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Determination of brachial artery stiffness prior to vascular access creation: reproducibility of pulse wave velocity assessment

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Abstract

Background. Despite routine ultrasound mapping of upper extremity arteries and veins, early thrombosis and nonmaturation remain frequent complications following vascular access (VA) surgery. Besides vascular diameters, brachial artery stiffness is assumed to play an important role; however, reproducibility of measurements has never been established. The purpose of this study was to determine within-session and between-session variabilities of pulse wave velocity (PWV) assessment by using ultrasonography and blood pressure registration.

Methods. Beat-to-beat changes in brachial artery diameter and pressure were obtained in 21 subjects in measurement sessions on Day 1 and Day 3. Each session consisted of three acquisitions. For each acquisition, systolic and diastolic diameter and pressure were determined and used for calculation of brachial artery PWV. Within-session variability of diameter and pressure, as well as the estimated PWV, was expressed using the intraclass correlation coefficient with corresponding coefficient of variation (CoV). Between-session variability was reported using Bland–Altman analysis in combination with CoV analysis.

Results. Significant agreement (P < 0.001) was obtained for all diameter and pressure measurements obtained on Day 1 and Day 3. Within-session CoV of pulse pressure, diastolic diameter and distension were 7.0, 1.6 and 18.3%, respectively. Subsequent estimation of local PWV resulted in a CoV of 10.6%. Between-session CoV was 15.1, 3.8 and 18.9% for pulse pressure, diastolic diameter and distension, respectively. For PWV estimation, this resulted in a CoV of 13.5%.

Conclusions. Diameter and pressure can be recorded accurately over the cardiac cycle, and calculations of distensibility, pulse pressure and PWV show a slight to moderate degree of variation. Larger studies elaborating on interindividual differences need to determine the clinical efficacy of PWV measurements prior to VA creation.

Keywords: arterial stiffness; arteriovenous fistula; duplex ultrasound; pulse wave velocity; reproducibility

Introduction

In patients with end-stage renal disease (ESRD) who require haemodialysis (HD) therapy, a well-functioning upper extremity vascular access (VA) is crucial and determines the success of treatment. Based on the reduced incidence of complications, lower management costs and decreased morbidity and mortality, an arteriovenous fistula (AVF) is the preferred VA for chronic HD compared to arteriovenous grafts and central venous catheters (CVC) [1].

In order to facilitate AVF creation in the majority of patients, a thorough preoperative vascular evaluation is advocated by both American and European guidelines in which duplex ultrasound (DUS) plays a central role [1, 2]. With DUS, diameter of upper extremity arteries and veins can be appraised that are currently the primary determinant for VA configuration in the individual patient. Although diameter thresholds are believed to be of great importance for the short- and long-term success of the VAs, early postoperative thrombosis and nonmaturation remain a clinical problem [3]. As such, other factors should be taken into consideration in an effort to reduce the number of failing fistulas.

One of the factors assumed to play a role in postoperative flow enhancement is vascular stiffness: more compliant vessels result in a larger post-operative dilatation with subsequent flow enhancement. Unfortunately, only few studies have addressed the relevancy of measuring local vascular mechanical properties prior to AVF creation [4–6]. Quantification of venous compliance was attempted by Planken et al. [4]; however, the substantial intraindividual variation of venous diameter over time hampered implementation of routine venous compliance measurements prior to AVF surgery. Arterial mechanical properties have been investigated in patients awaiting VA creation as well [5, 6]. Although these studies emphasize the potential benefit of measuring brachial artery stiffness, issues regarding reproducibility and intraindividual variation are not addressed.
Reproducibility of brachial PWV assessment

The purpose of the present study was to assess within-session and between-session variabilities of non-invasive brachial artery stiffness measurements by estimation of the local velocity of the pressure pulse (pulse wave velocity, PWV) [7]. To this end, beat-to-beat variation in brachial artery diameter, pressure and PWV are obtained in a heterogeneous population and investigated for their reproducibility.

Materials and methods

The current study was performed as part of the ‘patient-specific image-based computational modelling for improvement of short- and long-term outcome of vascular access in patients on haemodialysis therapy’ (ARCH Project, which is a 7th Framework European collaborative project with the aim to develop predictive tools and methodologies to aid clinical decision making and to improve the success after AVF creation (ARCH Project, ICT-224390).

