decrease distensibility by increasing intravascular diameter and directly increase distensibility by reducing the contribution of vascular muscle tone to arterial stiffness. The demonstrable effects of vasoactive drugs on PWV (29) show that the direct effects of changes in vascular tone override any passive consequence of stretch over the range of dilatation induced.

#### *Do the Observed Postexercise Changes in PWV Reflect Changes in Vascular Tone or Might They be Attributable to Changes in Heart Rate, Blood Viscosity, and/or Blood Pressure?*

Heart rate can probably be discounted as influencing PWV. Despite earlier *in vivo* pacing experiments suggesting an effect on PWV (24, 26), other studies showed no relationship (1), and no effect of heart rate was observed under controlled conditions *in vitro* (8). The time course of the steadily slowing heart rate clearly did not correspond to the more complex pattern of changes in PWV observed in this study. Blood viscosity can also be excluded as responsible for the changes in PWV. An increase of viscosity will decrease PWV, both directly and by increasing endothelial shear stress, NO release, and consequent vasodilatation, but viscosity was declining as PWV declined in the present study. A

contribution of changing blood pressure is more difficult to exclude.

The initial postexercise brachial artery pressure measurements show that systolic pressure was indeed high, coincident with a high PWV in the upper limb (although not in the just-exercised lower limb). The pressure measurements during the first few minutes thereafter were too infrequent to relate the time courses of declining PWV and pressure to each other usefully. The coincident disparity between digital and brachial systolic pressure indicates the presence of an initially high but similarly rapidly declining degree of vasoconstriction during these first few minutes. Between 10 and 60 min after exercise, blood pressure remained constant (and similar whether measured at the finger or the brachial artery) while PWV was continuing to change (see *Modeling of Postexercise Changes in PWV*). Changing pressure cannot thus be wholly responsible for the observed changes in PWV. The changes in PWV do however match what is known of the associated changes in vascular tone, which have been shown to influence PWV (as here measured) independently of any change in blood pressure. PWV thus appears to reflect the changes in vascular tone, which occur during recovery from exercise, without needing to postulate (but without necessarily excluding) a direct contribution also of pressure-related passive stretch.

#### *Method of Measuring PWV*

The measurement of pulse transit time depends critically on accurately timed identification of its potentially changing waveform. PWV has conventionally been measured by the timing of the foot of the wave (3), although this is inherently imprecise, and various techniques have been evolved to improve precision, such as identifying the point at which the sharp upstroke starts (3), taking the intercept of tangents between diastole and the systolic upstroke, or its first or its second derivative (19, 25). In the present study, the wave was characterized and timed by averaging three points along the first 50% of its rising phase during which its upstroke should be relatively uncontaminated by changes in waveform due to propagation and reflected waves (27). Its averaged sampling at three points is also likely to bring advantage over techniques relying on a single point. It was measured in relatively large upper and lower limb arteries, avoiding complexities inherent in the incorporation of small arteries and assumptions inherent in measuring carotid to femoral pulse transit times. The present study moreover is based primarily on the evidence of relative changes as measured over the same defined sections of these large arteries. The method provides an objective, sensitive but robust, and demonstrably reproducible measure of acute changes in pulsatile distensibility of limb conduit arteries, representative of large artery behavior as influenced by changes in vascular tone. It can thus also be used, for example, to assess changes in endothelial function as manifest through flow-related dilatation.

### Modeling of Postexercise Changes in PWV

Empirical modeling of the pattern of postexercise changes in PWV showed that it can be adequately described in the upper limb by a first-order system (i.e., a single independent dynamic variable), whereas a second-order system (i.e., two interdependent dominant variables) is needed adequately to describe it in the exercising lower limb (Fig. 5, Table 2). To a first approximation, these variables are represented by two exponentials (*exponential 1* and *exponential 2*) acting in opposite directions and characterized by their intercepts at time 0 ( $b_1$  and  $b_2$ , respectively), their rates of decline ( $s_1$  and  $s_2$ , respectively), and the offset  $c$  from the zero reference values of the preexercise basal PWV corresponding to an asymptote. The similarity of the values obtained for coefficient  $b_1$  and for exponent  $s_1$  in the upper and the lower limbs suggests that *exponential 1* has a similar origin in both limbs, consistent with recovery from a net systemic constrictor response to exercise operative in both limbs. *Exponential 2*, manifest only in the exercising lower limb, is consistent with recovery from the local dilator effects of exercise. The offset  $c$  is consistent in both cases with prolonged postexercise peripheral vasodilatation as previously reported (31). This offset and its later presumptive return to the preexercise baseline may be considered as reflecting a much slower third function whose characterization is outside the 60-min time frame of the present study.

The identified exponential functions reflect the consequence of multiple interactive mechanisms. These will be susceptible to alteration in disease and by pharmacological intervention. The present study provides no evidence about such alterations nor can it clarify whether the adequacy of the exponential fits reflects simply the algebraic sum of the component mechanisms or the integrative consequences of the phenomenon of entrainment. Some contribution of entrainment is suggested by the surprisingly low dimension (one- and two-dominant variables) of the dynamics required adequately to reproduce the pattern of recovery despite the multiplicity of potential mechanisms involved. Entrainment of a spatially extended array of diverse biological subsystems and in particular the synchronization of cellular activity to external or internal physiological stimuli are well documented in the literature (for review, see Ref. 15). Such studies have established that the inherently nonlinear nature of cellular oscillatory mechanisms allows the emergence of regular rhythmic activity, which may account for the low complexity of resulting dynamic patterns that is observed (32, 35).

### Pathophysiological Consequences

Whatever the mechanisms underlying these previously unreported changes in PWV immediately following exercise, the changes observed are physiologically relevant to cardiac loading and could be deleterious in disease states. The present study may provide a reference point against which to compare the effect of dis-

ease states and the basis for experimental dissection of the component mechanisms.

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