Noninvasive determination of local pulse wave velocity and wave intensity: changes with age and gender in the carotid and femoral arteries of healthy human

Alessandra Borlotti,1 Ashraf W. Khir,1 Ernst R. Rietzschel,2 Marc L. De Buyzere,2 Sebastian Vermeersch,3 and Patrick Segers3

1Brunel Institute for Bioengineering, Brunel University, Middlesex, United Kingdom; 2Department of Cardiovascular Diseases, Ghent University Hospital, Ghent, Belgium; and 3IBiTech-bioMMeda, Ghent University, Ghent, Belgium

Submitted 3 February 2012; accepted in final form 6 June 2012

Borlotti A, Khir AW, Rietzschel ER, De Buyzere ML, Vermeersch S, Segers P. Noninvasive determination of local pulse wave velocity and wave intensity: changes with age and gender in the carotid and femoral arteries of healthy human. J Appl Physiol 113: 727–735, 2012. First published June 7, 2012; doi:10.1152/japplphysiol.00164.2012.—We recently introduced noninvasive methods to assess local pulse wave velocity (PWV) and wave intensity (ndI) in arteries based on measurements of flow velocity (U) and diameter (D). Although the methods were validated in an experimental setting, clinical application remains lacking. The aim of this study was therefore to investigate the effect of age and gender on PWV and ndI in the carotid and femoral arteries of an existing population. We measured D and U in the carotid and femoral arteries of 1,774 healthy subjects aged 35-55 yr, a subgroup of the Asklepios population. With the use of the lnDU-loop method, we calculated local PWV, which was used to determine arterial distensibility (nDs). We then used the new algorithm to determine maximum forward and backward wave intensities (dUmax and dUmin, respectively) and the reflection index (nRI). On average, PWV was higher, and nDs was lower in the femoral than at the carotid arteries. At the carotid artery, PWV increased with age, but nDs, dUmax, and dUmin decreased; nRI did not change with age. At the femoral artery, PWV was higher, and nDs was lower in male, but all parameters did not change significantly with age in both women and men. We conclude that the carotid artery is more affected by the aging process than the femoral artery, even in healthy subjects. The new techniques provide mechanical and hemodynamic parameters, requiring only D and U measurements, both of which can be acquired using ultrasound equipment widely available today, hence their advantage for potential use in the clinical setting.

Wave speed; distensibility; wave separation; diameter; reflection index

There is an increasing interest in assessing arterial mechanical properties, as they offer valuable prognostic information. Of particular physiological and clinical interest is the “pulse wave velocity” (PWV), or wave speed (c), as it gives a direct measure of arterial distensibility (nDs). PWV is widely used to determine arterial stiffness, which is considered an early phenotype of vascular damage and a potential prognostic factor in assessing cardiovascular risk (2, 15, 16, 25). Local PWV has also been used as a surrogate marker for cardiovascular disease, including atherosclerosis (22), and proposed as an independent risk factor for cardiovascular events, such as coronary disease and stroke (4, 17). Although carotid-femoral PWV is widely used in clinical practice, it gives regional information about the properties of the vessels. A better understanding of the local properties of the arterial wall would be useful. For this reason, in the past few decades, several methods have been introduced to determine local c. Khir et al. (11) introduced the PU-loop method, which requires simultaneous measurements of pressure (P) and velocity (U) at the same site. The method relies on the linear relationship between P and U in the absence of reflections; the slope of the initial linear portion of the loop equals ρc, where ρ is blood density. Rabben et al. (30) used a similar technique: flow-area loop, which is based on the definition of the characteristic impedance. To accommodate the coexistence of incident and reflected waves, Davies et al. (6) introduced the sum of squares technique, although Kolyva et al. (14) questioned the effectiveness of this technique in the coronary circulation.

To understand the propagation of waves along the arterial system in the time domain, Parker and Jones (27) introduced the theoretical basis of wave intensity analysis (WIA). The method requires the simultaneous measurements of P and U at the same site and has been successfully applied to several locations along the arterial system: aorta (10, 12, 28, 31); coronary and carotid arteries (5, 24, 40, 45); venous system (44); left and right ventricles (20, 37); and intraoperatively in patients using the intra-aortic balloon pump (13). The usefulness of this analysis has been documented recently (39), including the evaluation of the working conditions of the heart and its interaction with the arterial system. To bypass the invasive nature of acquiring pressure, applanation tonometry has been used to provide pressure waveforms by calibrating arterial pressure waveforms (36). However, applanation tonometry can only be used with superficial arteries, as well as the need to accept the assumption that diastolic and mean or systolic pressure at the brachial artery are equal to those at the measurement site.