Study design and demographics

For this prospective observational study, a heterogeneous target population was obtained by recruiting healthy volunteers without any known cardiovascular risk factors (hypertension, diabetes mellitus and hypercholesterolaemia) and patients with ESRD awaiting their first VA creation from October 2010 to January 2011. Prior to enrollment, all subjects were subjected to a short duplex assessment of the brachial artery to rule out a variation in anatomy, for instance, a high brachial bifurcation. A total of 21 subjects participated, 12 healthy volunteers and 9 patients. Demographical and clinical factors of these subjects are listed in Table 1. The institutional ethics committee approved the study. Written informed consent was obtained from all subjects prior to enrollment.

Experimental setup

In order to evaluate variability of PWV, accurate and reproducible measurements of diameter and pressure in both the systolic and diastolic phases of the cardiac cycle are mandatory. In the study population, all measurements were performed between 7:30 am and 12:00 pm in a temperature-controlled room (range 21–23°C). Every participant was subjected to two measurement sessions (Day 1 and Day 2), each consisting of three acquisitions. Before each session, subjects were instructed to fast and abstain from exercise, nicotine, caffeine and alcohol in the 12 h preceding the examination. Subjects were placed in the supine position with the arm next to the body at heart level. Total session time was 30 min including patient preparation, acclimatization and image acquisition.

Patient preparation consisted of the following: firstly, a three-lead electrocardiogram (ECG) was connected to the patient in order to obtain information on the cardiac cycle. Secondly, a Nexfin device (BMEYE, Amsterdam, The Netherlands) was used to noninvasively obtain beat-to-beat brachial artery pressure. Thirdly, brachial artery diameter measurements were performed 5-cm proximal of the elbow fold with a MyLab70 ultrasound scanner (ESAOTE Europe, Maastricht, The Netherlands) equipped with a 23-mm linear multi-frequency probe (5–13 MHz) set at a frequency of 13 MHz. All measurements were performed in a longitudinal plane using B-mode and were done by the same physician (A.B.), yielding a six-second registration at 60 frames/s. Using ART.LAB software (ESAOTE Europe, 2010), diameters were determined in a selected region of interest of 12 mm in width (= footprint). Care was taken to visualize a straight segment for measurement and to avoid compression of the vessel. ECG and blood pressure registrations were directly transferred into the ultrasound scanner and simultaneously stored in a file together with the diameter measurements (LOG-file).

Data analysis

The LOG-files were analysed using an in-house written Matlab script (Mathworks Inc., MA), which was capable of composing a diameter and pressure waveform for each cardiac cycle, together with corresponding absolute values for maximum, minimum and mean pressure and diameter. In Figure 1, the flowchart from acquisition to data analysis is schematically visualized.

To determine within-session and between-session variabilities of brachial artery PWV estimation, maximum, minimum and mean pressure and diameter were calculated for every acquisition (Session 1: three acquisitions and Session 2: three acquisitions). Firstly, pressure and diameter measurements were analyzed for their variability. Subsequently, the obtained pressure and diameter data were used for calculation of PWV by making use of the following formula [8, 9]:

\[
PWV = \sqrt{\frac{D^2 - Dp}{\rho \cdot (2 \cdot D - AD + dAP)}}
\]

where \(D\) is diastolic diameter; \(AD\), distension; \(Dp\), pulse pressure; \(\rho\), density of blood (1055 kg/m³).

The present study was initiated to investigate the reproducibility of the measurement method and was therefore not designed, or powered, to detect differences in the measured parameters between healthy volunteers and patients with ESRD. Nonetheless, in order to exclude the presence of a measurement bias, a subgroup analysis (independent samples Mann–Whitney U-test) was performed to see whether the obtained data sets from healthy volunteers and patients with ESRD allowed for data pooling prior to further statistical assessment.

Statistical analysis

To assess within-session variability of brachial artery diameter, pressure and PWV, the intraclass correlation coefficients (ICC) for average measures and absolute agreement were calculated, together with the coefficient of variation (CoV). ICC values range between 0 and 1, with values approaching 1 indicating stronger agreement between measurements. Within-session variability in pressure, diameter and calculated PWV was visualized with Bland–Altman plots [10], with the bias expressed as the mean difference and reproducibility of the obtained measurements expressed by 2 SDs (95% confidence interval). Correlation coefficients were acquired by linear regression analysis. Statistical analyses were performed using SPSS (version 15.0, SPSS Inc., Chicago, IL). Differences were considered statistically significant if \(P < 0.05\).

