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Determination of age-related increases in large artery stiffness by digital pulse contour analysis

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ABSTRACT

The stiffness of the aorta can be determined by measuring carotid–femoral pulse wave velocity (PWV_{cf}). PWV may also influence the contour of the peripheral pulse, suggesting that contour analysis might be used to assess large artery stiffness. An index of large artery stiffness (SI_{DVP}) derived from the digital volume pulse (DVP) measured by transmission of IR light (photoplethysmography) was examined. SI_{DVP} was obtained from subject height and from the time delay between direct and reflected waves in the DVP. The timing of these components of the DVP is determined by PWV in the aorta and large arteries. SI_{DVP} was, therefore, expected to provide a measure of stiffness similar to PWV. SI_{DVP} was compared with PWV_{cf} obtained by applanation tonometry in 87 asymptomatic subjects (21–68 years; 29 women). The reproducibility of SI_{DVP} and PWV_{cf} and the response of SI_{DVP} to glyceryl trinitrate were assessed in subsets of subjects. The mean within-subject coefficient of variation of SI_{DVP}, for measurements at weekly intervals, was 9.6%. SI_{DVP} was correlated with PWV_{cf} ($r = 0.65$, $P < 0.0001$). SI_{DVP} and PWV_{cf} were each independently correlated with age and mean arterial blood pressure (MAP) with similar regression coefficients: $SI_{DVP} = 0.63 + 0.086 \times age + 0.042 \times MAP$ ($r = 0.69$, $P < 0.0001$); $PWV_{cf} = 0.76 + 0.080 \times age + 0.053 \times MAP$ ($r = 0.71$, $P < 0.0001$). Administration of glyceryl trinitrate (3, 30 and 300 μg/min intravenous; each dose for 15 min) in nine healthy men produced similar changes in SI_{DVP} and PWV_{cf}. Thus contour analysis of the DVP provides a simple, reproducible, non-invasive measure of large artery stiffness.

INTRODUCTION

Aging is accompanied by increased stiffness of large elastic arteries, leading to an increase in pulse wave velocity (PWV) [1–3]. Premature arterial aging, as determined by an elevated aortic PWV, is now recognized as a major risk factor for ischaemic heart disease [4–8]. An influence of vascular aging on the contour of the peripheral pressure and volume pulse in the upper limb is also well recognized [9]. This change in pulse contour may be due in part to increased large artery stiffness, with an increase in PWV decreasing the time taken for pressure waves reflected from the periphery of the circulation (mainly from the lower body) to return to the aorta and thence to the upper limb. Consequently, reflected waves arrive earlier in the cardiac cycle [10]. This raises the possibility that large artery stiffness may be assessed from the peripheral pulse. The digital volume pulse (DVP) may be obtained rapidly and simply by measuring the transmission of IR light through the finger pulp (photoplethysmography), making this a potentially attractive waveform to analyse.

We have demonstrated previously that the contour of the DVP contains similar information to that of the peripheral pressure pulse [11]. The contour of the DVP is determined mainly by characteristics of the systemic circulation, including pressure wave reflection and PWV of pressure waves in the aorta and large arteries [12]. In

Key words: arterial compliance, photoplethysmography, pulse wave velocity.

Abbreviations: DVP, digital volume pulse; GTN, glyceryl trinitrate; MAP, mean arterial pressure; PWV, pulse wave velocity; PWV_{cf}, carotid–femoral pulse wave velocity; SI_{DVP}, stiffness index derived from the digital volume pulse; ΔT_{DVP}, time between the systolic peak and the diastolic peak or the point of inflection.

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the present study we have examined the timing of discrete components of the DVP to formulate an index of the contour of the DVP expected to relate to large artery stiffness (SI_{DVP}). We have examined the relationship of SI_{DVP} to age in asymptomatic subjects on no drug treatment, and compared SI_{DVP} with values of PWV measured over the carotid-to-femoral region (PWV_{cf}). To examine the sensitivity or lack thereof of SI_{DVP} to changes in tone of small arteries, we used glyceryl trinitrate (GTN), which markedly influences the contour of the DVP [13], but has little effect on large artery PWV [14].