To avoid the difficulties of acquiring invasive measurements of P and U for the calculation of local c and WIA, Feng and Khir (7) presented the theoretical basis of noninvasive techniques that requires the measurements of diameter (D) and U. Local c is determined from the slope of the linear portion of the lnDU-loop, and the noninvasive ndI is defined as the product of change of D and change of U. Similar to traditional WIA, the method allows for the separation of waves into their forward and backward components and has been validated recently in vitro (19). In this work, the method is used for the first time with clinical data acquired using ultrasound measurements of D and U in the carotid and femoral arteries.

Address for reprint requests and other correspondence: A. W. Khir, Brunel Institute for Bioengineering, Brunel Univ., Uxbridge, Middlesex, UB8 3PH, UK (e-mail: ashras.khir@brunel.ac.uk).

http://www.jappl.org 8750-7587/12 Copyright © 2012 the American Physiological Society

727
The overall aim of this study is to use the new, noninvasive techniques to quantify the effect of age and gender on the arterial mechanical properties and hemodynamic parameters in the carotid and femoral arteries of a population of healthy subjects. The specific objectives are to noninvasively 1) determine local PWV using direct measurements of D and U, from which Ds can be calculated; 2) separate D and U waveforms into their forward and backward components; and 3) carry out the noninvasive WIA in healthy human vessels.

MATERIALS AND METHODS

Determination of Local PWV and Ds

PWV in this section will be expressed as c to conform to notations of c published previously. The theoretical basis of determining PWV noninvasively is described in our earlier work (7), and local c can be determined using the lnDU-loop method as

\[ c = \frac{1}{2} \frac{dU}{d \ln D} \]  

where dU and dlnD are the changes of U and D natural logarithm, respectively; (+) and (−) indicate the forward and backward directions, respectively. \( Equation \) 1 describes a linear relationship between lnD and U for unidirectional waves, and in this work, the linear portion of the lnDU-loop has been determined using a technique that was described previously (41). Figure 1 shows two typical examples of lnDU-loops, U and D waveforms at the carotid and femoral arteries for the same subject.

Substituting \( Eq. \) 1 in the Bramwell-Hill equation allows for the determination of local Ds

\[ D_s = \frac{4}{\rho} \left( \frac{d \ln D}{dU} \right)^2 \]  

where the fluid density \( \rho \) is assumed 1,050 kg/m³.

The Separation of D and U Waves

Changes in diameter, resulting from the forward and backward running waves, can be determined

\[ dD = \pm \frac{D}{2} \left( d \ln D \pm \frac{1}{2c} dU \right) \]  

and diameter waveforms in the forward and backward directions can be calculated by integrating \( Eq. \) 3

\[ D_\pm = \sum_{t=0}^{t} dD_\pm + D_0 \]  

where \( D_0 \) is the integration factor, which we chose arbitrarily as end diastolic diameter. Similarly, changes in velocity in the forward and backward direction can be calculated

---

Fig. 1. Velocity (U; A), lnDU-loops (B), and diameter natural logarithm (lnD; C) in carotid (solid lines) and femoral (dashed lines) arteries in a 40-yr-old female. Local pulse wave velocity (PWV) is 5.02 m/s and 9.59 m/s for the carotid and femoral artery, respectively. Gray lines indicate the initial linear part of the loop. D is expressed in meters.
\[ dU_z = \pm \frac{1}{2}(dU \pm 2c \ln D) \]  

(5)

and the velocity waveforms in the forward and backward directions can be calculated by integrating Eq. 5

\[ U_z = \sum_{n=0}^{k} dU_z + U_0 \]  

(6)

where \( U_0 \) is end diastolic \( U \).

