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Differential response of peripheral arterial compliance-related indices to a vasoconstrictive stimulus

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Abstract
Peripheral arterial elastic properties are greatly affected by cardiovascular as well as other pathologies, and their assessment can provide useful diagnostic indicators. The photoplethysmographic technique can provide finger blood volume and pressure waveforms non-invasively, which can then be processed statically or beat-to-beat to characterize parameters of the vessel wall mechanics. We employ an occlusion–deflation protocol in 48 healthy volunteers to study peripheral artery compliance-related indices over positive and negative transmural pressure values as well as under the influence of a valid vasoconstrictor (cigarette smoking). We calculate beat-to-beat indices (compliance index CI, distensibility index DI, three viscoelastic model parameters (compliance $C$, viscosity $R$ and inertia $L$), pressure–volume loop areas $A$ and damping factor DF as well as symmetrical ($C_{\text{max}}$) and asymmetrical ($C_{\text{max}}^A$) static compliance estimates, and their distributions over transmural pressure. All distributions are bell-shaped and centred on negative transmural pressure values. Distribution heights were significantly lower in the smoking group (w.r.t. the non-smoking group) for $C$, CI, DI and significantly higher in $R$ and DF. The estimated volume signal time lag was also significantly lower in the smoking group. Left and right distribution widths were significantly different in all parameters/groups but DI (both groups), $C_{\text{max}}^A$, $A$ (smoking group) and $L$ (non-smoking group), and positions of maxima/minima were significantly altered in $C_{\text{max}}^A$, $R$ and DF. $C$, DF and CI are seen to be most sensitive under this protocol, while $C_{\text{max}}$ and $C_{\text{max}}^A$ are seen to be insensitive. These quantities provide complementary, time- and transmural pressure-dependent information about arterial wall mechanics, and the choice
of index should depend on the physiological conditions at hand as well as relevant time resolution and transmural pressure range.

Keywords: photoplethysmography, limit-cycle area, compliance, Finapres

1. Introduction

Compliance and smooth muscle tone are the principal determinants of arterial wall haemodynamic behaviour. The compliance buffers pulsatile pressure changes; smooth muscle tone assures that the circulatory system envelops total blood volume with a sufficiently positive circulatory filling pressure. An individual’s compliance may, if low when compared to the healthy population average, indicate cardiovascular as well as other (renal, retinal, metabolic syndrome, diabetes) risks (Cernes et al 2008, Cheung et al 2007, Haluska et al 2008, Teede 2007, Toussaint and Kerr 2007). Further, it has been recently shown (Grey et al 2003) that a decrease in the elasticity of small blood vessels represents a significant and independent cardiovascular risk factor. Compliance is defined as the change in volume ($V$) for a given change in transmural pressure ($P$), and the relationship between vessel $P$ and $V$ is highly dynamic and nonlinear, especially in vivo. Its estimation therefore requires instantaneous monitoring of arterial blood pressure (ABP) and $V$ signals (Tanaka et al 2000) and reconstruction of the causal relationship between their pulsatile components. Blood $P$ waveform can be estimated non-invasively using Finapres (Wesseling et al 1986) while in the case of small finger arteries, volumetric waveforms can be recorded non-invasively through photoplethysmography (Lopez-Beltran et al 1998, Penaz 1954, 1975, Penaz et al 1976, Reisner et al 2008, Shelley 2007). The combination of these two signals has been used by several authors to estimate elastic properties of finger vessels (Allen and Murray 1999, Millasseau et al 2000, Penaz et al 1997).

Due to the viscous and inertial properties of arterial wall tissue (Armentano et al 1995, Bauer et al 1979, Busse et al 1981), correlated $V$ and $P$ changes cannot occur simultaneously, and their relative phase may not be stationary across consecutive heart cycles. Further, the elastic behaviour of the tissue is highly operating-point dependent, the crucial parameter being transmural $P$ (TMP, the difference between internal and external $P$). An accurate characterization of vessel behaviour therefore requires investigating a wide range of TMP values. Fixed TMP values have been employed by several authors (Bank et al 1999, Bank and Kaiser 1998, Lichtenstein et al 1998, Tanaka et al 2002). While the point of zero TMP (as controlled, for example, by externally applied occluding cuffs (Tanaka et al 2002)) represents the unloaded state of the artery (Penaz et al 1997) and has been seen to be most representative of viscoelastic changes in the arterial wall (Langewouters et al 1986), due to residual stress in the vessels (Matsumoto et al 2004, Raghavan et al 2004, Valenta et al 1997) it cannot be assumed to coincide with the point of maximum compliance, which has to be determined experimentally.

There is currently no reference standard for the estimation of arterial compliance (Jagomagi et al 2005, Tanaka and Sawada 2003) and arterial elastic properties in general, leading to a number of approaches which can be systemic, regional or strictly local (McVeigh et al 2002, Pannier et al 2002, Van Bortel et al 2002, Woodman et al 2005). In a beat-to-beat perspective, compliance is often estimated as the ratio of pulsatile variations in $P$ and $V$ (Talts et al 2006). Accurate estimation of the latter is still the object of discussion,
and several indices have been proposed, such as simple pulse V (PV), normalized pulse V (NPV) and double normalized pulse V (DNPV) (Tanaka et al 2000, 2002, Tanaka and Sawada 2003), the latter two leading to the definitions of compliance index (CI) and distensibility index (DI) (see section 2.2). Also, phase-plane analysis of ventricular P–V loops signals has shown a correlation between loops areas and ventricular elastance (the inverse of compliance) (Eucker et al 2001, 2002), and any valid viscoelastic model of the vessel which incorporates distensibility effects (Allen 2007, Allen and Murray 1999) should be able extract one or more compliance-related indices, whose diagnostic and prognostic value then needs to be investigated.