METHODS

Formulation of SI_{DVP}

The contour of the DVP is formed as a result of a complex interaction between the left ventricle and the systemic circulation. It usually exhibits an early systolic peak and a later peak or point of inflection that occurs a short time (ΔT_{DVP}) after the first peak in early diastole (Figure 1). The first peak is formed mainly by pressure transmitted along a direct path from the left ventricle to the finger (where it generates a change in blood volume). The second peak is formed in part by pressure transmitted along the aorta and large arteries to sites of impedance mismatch in the lower body, where it is reflected back up the aorta. ΔT_{DVP} can thus be used to infer the transit time taken for pressure to propagate along the aorta and large arteries to the major sites of reflection in the lower body and back to the root of the subclavian artery [12]. This path length is unknown, but can be assumed to be proportional to subject height (h). Since PWV over a given path equals path length/transit time, SI_{DVP} was formulated as $h/\Delta T_{DVP}$. Because of the complexities of the formation of the DVP, SI_{DVP} cannot be considered as a direct measure of large artery PWV. It should rather be considered simply as an index characterizing features of the contour of the DVP that are determined mainly by PWV in the aorta and large arteries, and hence by the stiffness of these arteries.

Acquisition of the DVP and signal processing

A photoplethysmograph (Micro Medical, Gillingham, Kent, U.K.) transmitting IR light at 940 nm, placed on

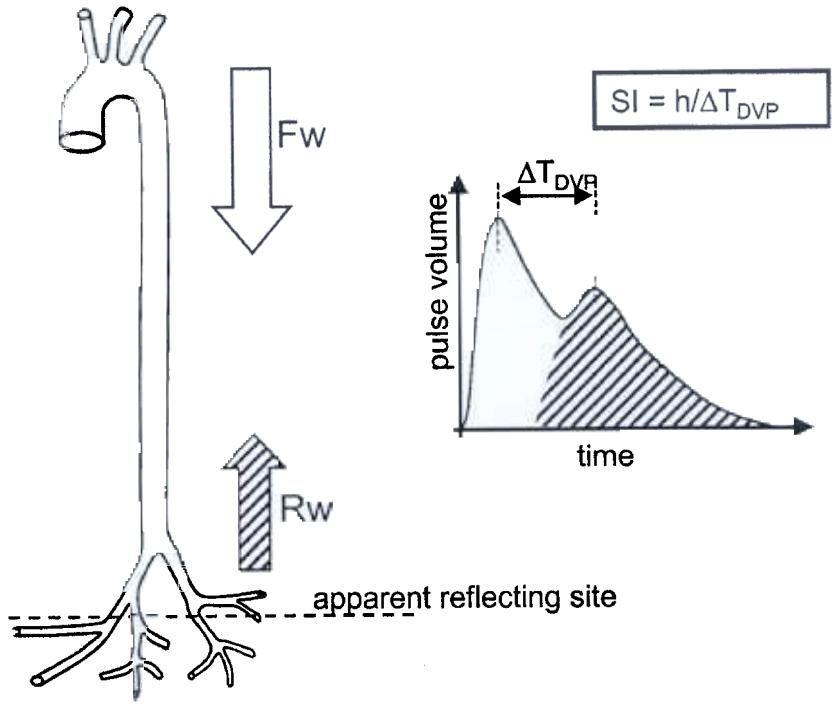

Figure 1 DVP recorded by measuring the transmission of IR light through the finger pulp

The systolic component of the waveform (open arrow/area) arises mainly from a forward-going pressure wave (Fw) transmitted along a direct path from the left ventricle to the finger. The diastolic component (hatched arrow/area) arises mainly from pressure waves transmitted along the aorta to small arteries in the lower body, from where they are then reflected back along the aorta as a reflected wave (Rw) which then travels to the finger. The upper limb provides a common conduit for both the directly transmitted pressure wave and the reflected wave and, therefore, has little influence on their relative timing. The time delay (ΔT_{DVP}) between the systolic and diastolic peaks (or, in the absence of a second peak, the point of inflection) is related to the transit time of pressure waves from the root of the subclavian artery to the apparent site of reflection and back to the subclavian artery. This path length can be assumed to be proportional to subject height (h), and an index of large artery stiffness (SI_{DVP}) can be formulated as: $SI_{DVP} = h/\Delta T_{DVP}$.