**Determination of Noninvasive \( \Delta dI \)**

The net noninvasive \( \Delta dI \) is defined as \( \Delta dI = \Delta dD U \) (7). With the use of the knowledge of \( c \), \( \Delta dI \) can be separated into its forward and backward components

\[ \Delta dI_z = \frac{1}{4(D/2c)}\left( \frac{D \pm D}{2c} \right)^2 \]  

(7)

Equation 7 shows that the noninvasive WIA has the same useful characteristic of the traditional analysis—positive for forward and negative for backward waves. In this study, peak intensities of the forward and backward compression waves (\( \Delta dI_{\text{max}} \) and \( \Delta dI_{\text{min}} \), respectively) were determined. The ratio of \( \Delta dI_{\text{min}} \) to \( \Delta dI_{\text{max}} \), termed in this work as the reflection index (\( \text{RI} \)), was calculated at the carotid and at the femoral sites.

Figure 2 shows typical \( D \), \( U \), and \( \Delta dI \) waveforms in the carotid and femoral arteries, separated into their forward and backward components. Examining \( \Delta dI \) waveforms, we can identify three peaks: a forward compression wave in early systole (first positive peak) due to the left ventricle (LV) contraction, a backward compression wave in midsystole (negative peak) due to reflections from the periphery, and a forward expansion wave at the end of systole (second positive peak) due to the reduction in LV rate of contraction. Those peaks are similar in shape and timing to those of traditional WIA.

**Study Population**

Data were drawn from the Asklepios Study database, which is a longitudinal population study designed to focus on the interplay between aging and cardiovascular haemodynamics (33) and comprised data from 1,774 subjects (934 women) aged 35–55 yr (average age 45.8 ± 6 yr), free from overt cardiovascular disease. The study protocol was approved by the Ethics Committee of Ghent University Hospital, and all subjects gave a written, informed consent. Basic clinical and hemodynamic characteristics of the population are presented in Table 1.
Table 1. Physical, hemodynamic, and biochemical characteristics of subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Gender</th>
<th>35–40</th>
<th>41–45</th>
<th>46–50</th>
<th>51–55</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD (mm)</td>
<td>Male</td>
<td>7.19</td>
<td>7.05</td>
<td>7.27</td>
<td>7.18</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>6.48</td>
<td>6.51</td>
<td>6.41</td>
<td>6.66</td>
</tr>
<tr>
<td>MD (mm)</td>
<td>Male</td>
<td>6.41</td>
<td>6.24</td>
<td>6.65</td>
<td>6.69</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>5.68</td>
<td>5.86</td>
<td>5.85</td>
<td>6.10</td>
</tr>
<tr>
<td>DD (mm)</td>
<td>Male</td>
<td>5.90</td>
<td>5.93</td>
<td>6.12</td>
<td>6.14</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>5.41</td>
<td>5.49</td>
<td>5.44</td>
<td>5.75</td>
</tr>
<tr>
<td>Femoral</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD (mm)</td>
<td>Male</td>
<td>9.13</td>
<td>9.36</td>
<td>9.59</td>
<td>9.71</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>7.35</td>
<td>7.67</td>
<td>7.56</td>
<td>8.09</td>
</tr>
<tr>
<td>MD (mm)</td>
<td>Male</td>
<td>8.70</td>
<td>8.87</td>
<td>8.97</td>
<td>9.08</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>6.86</td>
<td>6.93</td>
<td>6.97</td>
<td>7.27</td>
</tr>
<tr>
<td>DD (mm)</td>
<td>Male</td>
<td>8.46</td>
<td>8.61</td>
<td>8.72</td>
<td>8.84</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>6.61</td>
<td>6.68</td>
<td>6.70</td>
<td>6.99</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>Male</td>
<td>211</td>
<td>217</td>
<td>224</td>
<td>223</td>
</tr>
<tr>
<td>(mg/dl)</td>
<td>Female</td>
<td>205</td>
<td>208</td>
<td>215</td>
<td>227</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>Male</td>
<td>55</td>
<td>56</td>
<td>57</td>
<td>56</td>
</tr>
<tr>
<td>(mg/dl)</td>
<td>Female</td>
<td>71</td>
<td>70</td>
<td>70</td>
<td>72</td>
</tr>
<tr>
<td>Glycemia</td>
<td>Male</td>
<td>92</td>
<td>93</td>
<td>94</td>
<td>96</td>
</tr>
<tr>
<td>(mg/dl)</td>
<td>Female</td>
<td>87</td>
<td>87</td>
<td>89</td>
<td>93</td>
</tr>
</tbody>
</table>

Values are mean ± SD. SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; HR, heart rate; SD, systolic inner diameter (ID); MD, mean ID; DD, diastolic ID. Pressure was recorded at the brachial artery. *Significant change (P < 0.01) between male and female in the same age group; †significant change (P < 0.01) compared with the immediate-previous 1/2 age group.

