Reproducibility of derived central arterial waveforms in patients with chronic renal failure

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ABSTRACT

Arterial stiffness potently predicts mortality in dialysis patients. Pulse-wave analysis permits the non-invasive assessment of indices of arterial stiffness and the central pressure waveform by applanation tonometry. The aim of this study was to assess the reproducibility of pulse-wave analysis in patients with chronic renal failure. A total of 188 subjects (23 healthy controls, along with 71 pre-dialysis, 67 dialysis and 27 transplant patients) took part. Duplicate measurements were recorded of brachial blood pressure using the semi-automated Omron 705 device and of the radial artery pressure waveform using applanation tonometry. The central pressure aortic waveform was then obtained by application of a transfer function incorporated into the SphygmoCor software. Central aortic mean blood pressure (MBP), indices of arterial stiffness [augmentation index (AIx) and time to reflection (TR)] and the subendocardial viability ratio (SEVR) were analysed for intra-observer, inter-observer and long-term reproducibility using Bland–Altman plots. The mean (± S.D.) intra-observer difference was 0 ± 4% for AIx, 0 ± 20 ms for TR, 0 ± 3 mmHg for aortic MBP and 0 ± 18% for the SEVR. Inter-observer mean differences were 0 ± 3% for AIx, 1 ± 7 ms for TR, 1 ± 4 mmHg for aortic MBP and 1 ± 9% for the SEVR. For the long-term study, the mean differences were −1 ± 9% for AIx, −2 ± 13 mmHg for aortic MBP, −2 ± 12 ms for TR and 1 ± 29% for the SEVR. Pulse-wave analysis showed excellent reproducibility in all the studies, and is therefore suitable for use in all patients with chronic renal failure. Further prospective and interventional studies are now required to assess whether AIx and TR are important prognostic indices of cardiovascular events, and therefore relevant surrogate indices of arterial stiffness in this susceptible population.

INTRODUCTION

Increased conduit artery stiffness results in increased pulse-wave velocity, impaired damping of the pulse and earlier wave reflection, and is a potent predictor of mortality in patients undergoing haemodialysis [1].

Peripheral pulse pressure, obtained from the brachial artery using conventional sphygmomanometry, has been used successfully as an indirect measurement of arterial stiffness correlating with cardiovascular mortality in both healthy and hypertensive humans [2,3]. However, this is based on the assumption that peripheral blood pressure (BP) is an accurate surrogate for central BP and therefore represents the workload that is ‘seen’ by the heart. Whereas diastolic BP and mean BP (MBP) remain relatively constant throughout the arterial tree, systolic and pulse pressures do not [4,5], and therefore peripheral BP may not accurately reflect the actual aortic pulse

Key words: arterial stiffness, chronic renal failure, pulse-wave analysis, reproducibility.
Abbreviations: AIx, augmentation index; BP, blood pressure; CRF, chronic renal failure; ESRD, end-stage renal disease; MBP, mean blood pressure; SEVR, subendocardial viability ratio; TR, time to reflection.
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pressure and hence cardiovascular risk. Furthermore, measurement of systolic and diastolic BP alone gives no information on changes in pressure in relation to time within each cardiac cycle. The clinical significance of this results from the timing of wave reflections, which is determined by the interaction of left ventricular ejection, arterial length and compliance. When wave reflections arrive early, this occurs during systole, thereby augmenting central systolic BP, an adverse effect; however, when they arrive later in diastole, they boost myocardial perfusion, a beneficial effect [6,7].

Pulse-wave analysis employs the technique of applanation tonometry to obtain a peripheral pulse pressure waveform, from which central haemodynamic data are derived by application of a transfer function built into the SphygmoCor (PWV Medical, Sydney, Australia). Measurements obtained from pulse-wave analysis have been shown to be reproducible both in healthy subjects and in patients with known cardiovascular risk factors [8–10]. Indeed, studies using pulse-wave analysis on both haemodialysis patients and those with diabetes, itself the leading cause of end-stage renal disease (ESRD) [11], have already been published [12,13]. However, apart from a small study on six hospitalized haemodialysis patients that assessed intra-observer reproducibility [12], there is a paucity of data confirming that, in patients with chronic renal failure (CRF), pulse-wave analysis is a reliable, robust technique that can be used confidently for prospective longitudinal clinical studies. Pulse-wave velocity (another surrogate marker of arterial stiffness), as measured using the previously validated Complior automated device [14], has been shown to be a suitable endpoint in a large intervention study of patients with essential hypertension [15].