Smoking is known to be a major cardiovascular disease risk factor and is associated with an acute increase in ABP and heart rate as well as vasoconstriction. This is probably reflected in changes in arterial wall viscoelastic properties (Clyne et al 1982, Giannattasio et al 1994, 1996, Grassi et al 1995, Hanna 2006, Kool et al 1993). It has been seen to markedly affect the compliance of small arteries and arterioles (Brunel et al 1992), and this effect has been seen to occur immediately and to last up to 4 min after cessation of smoking and has been connected to compliance changes in the radial and brachial arteries (Cryer et al 1976, Giannattasio et al 1994, Marc et al 2000). We therefore expect arterial wall compliance-related indices to respond to a smoking stimulus with a negative variation.

The overall focus of this study is the assessment of possible non-invasive diagnostic techniques for pathologies with cardiovascular implications. We aimed to (1) apply the photoplethysmographic method to determine and quantify the behaviour of well-known compliance-related indices (Langewouters static compliance, CI and DI) over a wide TMP range; (2) apply a viscoelastic model of the arterial wall to extract and validate a dynamic (in the beat-to-beat sense) estimate of arterial compliance, viscosity and inertance; (3) investigate the significance of finger artery P–V loop areas; and (4) validate and quantify the TMP-dependent behaviour, distribution and sensitivity of various other compliance-related indices in the presence of a well-known interference with arterial elastic properties such as smoking.

2. Methods

2.1. Experiment

2.1.1. Subjects. Forty-eight healthy volunteers, aged 38.34 ± 2.33 years (males: 28, females: 20), all occasional smokers, were studied in a laboratory maintained at a temperature of 24–26 °C. Subjects were divided randomly into two groups (smoking (s) and non-smoking (ns)). All experiments were performed between 8:00 and 10:00 am. All subjects were advised to refrain from smoking and ingesting caffeine or non-prescription medicine on the day of the experiment. Subjects were excluded from the studies on the basis of pre-existing cardiovascular pathologies, both medicated and non-medicated. The ethics of the study were approved by the local institutional review board, and the study was carried out in accordance with the Declaration of Helsinki, 1975. Written informed consent was obtained from the healthy volunteers prior to the investigation.

2.1.2. Pressure and photoplethysmographic volume recording. The experimental apparatus is shown in figure 1. Two photoplethysmographic cuffs were wrapped on the middle phalanx of the index finger (pressure cuff) and middle finger (volume cuff). The finger photoplethysmographic device and Finapres device (Ohmeda 2300, Ohmeda Monitoring Systems, Englewood, CO, USA) were used to monitor volume and pressure cuff signals, respectively. Each cuff incorporated a near-infrared light-emitting diode (810 nm;
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External pressure control

Pressure measurement

Volume measurement

Figure 1. Experimental apparatus. SW1–3: switches.

L810-40K00, Ebisu Denshi Co., Osaka, Japan) (light source) and a photodiode (HPI-2464R5, Kodenshi Co., Tokyo, Japan) (photo-sensor). The occluding cuff (volume cuff) was used to compress the vessels and to control the TMP of the arteries. The air tank pressure can be controlled through the pump and switch SW1. Volume cuff pressure can then be shifted to tank pressure through SW2 and slowly brought back to zero through SW3 and the connected needle valve. Volume cuff pressure was controlled within the range of 0–200 mmHg and measured using a pressure transducer (Honeywell 142PC05G). Raw signals were stored on a PC via a 16-bit A/D converter with 1 ms sampling intervals for off-line analysis using Labview 7.1 (National Instruments, Austin, TX, USA).

2.1.3. Experimental procedure. The experimental protocol is shown in figure 2. Subjects were seated comfortably, their left hand resting on a table positioned at the heart height. At the outset, the subject was asked to rest for 10 min in a sitting position (basal phase, SW1/2/3 open, volume cuff pressure = 0 mmHg). Successively, SW2 was closed, rapidly raising cuff pressure to 200 mmHg, after which the system is maintained stationary for at least 5 min (inflated phase), in order to ensure as complete as possible emptying of all finger vessels. At the onset of the following deflating phase, SW3 was opened, allowing occluding pressure to slowly (20 min total) decay to approximately 0 mmHg. Hence, the protocol involves the complete and abrupt emptying of arteries (occlusion) followed by slow filling under increasing TMP, occurring over 20 min. Here, one group was instructed to smoke a cigarette (or two if necessary). Smoking and filling inception and termination coincided. TMP was calculated as the difference between ABP as measured by the Finapres and the external pressure applied by the volume cuff. Experimental data from the deflating phase were processed as described in section 2.2. Sample measured P–V curves are shown in figure 3, which highlight cardiac cycles in the form of P–V loops.