Measurements

Local arterial diameter. Arterial diameter distension waveforms were obtained by ultrasound echo wall tracking performed at the left common carotid artery and at the left common femoral artery using an ultrasonoraphic system (Vivid 7; GE Vingmed, Horten, Norway). This procedure has been described in detail elsewhere (29, 35, 43). Briefly, vessel boundary is selected manually at a given moment in time, and its movement is tracked automatically using a modified autocorrelation estimator (30). In this study, the vessel inner diameter (ID) was detected by tracking the lumen-intima boundary on both the anterior and posterior walls.

Local arterial velocity. Arterial flow velocities, in left common carotid artery and left common femoral artery, were obtained using a commercially available ultrasonographic system (Vivid 7; GE Vingmed). Images, in Digital Imaging and Communications in Medicine format, were processed offline with home-written programs in Matlab (MathWorks, Natick, MA). Maximum and minimum velocity envelopes were detected, and the average profile was used to calculate the local PWV using the lnDU-loop method. The correction for the angle between the flow and the ultrasound beam was applied where needed.

Since U and D were not recorded simultaneously, representative beats with similar heart rate (HR) were selected and aligned using peak of R-wave of ECG for each subject.

Biochemistry. Serum glucose, total cholesterol, and HDL cholesterol concentrations were measured on a Modular P system (Roche Diagnostics, Indianapolis, IN) in an ISO 9002-certified reference laboratory. Coefficient of variation of all tests was < 3%. Biochemical parameters are reported in Table 1.

Statistical Analysis

Data are presented as mean values ± SD, and bars in figures are SE. The population has been subdivided by gender into four half decades of age: 35–40, 41–45, 46–50, and 51–55. Effects of age and gender on PWV, aDs, aD–max, aD–min, and aRI were studied using analysis of covariance technique. These parameters were adjusted for mean arterial pressure (MAP), which was calculated as the averaged value of the calibrated brachial artery waveforms, HR, and body height. The analysis was also carried out, including glycemia, total cholesterol, and HDL cholesterol as covariates. Paired Student’s t-test was used to assess any significant difference between the same parameter in carotid and femoral artery. Values P < 0.01 were considered statistically significant. Statistical analyses were performed using SPSS 17.0 (SPSS, Chicago, IL). All data were collected by the same operator and analyzed by one analyzer. Reproducibility analysis was not carried out.
RESULTS

Local Mechanical Properties

Local PWV. In the femoral artery, PWV was, on average, higher than that at the carotid (10.98 ± 4.70 m/s vs. 4.03 ± 1.64 m/s; P < 0.001). In the carotid artery, PWV increased significantly with age (P < 0.001), and the difference between male and female was not statistically significant. In the femoral artery, PWV did not change with age but was found higher in men than women (11.43 ± 5.07 m/s vs. 10.52 ± 4.92 m/s; P < 0.001). Both carotid and femoral PWV did not reveal an age-gender interaction. When the biochemistry parameters were included to the analysis as covariates, the differences between male and female PWV in the femoral artery were attenuated. Figure 3A shows the changes of PWV with age and gender at the carotid and femoral arteries.

\( nDs \). Carotid arterynDs was, on average, higher than that of the femoral artery (87 ± 67·10^{-7} kPa/s vs. 15 ± 14·10^{-3} kPa/s; P < 0.001). Carotid \( nDs \) decreased with age (apart from men age 41–45 and 46–50; P < 0.001), and it was higher in females than males (91 ± 74·10^{-3} kPa/s vs. 77 ± 53·10^{-3} kPa/s; P < 0.01). In the femoral artery, \( nDs \) did not change with age and was higher in females than males (17 ± 15·10^{-3} kPa/s vs. 13 ± 11·10^{-3} kPa/s; P < 0.001). Inclusion of glycemia, total cholesterol, and HDL cholesterol to the analysis led to a decrease in the \( nDs \) differences between male and female at the femoral artery. Figure 3B shows the changes of \( nDs \) in the carotid and femoral arteries with age and gender.