Thus the aim of the present study was to assess long-term as well intra- and inter-observer reproducibility using pulse-wave analysis in patients with mild-to-moderate CRF, those on maintenance dialysis and those with a kidney transplant.

**METHODS**

**Subjects**

All subjects were recruited from the Department of Renal Medicine at Southmead Hospital, Bristol. The Local Research Ethics Committee granted ethical approval, and each subject gave informed verbal consent. A total of 188 subjects (108 male and 80 female) took part in the study, with a mean age of 56.1 ± 15 years. The group consisted of control subjects who were volunteer staff (n = 23), pre-dialysis patients (creatinine: mean, 321 ± 215 μmol/l; range, 77–116 μmol/l) (n = 71), patients undergoing maintenance dialysis (n = 67) and patients with a renal transplant (n = 27). For the intra-observer study, all subjects took part, and 35 subjects participated in the longer inter-observer study (18 males and 17 females), of which 11 were controls and 24 were patients. A further study on reproducibility over a 3-month period was conducted on 31 stable transplant patients (20 men and 11 women; mean age 46.2 ± 11.1 years).

**Peripheral BP**

Peripheral BP was recorded from the brachial artery and from the non-fistula arm where applicable, using a semi-automated oscillometric device (Omron 705 CP; Omron, Tokyo, Japan) which has been validated previously [16]. Measurements were made in duplicate in accordance with British Hypertension Society guidelines [17], and the mean of two stable measurements was recorded.

**Pulse-wave analysis**

The non-invasive technique of applanation tonometry to obtain pulse-wave analysis involved partially flattening the artery with a pencil-shaped tonometer containing a high-fidelity micromanometer (SPC-301; Millar Instruments, Houston, TX, U.S.A.) for periods long enough to obtain a good signal for a minimum of two recordings of 11 s each. Data were collected directly into a portable microcomputer equipped with SphygmoCor software (SCOR MM3; PWV Medical). After a minimum of 20 sequential waveforms had been acquired, the integral software was used to generate an averaged peripheral and corresponding central waveform (Figure 1) and aortic systolic, diastolic, mean and pulse pressures were derived using a validated mathematical transfer function [18–21].
Agreement of this mathematical transfer function with direct micrometer recordings of central pressure in the SphygmoCor has been confirmed in 15533 reports on 1604 patients by its developers [22].

The parameters studied for reproducibility were augmentation index (AIx), aortic MBP, time to reflection (TR) and the subendocardial viability ratio (SEVR). These were chosen as they are expected to be clinically useful (Figure 1). The AIx is the difference in height between the derived central systolic peaks expressed as a percentage of the pulse pressure. This shows the proportion of central systolic BP caused by early wave reflection, and is considered to be an index of the reflective properties of the vasculature and of pulse-wave velocity. The TR is measured from the foot of the central waveform to the first systolic shoulder (inflection point), and represents the composite travel time of the pulse wave to the periphery and its return [6]. It is therefore enhanced by increasing pulse-wave velocity, and is a further index of conduit artery stiffness. Lastly, the SEVR, which is the ratio of diastolic pressure time interval/systolic pressure time interval, is a sensitive measurement of the adequacy of subendocardial muscle perfusion in response to myocardial oxygen demand [23].

In the present study the radial artery was used in preference to the carotid artery, as it is easier to stabilize the artery on the underlying bone, is more comfortable for the subjects and precludes the adverse effects of inspiration and expiration on obtaining good-quality signals. All measurements were made in duplicate.