2.1.4. Statistics. Where appropriate, data were analysed using one-way ANOVA (factor: smoking or side of curve, as applicable) under the software GBStat (version 6.0, Dynamic Microsystems, Silver Spring, MD, USA). $p < 0.05$ was taken to be statistically significant; $p < 0.01$ was taken to be statistically highly significant. Data are presented as mean ± SEM.
Figure 2. Experimental protocol. ‘SMOKE’ phase during which one group of subjects was instructed to smoke continuously using their right hand.

Figure 3. Sample volume (vertical axis) and pressure (horizontal axis) recording from one subject during the deflating phase, including magnification of one loop (inset). For clarity, loops are plotted every ten cardiac cycles.

2.2. Theory

2.2.1. Arterial wall model and volume time lag. We model the arterial wall time-dependent $P(t) - V(t)$ relationship cycle by cycle with a compliance term $C_k$, a viscous term $R_k$ and an inertial term $L_k$ (Armentano et al 1995, Zocalo et al 2006):
\[ P(t) = \frac{1}{C_k} V(t) + R_k \frac{dV(t)}{dt} + L_k \frac{d^2V(t)}{dt^2}, \]  

(1)

where the subscript \( k \) denotes the \( k \)th cardiac cycle. By scaling equation (1) as \( t \sim t_0 t' \), \( P \sim P_0 P' \), \( V \sim V_0 P' \), dividing by the coefficient of the highest derivative and dropping the primes as is usual, we obtain the non-dimensional equation:

\[ \frac{1}{L_k} P_0 t_0^2 P(t) = \frac{1}{L_k C_k} t_0^2 V(t) + \frac{R_k}{L_k} t_0 \frac{dV(t)}{dt} + \frac{d^2V(t)}{dt^2}. \]  

(1a)

Assuming that the zeroth-order terms are both \( O(1) \), we obtain the time scale \( t_0 = \sqrt{L_k C_k} \) (hence recovering the \( k \)th characteristic time of the system). We can then choose \( V_0 \sim C_k P_0 \), obtaining

\[ P(t) = V(t) + 2DF_k \frac{dV(t)}{dt} + \frac{d^2V(t)}{dt^2}, \]  

(1b)

where the dimensionless parameter (Ghista 2004) \( DF_k = \frac{1}{2} R_k \sqrt{C_k L_k} \) is the damping factor (also called linewidth) of the system.

Taking the Laplace transform of equation (1), we have

\[ \mathcal{L} \{ P(s) \} = \frac{1}{C_k} \mathcal{L} \{ V(s) \} + s \mathcal{L} \{ R_k V(s) + s^2 L_k V(s) \} \]

\[ \text{setting } s = i \omega, \text{ we have the frequency-dependent } k \text{th transfer function} \]

\[ H_k(s) = \frac{P_k(s)}{V_k(s)} = H_k(\omega) = \frac{1}{C_k} + i \omega R_k - \omega^2 L_k. \]  

(2)

Estimating compliance as the beat-to-beat ratio of PV to pulse pressure (Jagomagi et al 2005) means that its inverse (complex elastance) is defined by \( H_k(\omega) \). We can estimate the \( k \)th frequency-dependent phase delay in \( V \) effects as \( \phi_{PV}^k(\omega) = \text{Arg} \{ H_k(\omega) \} \). Since it is known that the amplitude of the complex elastance rises steeply to a fairly constant level (Cox 1984) which is reached at frequencies below the heart rate, we estimate the \( k \)th time delay in \( V \) effects \( \Delta t_{PV}^k \) as

\[ \Delta t_{PV}^k = T_k \phi_{PV}^k \left( \frac{\omega k}{2\pi} \right) = T_k \left( \frac{2\pi}{T_k} \right) \text{Arg} \left[ \frac{2\pi}{T_k} \right]. \]  

(3)

where \( T_k \) is the duration of the \( k \)th cycle. During the estimation of static compliance indices (equation (5)), which assume simultaneous effects, the \( V \) signal is hence shifted preventively by \( \Delta t_{PV}^k \).

2.2.2. Asymmetrical parameter trends. The fitted parameters were seen to be distributed asymmetrically over the examined \( P \) interval with a central peak and different lateral widths (see figure 4). A suitable shape previously validated for arterial compliance-related indices (Talts et al 2006) was hence extracted as a trend as follows:

\[ y = \begin{cases} 
\frac{y_{\text{max}}}{1 + \left( \frac{p - p_0}{p_l} \right)^2} & p < p_0 \\
\frac{y_{\text{max}}}{1 + \left( \frac{p - p_0}{p_r} \right)^2} & p > p_0,
\end{cases} \]  

(4)

where \( y \) is the fitted parameter, \( p \) is TMP, \( (p_0, y_{\text{max}}) \) are the peak position and value, respectively, and \( (p_l, p_r) \) are left and right widths at half-maximum, respectively (figure 4).
2.2.3. Symmetrical and asymmetrical static compliance estimation. Minimum \( V \) and \( \text{TMP} \) were fitted to the asymmetrical relationship (Talts et al 2006) (integral of equation (4)):

\[
v(p) = \begin{cases} 
  p_lC_{\text{max}}\tan^{-1}\left(\frac{p-p_0}{p_l}\right) + p_0 & p < p_0 \\
  p_rC_{\text{max}}\tan^{-1}\left(\frac{p-p_0}{p_r}\right) + p_r & p \geq p_0,
\end{cases}
\]

yielding a maximum \( \frac{\mathrm{d}v(p)}{\mathrm{d}p}\bigg|_{\text{max}} = C_{\text{max}} \) at \( p = p_0 \). This was taken as an overall static compliance estimate (Talts et al 2006). Setting \( p_l = p_r = p_1 \), \( p_1C_{\text{max}} = F_1 \) and \( p_{0r} = F_2 \) reduces this model to the well-known symmetrical Langewouters model \( v(p) = F_1 \tan^{-1}\left(\frac{p-p_0}{p_1}\right) + F_2 \) (Langewouters et al 1986), which was also fitted for comparison, in which case the peak value is termed \( C_{\text{max}} \).