Local Hemodynamic Parameters

\( \mu dI \). The average \( \mu dI_{\text{max}} \) compression waves were \( 2.60 ± 1.41·10^{-7} \text{m}^2/\text{s} \) and \( 2.08 ± 1.14·10^{-7} \text{m}^2/\text{s} \) for the carotid and femoral artery, respectively, and those of the \( \mu dI_{\text{min}} \) compression waves were \( 0.38 ± 0.30·10^{-7} \text{m}^2/\text{s} \) and \( 0.42 ± 0.34·10^{-7} \text{m}^2/\text{s} \). Average \( \mu dI_{\text{max}} \) and \( \mu dI_{\text{min}} \) intensities decreased with age in the carotid (P < 0.001), and we found a significant dependence of the \( \mu dI_{\text{max}} \) compression wave on gender in this vessel—higher in male (2.92 ± 1.51·10^{-7} \text{m}^2/\text{s} vs. 2.29 ± 1.10·10^{-7} \text{m}^2/\text{s}; P < 0.001). In the femoral artery, average \( \mu dI_{\text{max}} \) and \( \mu dI_{\text{min}} \) wave intensities did not change significantly with age, and \( \mu dI_{\text{max}} \) compression wave was higher in female than male (2.28 ± 1.50·10^{-7} \text{m}^2/\text{s} vs. 1.93 ± 1.16·10^{-7} \text{m}^2/\text{s}; P < 0.001). Figure 4, A and B, displays the changes of \( \mu dI_{\text{max}} \) and \( \mu dI_{\text{min}} \) compression wave with one-half decade age and gender at the carotid and femoral arteries, respectively.

Reflection from the upper and lower body. \( nRI \), indicating wave reflections from the left leg, was higher than that in the upper body.

**Fig. 3.** Local PWV (A) and distensibility (\( nDs \); B) are shown as a function of age and gender at the carotid and femoral arteries. Local PWV and \( nDs \) were adjusted for mean arterial pressure (MAP), heart rate (HR), and body height. Error bars are SE.

**Fig. 4.** Forward (black scale and lines) and backward (gray scale and lines) compression waves (\( \mu dI_{\text{max}} \) and \( \mu dI_{\text{min}} \), respectively) at the carotid (A) and femoral (B) arteries as a function of age and gender. Parameters were adjusted for MAP, HR, and body height. Error bars are SE.
carotid artery, indicating reflections from the head (0.22 ± 0.14 vs. 0.15 ± 0.12; \( P < 0.001 \)). \( nRI \) from the left leg and head did not change significantly with age and in the carotid artery, is higher in female than male (0.16 ± 0.11 vs. 0.14 ± 0.11; \( P < 0.01 \)). Changes with age and gender of the \( nRI \) from the head and left leg are shown in Fig. 5, A and B, respectively.

**DISCUSSION**

In the present work, newly introduced noninvasive methods have been applied to determine local PWV, \( nDs \), and \( nDl \) in the carotid and femoral arteries in a population of healthy human subjects. The technique has already been validated in flexible tubes using in vitro experiments for the determination of PWV and \( nDl \) (19). However, the new techniques are applied in this work for the first time in vivo to assess the mechanical properties of arteries in a relatively large, healthy population. With the use of the lnDU-loop method, we determined local PWV, which was used with the Bramwell-Hill equation to determine local \( nDs \). We also carried out WIA noninvasively and calculated peak intensity and the \( nRI \). Changes of these parameters with age and gender were investigated in four one-half decade classes.

Local PWV in femoral artery is, on average, higher, and the \( nDs \) is lower than in the carotid artery. These dissimilarities between the two arteries were somewhat expected and can be explained taking into account their different geometry and wall composition. Femoral artery ID is, on average, larger than that of the carotid artery (7.9 ± 1.6 mm and 6.2 ± 0.7 mm, respectively; \( P < 0.001 \)). Also, content of smooth muscle in the femoral artery is higher than that in the carotid artery (18).