Protocol
All patients were studied during a visit to the Renal Outpatients Department; haemodialysis patients were studied on a non-dialysis day. Each subject lay supine for 5 min in a quiet room before BP recordings were taken. The arm used for pulse-wave analysis was extended, with the palm turned upwards, and positioned on a pillow for comfort and stability. The tonometer was then placed over the radial artery and positioned carefully where the pulse was most evident, and the signal of the pulse pressure waveform was recorded directly on to the attached SphygmoCor laptop computer. When a good-quality recording was obtained, data capture was stopped and the recording was saved.

The protocols for both intra- and inter-observer studies were the same as those used by the authors of a previous publication using the SphygmoCor [8]. For the intra-observer study, a single investigator took two measurements on the same subject, with a 2 min interval between the two measurements. For the inter-observer study, two investigators took two measurements each on two occasions, in random order. For the long-term reproducibility study, two measurements were recorded on two occasions with a time interval of between 2 and 16 weeks (median 7 weeks).

Analysis
All data were analysed as mean ± S.D. As the normal physiological range for AIx is from negative to positive values, the use of the coefficient of variance is inappropriate. Therefore the Bland–Altman method [24] was used for limits for agreement with respect to AIx, aortic MBP, TR and the SEVR. The mean of the dependent variable is plotted against the difference in mean, and limits of agreement are within 2 S.D. of the difference in means.

RESULTS

Intra-observer study
The means for pooled data for the whole study group (n = 188) are presented in Table 1. The differences in mean values are shown as Bland–Altman plots in Figure 2. The mean intra-observer difference was 0 ± 4% for AIx, 0 ± 20 ms for TR, 0 ± 3 mmHg for central aortic MBP and 0 ± 18% for the SEVR. Figure 2 shows the Bland–Altman plots for the individual data points. As can be seen, in each graph most of the data points fall well within 2 S.D., and reproducibility does not appear to be dependent on the underlying mean value. For both AIx and the SEVR there were six observations (3%) that fell outside 2 S.D., for TR there were three (2%) and for central aortic MBP there were eight (4%).

Inter-observer study
The mean ± S.D. pooled data for this group of observations (n = 35) were as follows: AIx, 20 ± 15% (range −13% to 57%); TR, 140 ± 11 ms (range 121–177 ms); central aortic MBP, 100 ± 13 mmHg (range 76–132 mmHg); SEVR, 157 ± 35% (range 66–231%). Inter-observer mean differences were 0 ± 3% for AIx, 1 ± 7 ms for TR, 1 ± 4 mmHg for central aortic MBP and 1 ± 9% for the SEVR. One observation only (3%) for both AIx and the SEVR, and two (5%) for both TR and central aortic MBP, lay outside 2 S.D. Figure 3 displays the Bland–Altman plots for these data, and shows that reproducibility was not dependent on the mean value.

Long-term reproducibility study
The pooled means were: AIx, 19 ± 14% (range −10% to 46%); TR, 142 ± 15 ms (range 125–200 ms); aortic MBP,

Table 1 Intra-observer results (n = 188)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± S.D.</th>
<th>Range</th>
</tr>
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<tbody>
<tr>
<td>Aortic MBP (mmHg)</td>
<td>104 ± 15</td>
<td>69–147</td>
</tr>
<tr>
<td>AIx (%)</td>
<td>23 ± 15</td>
<td>−21 to 59</td>
</tr>
<tr>
<td>TR (ms)</td>
<td>138 ± 12</td>
<td>100–186</td>
</tr>
<tr>
<td>SEVR (%)</td>
<td>158 ± 40</td>
<td>54–299</td>
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</tbody>
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Figure 2  Bland–Altman plot to show intra-observer reproducibility
Mean (± S.D.) differences \((n = 188)\) were: (A) AIx, 0.1 ± 4%; (B) TR, 0.3 ± 20 ms; (C) central aortic MBP, 0.1 ± 3 mmHg; (D) SEVR, 0.3 ± 18%.