Results

All measurements were performed successfully and resulted in a total of 126 files for analysis (21 subjects, six LOG-files each). During post-processing of these data sets, four LOG-files appeared to be of nondiagnostic quality due to subject movement and were therefore excluded from further analysis. In these subjects \((N = 4)\), session variability was calculated using at least two measurements. There were no significant differences in the within-session and between-session PWV CoV between healthy volunteers and patients with ESRD \([P = 0.570\ (Day\ 1), 0.177\ (Day\ 3)\], respectively\), and therefore allowed the pooling of the data for the subsequent

### Table 1. Demographical data of participants

<table>
<thead>
<tr>
<th>Total population</th>
<th>Healthy volunteers</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>21</td>
<td>12 (57%)</td>
</tr>
<tr>
<td>Age (±SD), years</td>
<td>44 (±25.6)</td>
<td>24 (±2.6)</td>
</tr>
<tr>
<td>Male participants</td>
<td>13/21 (62%)</td>
<td>5/12 (42%)</td>
</tr>
<tr>
<td>Length (±SD), cm</td>
<td>173 (±8.8)</td>
<td>171 (±8.5)</td>
</tr>
<tr>
<td>Weight (±SD), kg</td>
<td>73 (±17.7)</td>
<td>65 (±9.0)</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>6/29 (22.4%)</td>
<td>2 (11.1%)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>4 (19)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>9 (43)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>MDRD (±SD), ml/min</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Estimation of the glomerular filtration rate by using the Modification of Diet in Renal Disease (MDRD) formula. NA, not applicable.
statistical analyses on reproducibility of the measurement method. Furthermore, there were no significant differences in mean systolic, diastolic and pulse pressure as well as in systolic and diastolic diameter (Table 2).

Reproducibility of diameter and pressure

Within-session ICCs for pressure and diameter measurements are displayed in Table 3, together with their corresponding CoV: in both sessions, significant agreement between measurements is obtained ($P < 0.001$). In Table 4, results are listed of the analysis of variation for all individual subjects. Average CoV on the group level on Day 1 for pulse pressure, diastolic diameter and distension were 7.0, 1.6 and 18.3%, respectively. Similar values were obtained regarding the variation of pressure and diameter measurements on Day 3: 5.8, 1.5 and 17.1%, respectively (source data not shown).

Between-session variability of systolic and diastolic brachial artery diameter as well as distension yielded a mean variation of 0.12 ($\pm 0.26$), 0.12 ($\pm 0.26$) and 0.001 ($\pm 0.051$) mm, respectively, resulting in the CoV of 3.6, 3.8 and 18.9%, respectively. For systolic, diastolic and pulse pressure measurements, the mean variation was 9.49 ($\pm 20.24$), 3.13 ($\pm 14.12$) and 6.43 ($\pm 14.91$) mmHg, respectively, resulting in the CoV of 9.3, 11.0 and 15.1% (Figures 2 and 3).

Arterial stiffness

PWV calculation demonstrates an ICC agreement of 0.919 and 0.894 on Days 1 and 3, respectively (Table 3). Table 4 shows the individual CoV of PWV calculation: mean CoV regarding PWV calculation on Day 1 is 10.6%. Similar analysis for Day 3 resulted in a CoV of 10.4% (source data not shown).
## Table 2. Average pressure and diameter measurements

<table>
<thead>
<tr>
<th>Measurement moment</th>
<th>Day 1</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diastolic pressure (SE), mmHg</td>
<td>Systolic pressure (SE), mmHg</td>
</tr>
<tr>
<td></td>
<td>60.4 (2.71)</td>
<td>121.8 (6.84)</td>
</tr>
<tr>
<td></td>
<td>62.8 (2.92)</td>
<td>125.3 (6.82)</td>
</tr>
<tr>
<td></td>
<td>63.5 (2.54)</td>
<td>126.2 (6.50)</td>
</tr>
</tbody>
</table>

Day 1

1. 60.4 (2.71)
2. 62.8 (2.92)
3. 63.5 (2.54)

Day 3

4. 60.0 (3.02)
5. 60.7 (2.59)
6. 62.0 (2.85)

P-value: 0.134

CI, confidence interval.

*Wilks’-Lambda (multivariate test).