Our results show an increase of carotid local PWV and decrease of \( nDs \) with age. In contrast, we found that local PWV and \( nDs \) in the femoral artery do not change with age but are higher and lower in men than women, respectively. Our results are in line with those reported by Vermeersch et al. (43), who used the same population and derived local carotid and femoral \( nDs \) and local PWV using applanation tonometry and ultrasound wall tracking techniques. Other investigators (1, 3), who have studied the different behavior of elastic and muscular artery, reported that in general, elastic arteries are more affected by the aging process than the muscular one. In particular, Benetos et al. (1), studying the mechanical properties of carotid and femoral arteries in normotensive and hypertensive subjects, found that the carotid artery is a very compliant vessel in young subjects, but with age and increased blood pressure, the \( nDs \) of this artery decreases dramatically. This decrease is partially limited by the increase in diameter with age. On the other hand, they found that the femoral artery is less compliant but is not affected by either age or high blood pressure. Furthermore, Bortolotto et al. (3) compared the mechanical properties of central and peripheral arteries. In this case, the comparison was made between an old and a young group of subjects. Their findings showed that age affects the carotid but not the radial mechanical properties. Since they found that both arteries dilated with age, they concluded that at the level of the carotid artery, the increase in diameter does not compensate for the change in the elastic properties of the vessel. However, as seen in Table 1, our results indicate that the increase in diameter with age is not significant. This is most likely due to the narrow age range of our population. The causes behind the effect of age on central arteries are still not certain; elastic fibers can degenerate with age, which can lead to the dilation of the vessel, or atherosclerosis could be a key factor with the increase of age (34).

We analyzed whether including biochemical parameters (HDL cholesterol, total cholesterol, and glycemia) in the analyses would impact either the findings on gender differences or the results on the differential carotid and femoral age dependencies. Overall, inclusion of these biochemical parameters (which are heavily lifestyle influenced) did not materially affect our findings. Only the small gender difference in femoral PWV and \( nDs \) was attenuated by including HDL cholesterol in the model (as could, in part, be expected because of the known, pronounced gender difference in HDL cholesterol).

In the present work, the vessel ID has been detected by tracking the intima-lumen boundary for consistency with the mathematical formulation. This boundary may give a greater relative change in diameter compared with the media adventitia due to the assumption of wall incompressibility (42). Therefore, we expect higher values of local PWV and lower values of \( nDs \) using the outer diameter. Arterial diastolic diameter is, on average, larger in male than female in both sites (6.02 ± 0.90 mm vs. 5.52 ± 0.75 mm, \( P < 0.001 \) at the carotid; 6.74 mm ± 1.07 mm vs. 8.65 mm ± 1.29 mm, \( P < 0.001 \) at the femoral). However, significant dependence of local PWV on gender has been found only at the femoral artery. This is most likely due to the greater difference in diameter.
between male and female at this site (28% vs. 9% at the femoral and carotid arteries, respectively).

The traveling of waves in arteries implicates an exchange between the kinetic energy of the blood and the potential energy of the distending vessel wall. Therefore, changes in P, U, and D in arteries are inexorably related. Any perturbation of one of these parameters will cause a change in the other two. Since the distension of the arterial wall is linked with a change in pressure, waves can be defined as pressure-velocity waves or as diameter-velocity waves. In the present work, WIA is defined in terms of D and U for the useful noninvasive benefits. Therefore, although the reported intensity values may not have an apparent physical meaning, the noninvasive WIA is still considered a natural approach that does not contradict any of the other methods reporting intensity using P and U with different units (27, 39).

Examination of the basic mathematical formulation of invasive dl = dP/dU and noninvasive, dI = dD/dU indicated a potentially useful relationship between both techniques. Considering the relation between the changes in pressure and diameter, dl = (D/2ρc^2) dP Eq. 3 in Feng and Khir (7), it can be shown that dI = (D/2ρc^2)dD. Niki et al. (24) studied WIA at the carotid artery using the P and U traditional formulation in a population of 135 healthy subjects, with an age range of under 25 to above 65 yr. In agreement with our findings of the significant increase of local PWV with age, Niki et al. (24) found a significant increase in the stiffness parameter β with age, but the authors did not find significant changes in dl indices with age. We therefore extrapolate that dI results of the two studies are in line and believe that our results follow the theoretical prediction; the use of no significant change of dl reported by Niki et al. (24), together with our results of no significant change in D (apart from female in the last age halfdecade; Table 1) and a significant increase of PWV, all with respect to age, leads to a significant decrease in dI. Since this is the first detailed study of measurement of noninvasive dI in humans, there are no other similar results available for comparison.