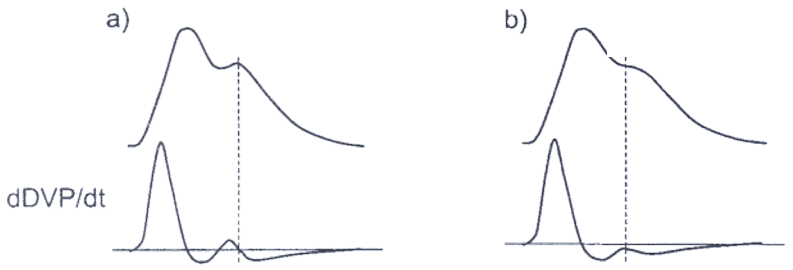

Figure 2 DVP and its first derivative (dDVP/dt) for waveforms exhibiting (a) a diastolic peak and (b) a point of inflection

The diastolic peak/inflection point is defined as the point at which dDVP/dt is closest to zero. The diastolic peak occurs when dDVP/dt is zero, whereas an inflection point occurs when dDVP/dt approaches zero.

the index finger of the right hand was used to obtain the DVP. The signal from the plethysmograph (Figure 2) was digitized using a 12-bit analogue-to-digital converter with a sampling frequency of 100 Hz. Software developed in-house was used to provide an objective measurement of SI_{DVP}. DVP waveforms were recorded over a 10 s period and ensemble-averaged to obtain a single waveform from which ΔT_{DVP} was determined as the time between the first systolic peak and the early diastolic peak/inflection point in the waveform. This point was defined as the point at which the first derivative of the waveform is closest to zero (Figures 1 and 2). SI_{DVP} was calculated from subject height and ΔT_{DVP}:

$$SI_{DVP} = h/\Delta T_{DVP}$$

Determination of PWV_{cf}

PWV_{cf} was determined by measuring the carotid-to-femoral transit time. Carotid and femoral pressure waveforms were obtained non-invasively by applanation tonometry using a Millar tonometer (Millar Instruments) and Sphygmocor analysis software (Atcor). Waveforms (obtained consecutively from the carotid and femoral arteries) were referenced to a concurrently recorded ECG, and transit time (Δt_{cf}) was computed from the foot-to-foot time difference between the carotid and femoral waveforms. The distance between the surface markings of the sternal notch and the femoral artery was used to estimate the difference in path length between the carotid and femoral arteries (l_{cf}), and PWV_{cf} was calculated from l_{cf} and Δt_{cf}:

$$'\Delta t$$

Relationships of SI_{DVP} and PWV_{cf} with age and blood pressure

The reproducibility of SI_{DVP} and PWV_{cf} was assessed in eight healthy men (aged 22–51 years) by obtaining three measurements separated by 1-week intervals but otherwise obtained under identical conditions. SI_{DVP} and PWV_{cf} were determined in 87 asymptomatic subjects (29 women; mean age 47 years, range 21–68 years) recruited from the local community of South East London in response to advertisement for cardiovascular screening. No subject had a previous history of cardiovascular disease or was receiving vasoactive drugs. All subjects were screened by physical examination and routine biochemistry. Subject characteristics are given in Table 1. Following at least 15 min of semi-supine rest, three consecutive measurements of SI_{DVP} and PWV_{cf} were made. Blood pressure was taken as the mean of three measurements obtained by mercury sphygmomanometry after each measurement of SI_{DVP} and PWV_{cf}.

Table 1 Subject characteristics

HDL, high-density lipoprotein.

Characteristic	Mean	S.D.	Range
Age (years)	47	13.8	21–68
Female/male	29/58		
Smokers/non-smokers	15/72		
Body mass index (kg/m^2)	25	3.6	18–36
Diastolic blood pressure (mmHg)	74	9	51–92
Systolic blood pressure (mmHg)	125	15	91–178
Total cholesterol (mmol/l)	5.1		3.1–7.6
Triacylglycerols (mmol/l)	1.6	1.0	0.5–4.7
HDL-cholesterol (mmol/l)	1.5	0.4	0.8–2.5