## Table 3. CoV and ICC of the measurements obtained in a single session

<table>
<thead>
<tr>
<th>Subject</th>
<th>Pulse pressure</th>
<th>Diastolic diameter</th>
<th>Distension</th>
<th>PWV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average (±SD)</td>
<td>CoV (%)</td>
<td>Average (±SD)</td>
<td>CoV (%)</td>
</tr>
<tr>
<td>1</td>
<td>75 (±0.1)</td>
<td>0</td>
<td>5.28 (±0.06)</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>123 (±2.1)</td>
<td>2</td>
<td>5.23 (±0.03)</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>80 (±12.6)</td>
<td>16</td>
<td>4.63 (±0.04)</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>65 (±3.9)</td>
<td>6</td>
<td>4.11 (±0.01)</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>61 (±2.9)</td>
<td>4</td>
<td>4.11 (±0.13)</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>44 (±4.9)</td>
<td>11</td>
<td>5.25 (±0.02)</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>78 (±2.8)</td>
<td>4</td>
<td>4.55 (±0.06)</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>88 (±4.4)</td>
<td>5</td>
<td>5.14 (±0.05)</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>42 (±0.6)</td>
<td>1</td>
<td>5.45 (±0.04)</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>63 (±5.1)</td>
<td>8</td>
<td>4.32 (±0.03)</td>
<td>1</td>
</tr>
<tr>
<td>11</td>
<td>39 (±2.4)</td>
<td>6</td>
<td>3.24 (±0.03)</td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>62 (±1.0)</td>
<td>2</td>
<td>3.26 (±0.06)</td>
<td>2</td>
</tr>
<tr>
<td>13</td>
<td>52 (±1.8)</td>
<td>4</td>
<td>4.28 (±0.17)</td>
<td>4</td>
</tr>
<tr>
<td>14</td>
<td>56 (±5.7)</td>
<td>10</td>
<td>3.28 (±0.11)</td>
<td>3</td>
</tr>
<tr>
<td>15</td>
<td>50 (±10.4)</td>
<td>21</td>
<td>3.96 (±0.09)</td>
<td>2</td>
</tr>
<tr>
<td>16</td>
<td>69 (±6.9)</td>
<td>10</td>
<td>4.18 (±0.12)</td>
<td>3</td>
</tr>
<tr>
<td>17</td>
<td>50 (±2.7)</td>
<td>5</td>
<td>3.98 (±0.05)</td>
<td>1</td>
</tr>
<tr>
<td>18</td>
<td>57 (±2.3)</td>
<td>4</td>
<td>2.97 (±0.08)</td>
<td>3</td>
</tr>
<tr>
<td>19</td>
<td>34 (±3.6)</td>
<td>11</td>
<td>3.13 (±0.04)</td>
<td>1</td>
</tr>
<tr>
<td>20</td>
<td>47 (±2.4)</td>
<td>5</td>
<td>2.83 (±0.03)</td>
<td>1</td>
</tr>
<tr>
<td>21</td>
<td>46 (±5.7)</td>
<td>13</td>
<td>3.03 (±0.06)</td>
<td>2</td>
</tr>
</tbody>
</table>

Average (%): 7.0

1.6

Average (±SD) 18.3

10.6

CI, confidence interval.

*P-value < 0.001.
Between-session variability of PWV measurements shows a higher degree of variation, as is evidenced by the linear regression and Bland–Altman analysis (Figure 4). Mean variation of PWV between Day 1 and Day 3 was 0.21 (±2.62) m/s, resulting in a CoV of 13.5%. Pearson correlation analysis revealed that variation in distension has the largest impact on PWV variation (Table 5).

**Discussion**

In the current study, we present within-session and between-session variabilities of brachial artery diameter and pressure measurements that are subsequently used for the estimation of local arterial stiffness by calculating PWV. Although within-session variability of systolic, diastolic and mean diameter as well as pressure showed relatively low CoV and good ICC values, within-session variability of PWV is slightly larger when these measurements are used for its calculation: there is an effect from diameter variability but also from pressure variability in the calculation of PWV. Reproducibility of measurements over time showed to be more susceptible to intraindividual variation: here, we report between-session CoV for systolic, diastolic and distension of 3.6, 3.8 and 18.9%, respectively. For systolic, diastolic and pulse pressure, larger CoV were
Reproducibility of brachial PWV assessment

![Graph showing mean pulse wave velocity](image)

**Table 5.** Correlation between the variation in PWV and variations of the measured values

<table>
<thead>
<tr>
<th>Day</th>
<th>Correlation Coefficient</th>
<th>Variation in PWV vs. Pulse Pressure</th>
<th>Variation in PWV vs. Diastolic Diameter</th>
<th>Variation in PWV vs. Distension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>0.496*</td>
<td>0.344</td>
<td>0.895**</td>
<td></td>
</tr>
<tr>
<td>Day 3</td>
<td>0.384</td>
<td>-0.162</td>
<td>0.935**</td>
<td>0.647**</td>
</tr>
<tr>
<td>Total</td>
<td>0.385</td>
<td>0.040</td>
<td>0.647**</td>
<td></td>
</tr>
</tbody>
</table>

*Correlation significant at α: 0.05 level. **Correlation significant at α: 0.01 level.

9.3, 11.0 and 15.1%, respectively. Ultimately, for PWV calculation, this results in a CoV of 13.5%.