Traditional WIA has already been used to determine the ratio of the reflected wave to that of the incident wave energy (9, 21) as an indicator of reflection. In our study, we termed the ratio of peak intensity of the reflected wave to that of the forward compression wave as the _RI_. The _RI_ carries a similar physical meaning to that of the well-established reflection coefficient. The latter provides a theoretical measure of the local reflection (at a single mismatched bifurcation, for example) and is calculated as the ratio of the local reflected to the incident pressure; however, the former gives an estimation of the accumulative reflected intensities (from several mismatched discontinuities, for example) arriving back to the measurement site. _RI_ can therefore give information about the peripheral arteries downstream of the measurement site. Our results show that _RI_ in the left femoral artery, indicating reflections from the left leg, is higher than in the carotid, indicating wave reflections from the head (0.22 ± 0.14 vs. 0.15 ± 0.12, respectively; _P_ < 0.001). This difference is most likely due to the different geometry of the bifurcations that the incident wave encounters along its path and the different mechanical properties of the vessel downstream. We did not find any significant change of this parameter with age.

Methodological Considerations

Several methods to assess local PWV noninvasively in human have been developed over the years. Some methods require either a linear relationship between brachial pressure waveform or the diameter waveform at the measurement site (8, 23, 32, 38). Some other methods convert the diameter waveform of a local superficial artery into the local pressure waveform by calibrating the former using systolic blood pressure, diastolic blood pressure, or MAP at the brachial artery (26, 43). The lnDU-loop method does not make any assumptions about the relation between pressure and diameter, and it does not require the measurement of the pressure waveform or its systolic, diastolic, or mean value to calibrate the diameter waveform of another artery. The main advantage of the new technique is that it is based only on D and U measurements that can easily be recorded noninvasively in the clinical environment with an ultrasound system.

The lnDU-loop and the _I_ methods provide an integrated analytical system that allows for the noninvasive assessment of local PWV and intensity in any location along the arterial tree. Moreover, diameter, velocity, and intensity waveforms can be separated into the forward and backward components to study the propagation of wave and obtain useful hemodynamic information about the downstream events, for example, from the arrival time of reflected waves.

Limitations

Although the theoretical basis of WIA requires simultaneous acquisition of the D and U waveforms, the measurements of this work were recorded sequentially. D and U were aligned by using the peak of the R-wave of ECG in similar HR beats. Furthermore, the interval time between the two recordings of D and U in our subjects was very short, we could assume that hemodynamics parameters did not alter significantly.

Conclusion

In this work, we demonstrate that local PWV and _I_ can be calculated in the human carotid and femoral arteries from direct noninvasive measurements of vessel D and U. The lnDU-loop and the _I_ are potential relevant tools to assess local arterial _Ds_ and the nature of wave reflections in the clinical environment, as they can be obtained totally noninvasively. Another important feature of these methods is that relying only on D and U waveforms, it can be carried out with ultrasonographic measurements, which are nowadays easily available in clinical practice. The new techniques also allow for the separation of D, U, and noninvasive intensity waveforms into their forward and backward components, which enables the determination of the _RI_. The carotid artery is more affected by the aging process than the femoral artery, even in healthy subjects. Local PWV, _I_, and hemodynamic _I_ parameters (except _RI_) have strong correlations with age at the carotid artery. The mechanical properties and hemodynamics parameters of the femoral artery are not significantly age dependent, but local PWV, _I_, and forward _I_ are significantly gender dependent. The validation of these findings strengthens the reliability and robustness of the new proposed technique.

ACKNOWLEDGMENTS

The Asklepios Study is indebted to the residents and general practitioners of Erpe-Mere and Nieuwerkerken for their help in completing the study. A.
Borlotti holds the Isambard Research Scholarship offered by Brunel University, which the authors gratefully acknowledge.

GRANTS

Support for the Asklepios Study is provided by the Fund for Scientific Research–Flanders (FWO Research Grants G042703 and G083810N).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS


REFERENCES