Effects of vasoactive drugs on SI_{DVP} and PWV_{cf}

The contour of the DVP is markedly influenced by tone in muscular arteries [12]. If SI_{DVP} is to provide a useful measure of stiffness in large elastic arteries, it is therefore important to establish whether it is sensitive to changes in smooth muscle tone in small arteries, independent of changes in large artery PWV. The effects of the vasodilator GTN were therefore examined in nine healthy normotensive men aged 23–45 years. Subjects attended on 2 days according to a single-blind randomized, two-

phase, placebo-controlled crossover study design. Following 30 min of supine rest, subjects received an intravenous infusion of saline for 15 min and then, on separate days, intravenous infusions of GTN (3, 30 and 300 μg/min; David Bull Laboratories; each dose for 15 min) and 0.9% saline vehicle. PWV_{cf} and SI_{DVP} were determined at 5 min intervals during the baseline period and at the end of each 15 min infusion of drug/placebo.

Ethics

All protocols were approved by St. Thomas' Hospital Research Ethics Committee, and all subjects gave informed consent.

Statistics

Subject characteristics are presented as means ± S.D. Reproducibility was expressed as the mean within-subject S.D. and within-subject coefficient of variation [15]. Results are presented as means ± S.E.M. Associations between SI_{DVP} and age, systolic blood pressure, diastolic blood pressure, mean arterial pressure (MAP; calculated as diastolic pressure plus one-third of pulse pressure), pulse pressure and total serum cholesterol, and between PWV_{cf} and these variables, were examined using univariate and multiple regression analysis. Because of co-linearity and because systolic blood pressure and pulse pressure are influenced by arterial stiffness, the only blood pressure measurement used in multiple regression analysis was MAP. The effects of drugs on haemodynamic measurements were examined using ANOVA for repeated measures.

RESULTS

Reproducibility

The mean value of SI_{DVP} in all subjects (8.4 m/s; $n = 87$) was of similar magnitude to that of PWV_{cf} (9.3 m/s). The mean within-subject S.D.s of SI_{DVP} and PWV_{cf} in the subset of subjects who participated in the reproducibility study ($n = 8$) were 0.062 m/s and 0.068 m/s respectively. Within-subject coefficients of variation were 9.6% and 8.8% for SI_{DVP} and PWV_{cf} respectively (not significant).

Relationships of SI_{DVP} and PWV_{cf} with age and blood pressure

Typical DVP traces in subjects of differing ages are shown in Figure 3. SI_{DVP} was correlated with PWV_{cf} ($r = 0.65$, $P < 0.0001$; Figure 4). A slightly higher correlation was obtained for the relationship between ΔT_{DVP} and aorto–femoral transit time ($r = 0.70$, $P < 0.0001$). By univariate analysis, SI_{DVP} was correlated significantly with age ($r = 0.67$, $P < 0.0001$), systolic blood pressure ($r = 0.32$, $P < 0.01$), diastolic blood pressure ($r = 0.48$, $P < 0.0001$), MAP ($r = 0.45$, $P < 0.0001$) and total cholesterol ($r = 0.41$, $P < 0.01$), but not with pulse pressure. PWV_{cf} was correlated significantly with age ($r = 0.67$, $P < 0.001$), systolic blood pressure ($r = 0.47$, $P < 0.0001$), diastolic blood pressure ($r = 0.44$, $P < 0.0001$) and MAP ($r = 0.50$, $P < 0.0001$), and weakly with pulse pressure ($r = 0.25$, $P < 0.05$), but not with total cholesterol. Multiple regression analysis demonstrated SI_{DVP} and PWV_{cf} to be independently correlated with age and MAP (Figure 5) ($r = 0.69$ and $r = 0.71$ for SI_{DVP} and PWV_{cf} respectively; each $P < 0.001$ for age and $P < 0.5$ for MAP). Regression coefficients relating SI_{DVP} and PWV_{cf} to age (0.86 and 0.80 m · s^{-1} · $year^{-1}$ for SI_{DVP} and PWV_{cf} respectively) and to MAP (0.042 and 0.053 m · s^{-1} · $mmHg^{-1}$ for SI_{DVP} and PWV_{cf} respectively) were similar.

