End-stage renal disease in children: management, outcomes, improvement of care
Tromp, W.F.

Citation for published version (APA):

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REPRODUCIBILITY OF PULSE WAVE VELOCITY MEASUREMENT IN CHILDREN WITH END-STAGE RENAL DISEASE

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Submitted
ABSTRACT

Background. Carotid-femoral pulse wave velocity (PWV_{cf}) is considered to be an important predictor of cardiovascular outcome in children with end-stage renal disease (ESRD). We studied the intra-observer reproducibility of the PWV_{cf} measured by SphygmoCor in children with ESRD.

Methods. PWV_{cf} was measured twice in 51 patients aged 6 -18 years with ESRD using applanation tonometry (SphygmoCor) by a single well-trained investigator during one visit. Intra-observer reproducibility was assessed by the Bland-Altman method. Limits of agreement (LoA), intraclass correlation coefficient (ICC), smallest detectable change (SDC) and coefficient of variation (CV) were calculated.

Results. Measurements in 48 children could be used for analysis. Mean PWV_{cf} in all measurements was 4.8 m/s, mean difference [95% Confidence Interval] between the repeated measurements was 0.16 [-0.01 - 0.32] m/s, the LoA were -0.91 - 1.23 m/s. Results were similar for children aged 6-10 years and for children aged 11-18 years. The ICC was 0.78, the SDC was 1.05 m/s and the CV was 5.8 %.

Conclusions. In individual children and adolescents changes in PWV_{cf} smaller than 1.05 m/s can not be distinguished from measurement error. Therefore the SphygmoCor device is not suitable to monitor changes in PWV over time in individual children with ESRD.
INTRODUCTION

Cardiovascular disease is the main cause of death in young patients with end-stage renal disease (ESRD) 1. Carotid-femoral pulse wave velocity (PWV$_{cf}$) has been shown to be an early predictor of cardiovascular mortality in studies in adults with ESRD 2. In children with ESRD, PWV measurements are used for research purposes as an indicator for cardiovascular outcome 3-6. To our knowledge this technique is not used for clinical purposes in children yet. A reliable tool for early detection of cardiovascular disease would be helpful in the clinical management of these children in order to reduce mortality.

PWV$_{cf}$ is measured non-invasively by applanation tonometry with the SphygmoCor device. This device is widely used, and reproducibility studies have been performed in adults 7,8. Recently, Frimodt-Møller et al 8 performed a reproducibility study with the SphygmoCor in adults with chronic kidney disease. The authors conclude that aortic PWV measurements with the SphygmoCor are reproducible in adults.

Until now, a careful investigation of the reproducibility of this device in children is missing. We hypothesize that the reproducibility in children may be lower than in adults. For a successful measurement the participant must be able to lie still during a 20-30 minutes’ examination which might be a challenge for young children. Also, for anatomical reasons, the placement of the tonometer at site of the artery can be more difficult in children.

Good reproducibility of the measurement is important for correct interpretation of research data. Random measurement variation can be compensated for by increasing sample sizes in clinical research. In the clinical setting, however, erroneous measurements might distort clinical treatment decisions for individual patients with respect to prevention of adverse cardiovascular outcome. Therefore, we assessed the intra-observer reproducibility of the PWV$_{cf}$ measured by SphygmoCor in children with ESRD, and compared these results with those found in other studies.

METHODS

Participants

In this study, children with ESRD were included who were treated with renal replacement therapy (RRT) in any of the 9 hospitals involved in the RICH-Q (Renal Insufficiency therapy in Children – Quality assessment and improvement) project. ESRD is defined as the situation of chronic irreversible renal injury for which RRT is necessary. RICH-Q is a multicenter cohort study that started in 2007. By registering clinical, hemodynamic and blood chemistry data and peer reviewing the results the treating physicians aim to continuously improve the quality of care. As part of RICH-Q the cardiovascular morbidity in children with ESRD was assessed by measuring the PWV$_{cf}$. The first 51 patients aged 6 years or more who were included in the RICH-Q project, participated in this reproducibility study.
Written informed consent was obtained from all participants and their parents and ethical approval has been given by the ethical review boards of all participating hospitals in the RICH-Q study.

**Measurement of PWV**

PWV$_{cf}$ was measured twice during one session using the SphygmoCor device (PWV Medical Sydney Australia). Prior to the measurements the participants took 10 minutes of rest lying supine. As part of the procedure blood pressure and heart rate were measured before start of the first PWV$_{cf}$ measurement with an automatic oscillometric device (Model MX3 Plus, Omron Matsusaka, Tokyo, Japan). PWV$_{cf}$ was determined by sequential acquisition of pressure waves from the carotid and the femoral arteries by applanation tonometry (Millar Instruments, Houston, Texas). Wave transit time (t) was calculated by the system software, using the R-wave on the simultaneously recorded ECG as reference frame. The distance traveled by the pulse wave was measured in a straight line to reduce the influence of body contours. The carotid to femoral path length (D) was defined as the distance between the recording sites at the femoral artery to the suprasternal notch minus the distance from the recording site at the carotid artery to the suprasternal notch. PWV$_{cf}$ was calculated as D/t. PWV$_{cf}$ was measured over 10 consecutive heartbeats to cover a complete respiratory cycle. The measurement was repeated at the same occasion, immediately after the first measurement. The whole procedure took around 30 minutes, depending on the cooperation of the patient.