2.2.4. Loop areas. Total mechanical work done by the blood on the arterial wall during the \( k \)th cycle can be expressed as

\[
W_k = \oint P_k(V_k) \, dV_k = \int P_k(t) \frac{dV_k(t)}{dt} \, dt = \int P_k(t) \frac{dV_k(t)}{dP_k(t)} \, dP_k(t) \, dt
\]

\[
= \int C_k(t) P_k(t) \frac{dP_k(t)}{dt} \, dt,
\]

where the integrals are computed over the complete cycle. Assuming the tissue description in equation (1) and inserting a sinusoidal driving \( P \) function \( P(t) = P_0 \cos(\omega t) \), the steady-state solution to equation (1) is

\[
V_k(t) = \frac{P_0}{\omega} \frac{1}{R_k^2 + \left(\omega L_k - \frac{1}{C_k}\right)^2} \sin(\omega t - \phi_k);
\]

\[
\phi_k = \tan^{-1}\left[ \frac{1}{R_k} \left(\omega L_k - \frac{1}{C_k}\right) \right].
\]

Figure 4. Asymmetrical shape used for fitting distributions of compliance-related indices (vertical axis) of transmural pressure (horizontal axis). \((p_0, y_{\text{max}})\): peak position and value, respectively; \((p_l, p_r)\): left and right half-maximum widths, respectively.
Substituting from equation (7) and setting a frequency $\omega_k$, equation (6) can be integrated over one cycle from $[t, 0, \frac{2\pi}{\omega_k}]$ obtaining

$$W_k = \pi P_0^2 \frac{R_k}{\omega_k\left(R_k^2 + \left(\frac{1}{C_{\text{eq}}} - L_{\text{eq}}\omega_k\right)^2\right)},$$

(8)

We note that $W_k$ increases monotonically with $C_k$ as long as $0 \leq C_k \leq 1/(\omega_k^2 L)$, which is always the case for our range of signals (data not shown).

2.2.5. Compliance index and distensibility index. Assuming that the Lambert–Beer law is valid for the fingertip (Tanaka et al 2002), we can relate the intensity of incident light $I_0$ to the transmitted light both in normal (i.e. in the presence of both blood and tissue) conditions ($I$) and in occluded conditions ($I_t$, i.e. in the presence of tissue only) as follows:

$$\frac{I}{I_0} = \exp(-\varepsilon_a C_a V_a - \varepsilon_v C_v V_v - \varepsilon_t C_t V_t); \quad \frac{I_t}{I_0} = \exp(-\varepsilon_t C_t V_t),$$

(9)

where $\varepsilon_a$, $\varepsilon_v$, $\varepsilon_t$ are the absorption coefficients of arterial, venous and tissue, respectively, $C_a$, $C_v$, $C_t$ are respective concentrations and $V_a$, $V_v$, $V_t$ are respective volumes in the segment considered. We derive

$$\frac{I}{I_t} = e^{-\varepsilon CV}, \quad \varepsilon = \frac{(\varepsilon_a V_a + \varepsilon_v V_v)}{V}, \quad V = V_a + V_v,$$

(10)

and we have assumed $C_a = C_v = C$, the mean concentration of total blood. Noting that the total blood $V$ consists of a pulsatile arterial component and a venous component, differentiating equation (10) we obtain the NPV (Sawada et al 2001) and DNPV (Tanaka et al 2000) in terms of the pulsatile component of the arterial blood volume $\Delta V_a$:

$$\text{NPV}_k = \frac{\Delta I/I}{\varepsilon C \Delta V_a}; \quad \text{DNPV}_k = \frac{\Delta V_a/V}{\ln(I/I)},$$

(11)

assuming that $\Delta V_a$ is small compared to $V$. Cycle-specific CI and DI are then defined as

$$\text{CI}_k = \frac{\text{NPV}_k}{\text{PP}_k}; \quad \text{DI}_k = \frac{\text{DNPV}_k}{\text{PP}_k},$$

(12)

where the pulse pressure PP is the $P$ excursion during one cycle (systolic–diastolic). The above indices are estimated cycle by cycle.

2.2.6. Rationale and physiological interpretation of indices. The indices we compute reflect different angles from which the viscoelastic properties of the vessel can be observed.

Model R, L, C. The arterial wall is modelled as a material which exhibits properties of pure elasticity ($1/C$) since it is deformable (like most biological materials), viscosity ($R$) since it contains significant amount of viscous smooth muscle, especially when contracted, and inertia ($L$) which accounts for latency in responding with deformation (volume variation) to a stimulus such as pressure increase.

Model DF. Assuming the above interpretation, DF gives an idea of how good the arterial wall is at ‘transmitting’ stimuli—a higher DF signifies less responsiveness of the mechanical structure over certain frequency bands, loosely speaking a less adaptable/versatile vessel wall.