Figure 3  Bland–Altman plot to show inter-observer reproducibility
Mean (± S.D.) differences \((n = 35)\) were: (A) AIx, 0.1 ± 3%; (B) TR, 1.3 ± 7 ms; (C) central aortic MBP, 1.2 ± 4 mmHg; (D) SEVR, 0.6 ± 9%.
**Figure 4** Bland–Altman plot to show long-term reproducibility

Mean (± S.D.) differences (n = 31) were: (A) AIx, −0.8 ± 9%; (B) TR, −1.5 ± 12 ms; (C) central aortic MBP, −2.4 ± 13 mmHg; (D) SEVR, 1.0 ± 29%.

102 ± 10 mmHg (range 78–132 mmHg); SEVR, 164 ± 33% (range 116–241%). Figure 4 shows the Bland–Altman plots of the mean differences plotted against the pooled mean values. The mean difference for AIx was −1 ± 9% and that for aortic MBP was −2 ± 13 mmHg, with two data points (6%) falling outside 2 S.D. for both parameters. For TR and the SEVR the mean differences were −2 ± 12 ms and 1 ± 29% respectively, with all but one observation (3%) lying within 2 S.D. These results are comparable with both other studies.

**DISCUSSION**

Increasing pulse pressure and surrogate indices of arterial stiffness, such as pulse-wave velocity, which reflect conduit artery changes have been consistently and strongly linked to cardiovascular morbidity and mortality in the healthy population [2], and in patients with hypertension [26], coronary heart disease [27] or ESRD [1,25,28]. Indeed, London et al. [25] have shown recently that early wave reflections (AIx) independently predict mortality in haemodialysis patients, and Guerin et al. [28] have demonstrated that a reduction in aortic pulse-wave velocity, independent of BP changes, was associated with increased survival in patients treated with angiotensin-converting enzyme inhibitors. These studies accentuate the need for further long-term intervention clinical studies assessing arterial stiffness with respect to cardiovascular risk.

Pulse-wave analysis is a portable, non-invasive, simple technique that permits assessment of aortic BP and indices of arterial stiffness. Our results showed excellent reproducibility in all three studies, with more than 95% of the variability falling within 2 S.D.s for all parameters studied, in accordance with the guidelines of the British Standards Institution [29]. Furthermore, our results concur with the results of previously reported reproducibility studies of pulse-wave analysis using the SphygmoCor [8–10]. In two of these previous studies, aortic BP was compared with peripheral BP and was found to be significantly different, suggesting that the latter is not a perfect surrogate for the former [9,10]. Moreover, when examining the difference between aortic systolic BP and peripheral systolic BP, Filipovsky et al. [10] showed an inverse correlation with age, which suggests that aortic BP is likely to be more accurate with respect to assessing cardiovascular risk. We therefore elected to also investigate the reproducibility of the derived central aortic MBP, and found it to be reliably reproducible.

The transfer function relating to the central pressure waveform has been validated in non-renal patients, but not in those with renal disease. Therefore it is theore-
tically possible that the transfer function is invalid in renal patients, especially given that vascular calcification is common [30–32]. However, the measurement of brachial BP is an accepted clinical tool in the management of CRF patients, and is equally likely to be inaccurate, and yet has known prognostic significance. Indeed, using applanation tonometry, both pulse-wave velocity and Aix have been shown to be superior predictors of both all-cause and cardiovascular mortality in haemodialysis patients compared with peripheral BP [1,25]. Furthermore, given that use of the SphygmoCor to measure central pressures has already been validated with direct arterial micromanometer pressures [22], it would be unethical to do this in CRF patients without first assessing its reproducibility non-invasively.

The aim of the present study was to investigate whether pulse-wave analysis is a simple, reproducible and robust method that will be suitable for assessing cardiovascular outcome in both longitudinal and interventional studies in patients with mild-to-moderate CRF and ESRD. Our results show that pulse-wave analysis is highly reproducible for one or more observers, and additionally for long-term assessment, and can therefore be used confidently for such studies in CRF patients. Whereas similar reproducibility studies have been carried out in patients with essential hypertension or diabetes, and in those undergoing haemodialysis, the present study is the first to confirm the validity of the method in patients with chronic renal disease of varying severity.

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