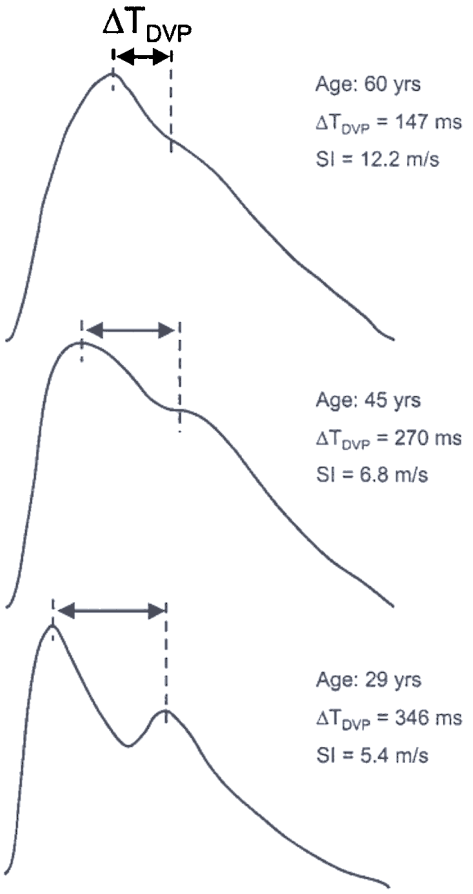

Figure 3 Typical DVP waveforms recorded in normotensive men, showing that the characteristics change with age

The time delay between the systolic and diastolic peaks or, in the absence of a second peak, the point of inflection (ΔT_{DVP}) decreases with age as a consequence of increased large artery stiffness and increased PWV of pressure waves in the aorta and large arteries. SI_{DVP} ($= h/\Delta T_{DVP}$) increases with age.

Effects of GTN on SI_{DVP} and PWV_{cf}

During the intravenous infusion of saline vehicle there were no significant changes in heart rate, blood pressure, SI_{DVP} or PWV_{cf}. GTN decreased blood pressure from

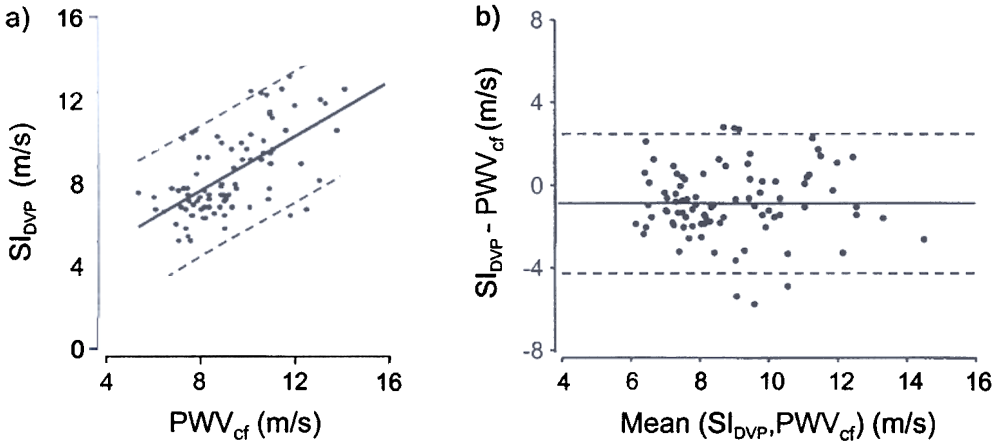

Figure 4 **Relationship between SI_{DVP} and PWV_{cf}**

(a) Scatter plot ($r = 0.65$, $P < 0.0001$); (b) Bland–Altman plot. Broken lines represent 2S.D.s from the regression line or from the mean difference between the measurements.