A. A certain amount of energy is required in order to deform the artery at each cycle. $A$ is a measure of how much work blood does on the arterial wall.

C. Since NPV (see section 2.2) is directly proportional to $\Delta V_a$, CI (which is NPV divided by pulse pressure) can be regarded as a compliance index which is mostly indicative of alpha-
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adrenergically mediated finger vascular tone. It is dimensional and also sensitive to changes in haematocrit.

DI. This index uses DNPV (instead of NPV, see section 2.2), which is then divided by pulse pressure. It is therefore also an index of alpha-adrenergic vascular sympathetic nerve activity-related compliance; however, it is adimensional and does not depend on blood concentration.

\(C_{\text{max}}\) quantifies the overall (across the entire TMP range) maximum compliance of the vessel in an idealized situation where it is purely compliant (i.e. neglecting viscosity due to smooth muscle tone and/or inertia).

\(C_{\text{max}}^{A}\) is similar to \(C_{\text{max}}\) in that it does not take into account the dynamic properties of the system, but it is able to incorporate asymmetric behaviour over the TMP range and may therefore be a more accurate first indicator of overall maximum compliance.

2.2.7. Numerics. Nonlinear regressions as well as all other numerical procedures are implemented as proprietary code in Mathematica® 6.01, Wolfram Research, Inc.

3. Results

3.1. Compliance-related indices versus TMP

Figure 5 shows sample distributions of various compliance-related indices (see the figure legend) from two subjects [protocol with smoking (s) and without (ns)] over TMP along with the curves fitted from equation (4) (or its inverse in the case of figures 5(a)–(h)). The goodness-of-fit was evaluated as \(R^2 = 1 - \frac{\text{SSE}}{\text{SST}}\) and was 0.965 on average. Also shown is the probable vessel configuration (see section 4.4.4) as a function of TMP according to Wesseling et al (1995). One point corresponds to one complete cardiac cycle from which one value of any particular index is extracted (see section 2.2). All indices are seen to be distributed asymmetrically in a bell-shaped fashion, with a peak which is generally not at the zero TMP point. The maximum (minimum for \(R\)) value for any particular subjects is taken as representative and included in the statistical analysis below. In s, we see lowered (raised for \(R\), \(L\) and DF) and shifted distributions in all compliance-related indices (w.r.t. ns).

Figure 4(f) shows sample estimated time lags in \(V\) effects over the mean TMP (figure 3). The delay in \(V\) effects is seen to increase with increasing TMP, with a plateau over positive values of this parameter. Variations in the average position and peak heights as well as lateral half-maximum widths of the curves are quantified below.

3.2. Effect of smoking on compliance-related indices and time delay

Figure 6 compares s to ns in terms of the averaged peak values (\(y_{\text{max}}\) in equation (4)) of compliance-related indices defined in section 2.2 (some of which are shown in figure 5), including the static compliance estimates \(C_{\text{max}}^{A}\) and \(C_{\text{max}}\) (equation (5)). We see a significant reduction in the maximum value of \(C\), and CI, as well as a significant decrease in DI (s w.r.t. ns). We also note a significant increase in the minimum \(R\) and maximum \(L\) and DF. No noticeable difference between groups is seen in \(C_{\text{max}}^{A}\) or \(C_{\text{max}}\), as calculated with either the asymmetrical or the symmetrical static compliance model, respectively. The probability of the null hypothesis for variations in \(A\) under smoking was \(p = 0.06\). Figure 6 (inset) compares s to ns in terms of the maximum volume time lag, which is significantly decreased in s (w.r.t. ns),
Figure 5. (a)–(e), (g)–(h) Sample distributions of several elasticity-related indices (vertical axes) over the mean TMP (horizontal axis), under baseline conditions (ns) and under the influence of smoke (s). Also shown: probable vessel configurations as a function of TMP according to Wesseling et al (1995). Every dot corresponds to one cardiac cycle from which the parameter value is extracted. Fitted curves (equation (4)) are also shown. (f) Sample distribution of the estimated volume time lag (vertical axis) over the mean TMP (horizontal axis). Every dot corresponds to one cardiac cycle from which the parameter value is extracted.
and maximum characteristic time of the system, which did not differ significantly within groups.

From a physiological point of view, in the s group (w.r.t. the ns group) we are seeing a vessel which is more viscous, less distensible (effects on $C$, $R$, $CI$, $DI$) and less accommodating/responsive to the pressure stimulus (effects on $L$ and $DF$).

3.3. Asymmetrical behaviour of the vessel and the effect of smoking on the position and shape of curves

Figure 7(a) compares s to ns in terms of the averaged peak position values ($p_0$ in equation (4)). It is interesting to note that the position of peaks of all indices in all groups is at a negative TMP value. This value is shifted in s (w.r.t. ns), significantly towards zero in the case of $C_{max}$ and $R$, and significantly towards more negative TMP in the case of $DF$.

Figures 7(b) and (c) compare s to ns in terms of the averaged values of the left and right half-maximum widths respectively ($p_l$ and $p_r$ in equation (4), respectively). While the left width of the curve was increased significantly for $C_{max}$ and decreased significantly for $DF$ only (s w.r.t. ns), the right width of the curves was reduced in s (w.r.t. ns) in a highly significant manner in the case of $CI$ and $A$, and in a significant manner in the case of $C$ and $DF$. Note that the two widths of the $C_{max}$ curve are equal by definition.