Arterial stiffness parameters can be measured using a variety of techniques [11, 12]. According to the Expert Consensus Document [7], quantification of aortic-femoral PWV is considered the ‘gold standard’ measurement for determination of arterial stiffness given the simple, noninvasive and reproducible method. More importantly, when measured over the aortic-femoral tract, it provides a patient-specific risk estimation for cardiovascular mortality [12–16]. However, this predictive power cannot readily be translated to arteries outside the aortic tract because of a profound heterogeneity in the molecular, cellular and histological structure of the arterial vascular tree [16]. Therefore, only a limited number of studies exist which elaborate on determination of local arterial stiffness [16–20]. Nevertheless, these studies emphasize that measurement of local arterial stiffness might have a predictive value in the development of cerebral ischaemia and peripheral arterial disease when measured in the carotid and femoral arteries, respectively.

In patients awaiting VA creation, arterial stiffness might play a role in fistula maturation as well: increased vascular stiffness hampers post-operative dilatation of the inflow artery, thereby limiting flow enhancement and increasing the risk of fistula failure [5, 6]. In an attempt to identify patients with an increased risk for fistula failure, Malovrh [5] investigated the resistance index (RI) at reactive hyperaemia (RH) as a prognostic parameter and concluded that an RI at RH > 0.7 was associated with an increased risk of fistula failure. The recent study of Kheda et al. concluded that patients showing nonmaturation generally had a lower small artery elasticity index compared to patients with matured fistulas. Remarkably, no significant difference between large artery elasticity index could be identified [6].

The acquisition technique used in our study consists of longitudinal echo tracking of the brachial artery lumen with simultaneous ECG and pressure registration. This technique, first described by Brands et al. [21], is well validated for determination of arterial stiffness parameters in the carotid artery but has never been utilized in other vascular beds. Although systolic, diastolic and mean brachial artery diameter and pressure measurements showed good reproducibility, both within-session and between-session variabilities of PWV measurements were significantly larger. This might be due to the relatively large variation in distension and pulse pressure values, derived from the raw acquisition. A possible explanation for this variation might be found in the presence of heart rate variability, resulting in differences in stroke volume, thereby affecting beat-to-beat variability in distension and pulse pressure.

The CoV for distension measurements reported in this study is larger than the one established by Brands et al. [21]. This discrepancy is most likely induced by the substantially smaller diameter of the brachial artery compared to the carotid artery, being closer to the resolution of the wall tracking algorithm of the ultrasound system. In an effort to reduce the variability in PWV estimation, the use of high frame rate B-mode (fast-B-mode, FBM) instead of B-mode ultrasound could be considered. FBM uses phase information of the echo signal for tracking the wall more accurately and, consequently, allows to obtain more functional characteristics of the arterial wall (e.g. perpendicular vessel wall velocity during systole).

For acquisition of systolic, diastolic and mean brachial artery pressure, we used the BMEye NexFin device, which is able to produce a continuous pressure waveform on a beat-to-beat basis. This approach might be superior to the technique used by Simova et al. [20], who used incident upper arm blood pressure measurements for the calculation of the stiffness parameters. We believe that detection of beat-to-beat fluctuations in blood pressure results in more accurate estimation of PWV and therefore, our study was able to provide an acceptable CoV regarding brachial artery PWV measurements using a single observer.
As a limitation of this study, we should point out the lack of an interobserver comparison of the obtained measurements. However, given the fact that this issue has been satisfactorily addressed by previous studies using similar echo-tracking techniques [22, 23], in combination with the simple nature of experimental setup and its measurements, it was deemed unnecessary. As a further limitation of this study, one might consider the pressure registration using a finger cuff. Though not measured at the exact same location as the ultrasound acquisition, the extrapolation algorithm for finger-to-brachial pressure in the Nexfin system is well validated [24]. Moreover, this method is considered noninvasive and facilitates acquisition of the complete pressure waveform, in contrast to earlier performed studies in which pressure registration was performed once per session or in limited intervals.

In conclusion, we investigated the reproducibility of brachial artery diameter and pressure acquisitions, as well as the reproducibility of PWV estimation in healthy volunteers and patients with ESRD. Both diameter and pressure can be recorded accurately over the cardiac cycle, and calculations of distensibility, pulse pressure and PWV show a slight to moderate degree of variation. Interindividual differences, as well as the relation between preoperative PWV and post-operative flow enhancement, determine the clinical efficacy of preoperative PWV measurements, being susceptible to a CoV of 13%. These issues are currently being investigated.

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Conflict of interest statement. None declared.

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