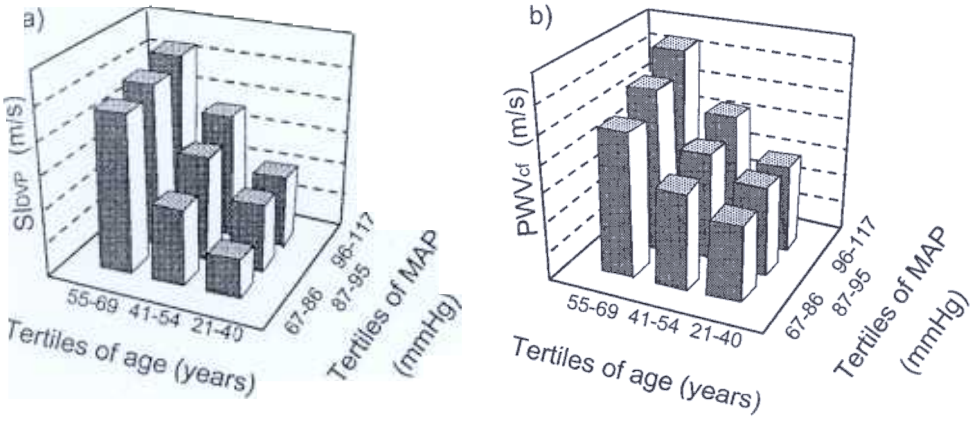

Figure 5 **Relationships of (a) SI_{DVP} and (b) PWV_{cf} with age and MAP**

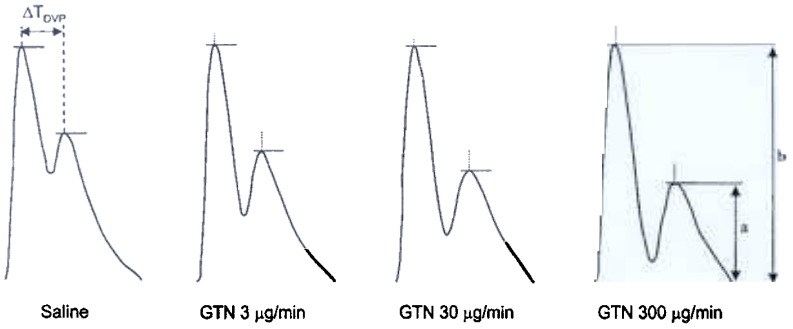

Figure 6 **Effects of intravenous infusions of GTN on DVP in a healthy subject**

The major change is in the height of the diastolic component of the waveform (assessed by the reflection index; RI = a/b) rather than in ΔT_{DVP} or SI_{DVP}.

$125 \pm 5/62 \pm 2$ to $109 \pm 4/48 \pm 1$ mmHg ($P < 0.001$). GTN produced profound changes in the height of the diastolic peak of the DVP relative to the systolic peak (Figure 6), reducing the diastolic peak/systolic peak reflection index from $64 \pm 3\%$ to $29 \pm 6\%$ ($P < 0.0001$). The effects on SI_{DVP} were relatively modest, and of

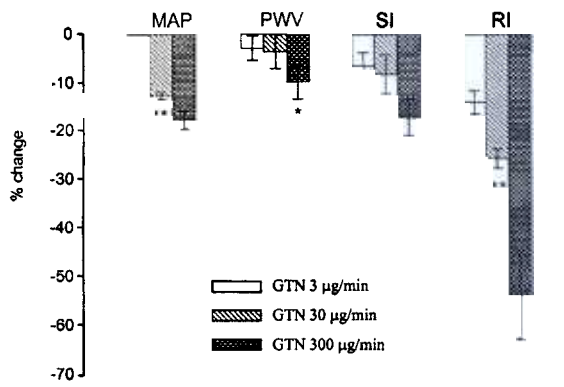

Figure 7 Changes from baseline following GTN in MAP, SI_{DVP}, PWV_{cf} and reflection index (RI)

The reflection index was computed as the height of the diastolic peak of the DVP relative to that of the systolic peak in healthy subjects ($n = 9$). Significance of differences: $^{*}P < 0.05$, $^{**}P < 0.01$ compared with baseline.

comparable magnitude to those on PWV_{cf} (Figure 7). At the highest dose, GTN decreased SI_{DVP} by 1.2 m/s (from 6.5 ± 0.19 m/s at baseline to 5.3 ± 0.27 m/s; $P < 0.001$), and PWV_{cf} by 0.9 m/s (from 8.1 to 7.2 m/s; $P < 0.05$).