Also shown in figure 7(b) is the comparison of the left half-maximum width to the right half-maximum width for all groups and all parameters. The high asymmetry of the distributions of all compliance-related parameters over TMP is reflected in highly significant
Figure 7. (a) Comparison (s versus ns groups) of position of peaks \( (p_0 \text{ in equation (4), fitted for all parameters, see section 2.2.}) \) (b) Comparison (s versus ns groups) of left half-maximum widths \( (p_l \text{ in equation (4), fitted for all parameters, see section 2.2}) \) and comparison to right half-maximum widths. (c) Comparison (s versus ns groups) of left half-maximum widths \( (p_l \text{ in equation (4), fitted for all parameters, see section 2.2}) \). \* \( p < 0.05, \; \* \* \; p < 0.01 \) (factor: smoking), \# \# \; p < 0.01 (factor: side of curve); ns: baseline (dashed bars); s: under the influence of smoke (solid bars). Cmax-A corresponds to \( C_{\text{max}}^A \) in equation (5).
differences between the left and right widths of most curves (all but DI (both groups), $C^A_{\text{max}}$ and $A$ (s only) and $L$ (ns only), indicated by hashes, see the figure legend), indicating differentially altered vessel behaviour during negative or positive strain/TMP.

In the interpretation of the position of curve maximum as an index of residual stress in the vessel, the above could indicate a tendency towards a reduction of the latter in s w.r.t. ns. The differences between s and ns in the compliance-related properties of the vessel are reflected not only in maximum index values (see above) but also in the behaviour over the whole physiological operating range (narrower curves over positive TMP).

4. Discussion

4.1. Compliance-related indices

We have employed a number of techniques to derive indices related to the viscoelastic properties of the finger artery, most of which are dynamic in a beat-to-beat sense (apart from $C^A_{\text{max}}$ and the Langewouters parameter $C_{\text{max}}$). Since the protocol involves slow variation of TMP effected through deflation of the occluding cuff, this allows us to estimate the dependence of these indices on TMP.

4.1.1. Viscoelastic model of vessel walls. The second-order viscoelastic model for arterial walls has been successfully employed in characterizing arterial wall dynamics (Armentano et al 1995, Gamero et al 2001, Zocalo et al 2006), and explicit characterization of time and/or frequency dependence is necessary due to the presence of viscous components in the arterial walls (Gamero et al 2001), which cannot be separately accounted for using power spectral methods (Gow and Taylor 1968). While several constitutive models were developed which aimed at extracting physiologically relevant haemodynamic parameters (Hayashi 1993, Langewouters et al 1986, Wuyts et al 1995), this model allows us to dissect elasticity, viscosity and inertia (Gamero et al 2001). The parameters $C$, $R$ and $L$ govern the shape of the $P$–$V$ loop and are therefore representative of waveform-related (rather than extremal value-related) characteristics of the $P$–$V$ signals. It has been shown that at constant TMP viscoelastic parameters can be considered stationary (Gamero et al 2001), justifying successive, beat-to-beat estimates at different TMP values. The model can be easily non-dimensionalized, allowing the extraction of a single, non-dimensional parameter (DF) which responds robustly to the vasoconstrictive stimulus. The model was seen to fit the data well, with confidence interval widths which were at most 5% of parameter values (data not shown). Our protocol highlighted a strong dependence of all these parameters on TMP, producing bell-shaped curves which are reminiscent of the Langewouters arctangent model, allowing us to employ a uniform, nonlinear asymmetrical fit shape (Talts et al 2006) across all parameters. Possible extensions to more parameters have been performed (e.g. higher order autoregressive model with exogenous input (Gamero et al 2001)); however, these models produce parameters which are not easily interpreted in a physiological context. In this study, estimating the time delay in $V$ effects at maximum transfer amplitude through the viscoelastic model revealed a strong dependence of this parameter on TMP, confirming the dynamic and non-stationary nature of arterial wall mechanics (Armentano et al 1995). The order of magnitude of this delay (100 ms) is in accordance with previous reports (Talts et al 2006).

4.1.2. Normalized indices. While arterial compliance has often been calculated using PV, the latter can only be defined as $\Delta J$ (see equation (11)) and hence is not in direct proportion to the pulsatile component of the arterial blood volume. Further, while it is easy to measure and fairly
sensitive to stress (Sawada et al 2001), its haemodynamic significance is not strictly defined, and it can only be measured in a gain-dependent relative manner which yields arbitrary units (mV). In contrast, NPV is unitless, in direct proportionality to the pulsatile component of the arterial blood volume $\Delta V_a$, and can therefore be processed as an absolute value. Further, since the change in venous vascular tone in the finger appears to accompany those in the arterial ones (Gow 1980), the fact that the total blood volume-related signal $I$ also enters the definition of NPV (but not PV) makes it more sensitive than PV to stressful stimulation (Sawada et al 2001). Clearly, the use of this value (and its correlated index CI) requires the assumption of small $\Delta V_a$ and that the parameters $\varepsilon$ and $C$ (as well as finger tissue characteristics) show little variation across subjects. These assumptions may be unjustified in the case of pathologies which significantly alter the content and/or thickness of blood or in the presence of excessive variations in finger size across subjects, in which case length-normalized plethysmography seems more appropriate (Aldrich et al 2002).

This limitation can be overcome through the definition of the DNPV (Tanaka et al 2000) (and its associated index DI), which also shares some of the advantages of NPV (unitless and obtainable beat by beat), and whose validity in determining vascular tone also under stressful stimuli has been established (Tanaka et al 2000). However, this comes at the cost of a high variability, especially at low or negative TMP values (which we indeed observe in figure 6 as a relatively high SEM), and of a sharp (and meaningless) rise of the index as we approach complete occlusion (i.e. near zero total blood $V$). Clearly, both CI and DI are sensitive to cycle-specific variations in $P$–$V$ extremal values and not to other waveform characteristics.

4.1.3. Static estimates. The arctangent model (Langewouters et al 1986) provides a way of analysing static $P$–$V$ relationships and of deriving (through differentiation) an estimate of compliance. It should be noted that (1) this model assumed a thin walled, purely compliant artery, while the finger artery displays substantial viscous behaviour, especially when contracted (Wesseling et al 1995), and it is hence not able to incorporate the highly asymmetrical (w.r.t. TMP) elastic properties of the vessel, and (2) the arctangent function is fitted by connecting consecutive $P$–$V$ minima which are extracted beat by beat. It could be argued that, since the system does not actually trace this path in $P$–$V$ space, this derivative is not a physical property (compliance) of the system in its strict definition—it can however be interpreted as an average trend. The loop shape or within-loop extremal values do not affect this index, which only takes into account one point per loop. The arctangent function can be made asymmetrical (Talts et al 2006) (equation (5)), providing a more flexible way of performing the above-described estimate and offering additional parameters (left and right widths) which can help quantify arterial wall behaviour. Evidently, time dependence is not included in these models, which assume immediate transfer, and this shortcoming can be partially overcome only by estimating the TMP- and frequency-dependent phase shift and reversing it (see section 2.2).

4.1.4. Loop areas. Pressure waveforms (either arterial, measured non-invasively or left-ventricular, measured invasively) are rarely used for more than estimating peak-systolic and end-diastolic pressure, and never beyond the measurement of selected points of left ventricular pressure contour and its time derivative. It has been shown that, by treating the tissue as a nonlinear driven oscillator, additional information can be obtained from the $P$–$V$ loop (Eucker et al 2002) such as dynamic stiffness of the system ($dP/dV$) or time-varying elastance, which is a load-independent estimate of the elastic properties of tissue. While this analysis was performed for an actively contracting ventricle, where the $P$ signal is the output, in our analysis a $P$ driving function gives rise to a $V$ signal which is the result of a nonlinear filtering
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4.2. Distribution of indices and curve fit

All compliance-related parameters were seen to be distributed in a highly asymmetrical manner, peaking on a negative TMP value, with a consistently longer tail in the region of positive TMP values. This has been previously reported in the case of asymmetrical static compliance estimates (Raamat et al. 2008, Talts et al. 2006)—we extend this result to all computed indices, model-derived and not. This was expected as vessel behaviour in the negative TMP region cannot be explained by pure compression strain, as other effects such as whole vessel deformation/shape change take place, augmenting apparent material stiffness. Further, as is well known, blood vessels in their unloaded state present a variable degree of residual stress, which can readily be seen through radial cutting and has recently been investigated as an additional variable to be taken into account in reliable simulations of cardiovascular system mechanics (Balzani et al. 2006, Matsumoto et al. 2004, Raghavan et al. 2004). By spanning a wide range of TMP values, we are able to estimate the TMP at which compliance indices are largest. This was consistently seen to be around −10 mmHg, in accordance with the literature (Talts et al. 2006). Assuming that this point corresponds to zero internal stress, this value could be used to estimate true residual stress though mechanical tissue models (the simplest of which could be Laplace’s law). Due to the definition of DI, its value is highly variable in the negative TMP range (see above) and we cannot consider the estimates for peak positions and left/right widths to be as reliable as for the other indices. This does not, however, affect the estimate of its peak value.

4.3. Influence of smoking and sensitivity of indices

One way of assessing the validity of a compliance-related index is determining its sensitivity to a stimulus which is known to alter viscoelastic properties of the tissue. Smoking is a well-known vasoconstrictor, which profoundly affects peripheral arterial elastic properties (Duprez and Cohn 2007, Marc et al. 2000). We expand the demonstration of the magnitude and immediacy of such effects to a number of compliance-related indices. Several parameters responded to this stimulus with a sharp decrease, both in their peak values and in their distributions. The most responsive parameters were model estimated C and R as well as CI (highly significant differences); while DI was significantly decreased, DF was significantly increased in s w.r.t. ns and the effect on A was almost significant (p = 0.06). The static arctangent model (symmetrical or not) was not able to detect the influence of the stimulus (no difference in Cmax or CΔmax), indicating that it is more tied to the P–V waveform (loop shape) rather than to the distribution of P–V minima. This may signify an effect of smoking...
on the dynamic rather than static components of arterial elasticity. Also, the position of the curve peak (which in our hypothesis is representative of residual stress in the vessel) was significantly shifted closer to zero in $C_{\text{max}}$ and $R$, possibly indicating an acute reduction in residual stress in the vessel. Since the latter is a physiological and necessary property of the artery, this reduction could be effected through different mechanisms than the overall stiffening of the artery resulting from smoking. Asymmetrical stiffening is also evident in the differential altering of curve widths, with a much more pronounced effect in more parameters on right width (dynamic range under distension through (mostly) positive TMP).