DISCUSSION

A number of indirect and direct measures of large artery stiffness have been proposed. PWV is inversely related to arterial distensibility by the Bramwell–Hill equation [1]. Its determination over the carotid–femoral region is the most direct measurement of large artery stiffness that has been applied in large numbers of subjects. Laurent et al. [8] have shown it to be a powerful independent predictor of all-cause and cardiovascular mortality. Of the indirect measures, pulse pressure has been widely used. The observation that pulse pressure is strongly associated with cardiovascular events [16–20] has been attributed to the relationship between pulse pressure and aortic stiffness. Pulse pressure is determined mainly by large artery stiffness and cardiac output, although it is also influenced by peripheral resistance [21]. The relationship between pulse pressure and PWV is, however, relatively weak (in the present study a correlation coefficient of only $r = 0.25$ was observed). Various types of pulse wave analysis have been used to provide indirect estimates of large artery stiffness. Systemic arterial compliance can be derived from the contour of the carotid pressure pulse waveform and simultaneous measurements of cardiac output [22,23], but is influenced by peripheral as well as aortic compliance. The calculation also makes assumptions regarding the formation of the central pulse waveform [24]. Assumptions regarding the validity of Windkessel models of the arterial tree and problems in the estimation of cardiac output also underlie other 'diastolic decay' methods for estimating arterial compliance from the peripheral pressure waveform [24]. The aortic augmentation index, derived from the carotid pressure pulse or from the radial pressure pulse with the use of a radial-to-central pulse transfer function, has been proposed as a measure of arterial stiffness. However, although the aortic augmentation index exhibits a reasonable correlation with PWV_{cf} under basal conditions, vasoactive drugs cause it to change markedly and independently of PWV_{cf} [14]. Analysis of the second derivative of the DVP ('acceleration plethysmography') has been used by Takazawa and colleagues [25] to derive indices of age-related changes and of vascular tone, but the physical interpretation of these indices remains obscure. Furthermore, the degree to which these indices are inter-related and the extent to which they depend upon arterial tone, arterial stiffness, other factors or the interaction between them is unknown.

The present study describes an index, SI_{DVP}, of the contour of the DVP that is influenced by the PWV of pressure waves in the aorta and large arteries. SI_{DVP} cannot be expected to provide identical information to PWV_{cf}, since the contour of the peripheral pulse is complex and SI_{DVP} is likely to be influenced by factors other than PWV, such as the characteristics of ventricular ejection and the exact distribution of sites of pressure wave reflection. Furthermore, since the major site of pressure wave reflection lies distal to the femoral arteries, SI_{DVP} will be influenced by the distensibility of these arteries in addition to that of the aorta, and it is notable that age-related changes seen in elastic arteries are not seen in muscular arteries [26]. Despite these reservations, the correlation between SI_{DVP} and PWV_{cf} is striking, being higher than that reported for other widely used indices of arterial stiffness, such as systemic arterial compliance, for which the correlation with PWV_{cf} has been reported to be 0.47 in healthy subjects [27]. The similarity of the relationship between SI_{DVP}, age and blood pressure and that between PWV_{cf}, age and blood pressure further supports the concept that SI_{DVP} and PWV_{cf} are influenced by similar factors. Although we studied subjects with a large range of values of aortic stiffness, our study does not validate the use of SI_{DVP} in older subjects with hypertension or other risk factors for atherosclerosis that have PWV_{cf} values exceeding those seen in the present study.

In addition to the timing of reflected pressure waves, the contour of the peripheral pulse is influenced by the amplitude of pressure wave reflection, with this amplitude determining the height of the diastolic component of the DVP. Pressure wave reflection is dependent on the vascular tone of small muscular arteries, and vasoactive drugs may influence reflection independently of effects on large artery stiffness and hence PWV. To investigate whether such changes in reflection influence SI_{DVP}, we examined the effects of GTN on SI_{DVP} and PWV. As

expected, GTN caused large changes in the contour of the DVP, but these were limited mainly to an alteration in the height of the diastolic component, so that changes in ΔT_{DVP} and hence SI_{DVP} were modest and of comparable magnitude to those in PWV_{cf}, supporting the concept that SI_{DVP} is influenced predominantly by the stiffness of large elastic arteries.

In conclusion, we describe an index of vascular stiffness, SI_{DVP}, derived from the DVP. SI_{DVP} is correlated with PWV_{cf}, varies with age and blood pressure in a similar manner to PWV_{cf}, and is influenced by vasoactive drugs to a similar extent as is PWV_{cf}. The method for acquiring SI_{DVP} is simple, inexpensive, rapid and requires no special training. It is suitable for use in large-scale

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