4.4. Limitations and extensions

4.4.1. Pressure recordings in adjacent fingers. While the photoplethysmographic technique for finger compliance estimation has been widely employed, albeit mostly in the realm of positive TMP (Bochmann et al 1995, Jagomagi et al 2005, Lopez-Beltran et al 1998, Marc et al 2000, Raamat et al 2007, 2008), it clearly relies on the assumption of equivalent pressure recordings in adjacent fingers. The variability introduced by the fact that the fingers are different has been shown to be no larger than the one originating from re-insertion on the same finger (Lal et al 1993) and not statistically significant. Estimating pressure in adjacent fingers with two different methods (volume-clamp versus oscillometric) has led to statistically significant differences which, however, cannot be considered clinically relevant (Raamat et al 2001). However, it is also known that measurements in adjacent fingers influence each other. These factors may influence the accuracy of the positioning of the curves along the TMP axis (figures 5 and 7(a)).

4.4.2. Applicability of the Lambert–Beer law. While transmission in the plethysmograph decreases linearly with vessel diameter (and hence circumference (Wesseling et al 1995)), it has been shown through the use of a strain gauge (Cejnar et al 1993) that the volume signal can be fitted well by the Lambert–Beer law or by a simplified version of Kubelka’s light scatter equation (Shimada et al 1984). While the latter was seen to be slightly more accurate, we selected the former, which is widely applied in the literature, for comparability. Comparability of all indices across subjects (apart from DI) also demands similar blood absorption coefficients and concentrations—a condition which is not necessarily warranted especially in the presence of pathologies.

4.4.3. Confounding effects in the volume cuff. It is possible for the field of view of the plethysmograph to be sensitive to regions outside of the volume cuff, where no effective pressure is applied. However, a deviation of ±5 mm from the diode–photosensor axis has been seen to alter transmission by a factor 2 (Wesseling et al 1995), although this variation flattens with increasing distance. It has been seen that our cuff is 30 mm in length, and therefore applies pressure over ±15 mm from the plethysmograph; this effect can probably be considered negligible. The presence of other vessels such as veins, venules, arterioles, the venous plexus and the capillaries may represent an additional confounding factor in the volume signal, as these may have been partially refilled at subsystolic pressures. Indeed, it has been shown (Wesseling et al 1995) that the entirety of the vessels as seen by the plethysmograph can on occasions reopen at a TMP value as far as 15 mmHg away from the point where it closed, and that hysteresis can occur in the positive TMP range, although these cases were deemed as extreme by the authors.
4.4.4. Behaviour of the vessel under the volume cuff. In the negative TMP range, the vessel is no longer circular (see also figure 5) and may be cycling between open and collapsed if operating near the TMP at which full collapse occurs (which has been seen to vary approximately between $-25$ and $-50$ mmHg (Wesseling et al 1995)). Of course, this implies an inhomogeneous distribution of stress and therefore compliance-related properties become region dependent. Indeed we observed large plethysmographic fluctuations in the negative TMP range, which are reflected in higher scattering of the points around the fitted curve (as shown by a higher goodness-of-fit when these points are excluded), as well as a lower explained variance ($-15\%$ on average) when fitting the viscoelastic model parameters to the actual waveforms, which could be seen as a quantification of how much the assumption of a circular vessel is less applicable in negative TMP ranges. Part of the asymmetry in compliance-related index distributions could therefore result not purely from differences in material behaviour or smooth muscle tone, but also from differential effects due to vessel state (open versus collapsed), which in turn can have an effect on the blood flow regime in and out of the vessel. Further, when volume signals are very small, as in the case of extremely low negative TMP (closed vessel), basal and incremental volume signals become extremely noisy, influencing the accuracy of parameter estimates, especially CI and DI. All of the above renders the physical interpretation of the equations less immediate when looking below $-25$ mmHg TMP and further.

4.5. Further remarks

We have seen a high sensitivity of several parameters to a valid stiffening stimulus, and differential mechanisms of stiffening can be inferred for this stimulus through examining the definitions and significance of the different indices. We chose to quantify the distributions in terms of a unified asymmetrical shape which allowed comparison across compliance-related indices. Short of implementing a beat-to-beat nonlinear fitting procedure to yield the more sensitive viscoelastic parameters defined in equation (1), CI seems to be the most appropriate to detect variations in maximum finger arterial compliance, while more in-depth, waveform-related information can be obtained through the estimate of $A$. Further comparisons could be performed using ulcer stimuli which are known to alter peripheral compliance such as hyperaemia (Tanaka et al 2002), cold exposure (Raamat et al 2007) or pathologies which affect vascular compliance such as metabolic syndrome or diabetes (Haluska et al 2008).

5. Conclusions

Non-invasive assessment of peripheral vascular compliance can be an important aid in the diagnosis and study of all conditions which modify vascular tone. Exhaustive characterization requires studying multiple indices, which can be differentially altered, over a wide TMP pressure range. With an appropriate protocol, it can provide a wealth of additional information about vessel wall behaviour and characteristics, and the choice of index (or indices) should depend mainly on the TMP range of interest and on a cost–benefit assessment of sensitivity versus computational complexity and time resolution. For reliable characterization, dynamic beat-to-beat indices should be preferred, as they take into account waveform characteristics and stem from paths in $P$–$V$ and/or phase space which are actually traced by the system.
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