**Quality Control**

To assure good quality of the measurements, the following rules, as described previously[8], were taken into account: 1) Visually acceptable pulse-waveforms and a mean pulse height above 80mV were required and 2) the standard deviation (SD) of the time differences between the ECG-signal and the signal from the recording sites over the 10 consecutive heartbeats should be less than 10% of the mean value.

**Statistical Analysis**

Bland-Altman plots were made to assess intra-observer reproducibility. In a Bland-Altman plot the difference between two measurements per patient is plotted against the mean of two measurements per patient. If differences are associated with mean values, a correction has to be applied. The 95% Confidence Interval (CI) of the mean difference should include zero to exclude systematic differences. The limits of agreement (LoA) (i.e. mean difference ± two times the Standard Deviation of the differences per patient) indicate the range between successive measurements in a patient without real change. Only changes greater than the LoA can be interpreted as “real” change, not due to measurement error. To investigate if there was a difference in performance of the measurement instrument between younger children and adolescents two age subgroups (6 – 10 years and 11-18 years) were analyzed separately.

Intraclass correlation coefficients (ICC), smallest detectable change (SDC) and coefficient of variation (CV) were calculated for comparison with earlier studies. These
studies used the same device in adults, or a similar device in children. The ICC is a measure of the reliability of a measurement instrument. It is calculated as a ratio of the variance of interest over the sum of the variance of interest plus error \(^2\). ANOVA is used to calculate the variance components. The ICC was calculated according to the following formula: 11

\[
\text{ICC} = \frac{\sigma_p^2}{\sigma_p^2 + \sigma_m^2 + \sigma_e^2}
\]

\(\sigma_p^2\) = variance due to patients
\(\sigma_m^2\) = variance due to measurements
\(\sigma_e^2\) = error variance

The SDC can be calculated from the error variance as:

\[
\text{SDC} = 1.96 \times \sqrt{2 \times \sqrt{\sigma_e^2}}\]

It is comparable to the LoA, and denotes the smallest change in an individual that can be interpreted as a "real" change, above measurement error. The smallest detectable change of a group is inversely related to the size of the group, n, according to the following formula:

\[
\text{SDC}_{\text{group}} = \frac{\text{SDC}}{\sqrt{n}}.
\]

The CV was calculated by the following formula:

\[
\text{CV} = \frac{\text{SD}_{\text{diff}}}{\overline{\text{grand mean}}} = \text{standard deviation of the mean difference between several measurements in one individual}
\]

\(\overline{\text{grand mean}} = \text{mean of all measurements in all individuals}\)

All analyses were performed using SPSS 16.2.

RESULTS

Patients
51 children with ESRD, median (range) age 14 (6-18) years, 69 % male were included in this reproducibility study. 16 children were treated with maintenance hemodialysis, 8 with peritoneal dialysis and 27 had received a kidney transplantation during the year preceding the measurement.

PWV\(_{cf}\) measurements
In three of the 51 patients the PWV\(_{cf}\) values obtained by the SphygmoCor were rejected for quality control reasons as described earlier. Results of repeated measurements suitable for analysis were obtained in 48 patients, median (range) age 12 (6-18) years, 69 % male. The median (range) duration of ESRD was 1.8 (0 -14.1) years.

Median (range) PWV\(_{cf}\) of the 48 subjects was 4.7 (2.9 – 6.7) m/s. Mean (SD) PWV\(_{cf}\) was 4.8 \pm 0.8 m/s. The mean difference [95% CI] between the repeated measurements was 0.16 [-0.01 - 0.32] m/s. The LoA were -0.91 - 1.23 m/s. The Bland-Altman plot is shown in Figure 1.
In the subgroup aged 6 - 10 years (n=16) mean (SD) PWV<sub>cf</sub> was 4.4 ± 0.6 m/s. The mean difference was 0.12 [-0.17 - 0.40] m/s, and the LoA were -0.95 - 1.19 m/s (Figure 2). The (SD) PWV<sub>cf</sub> in the subgroup aged 11 - 18 years (n=32) was 5.0 ± 0.8 m/s. The mean difference was 0.18 [-0.01 - 0.38] m/s and the LoA were -0.89 - 1.26 m/s (Figure 3).

The estimates of the variance components of the measurements are shown in Table 1. The ICC was 0.78. The SDC was 1.05 m/s, and the CV was 5.8 %.

Figure 1. Bland Altman plot of repeated SphygmoCor measurements in all 48 ESRD patients.

Figure 2. Bland Altman plot of repeated SphygmoCor measurements in 16 ESRD patients aged 6 - 10 years.
Discussion

In this reproducibility study we found that the SDC of the SphygmoCor in a pediatric population can be up to 1.05 m/s. This means that changes in an individual less than 1.05 m/s cannot be distinguished from random error. In pediatric studies the range of measurement results is small, in this study including children with ESRD PWV$_{cf}$ ranged from 2.9 to 6.7 m/s. The expected change in PWV$_{cf}$ over time in healthy children is 0.11 m/s per year$^{13}$. Consequently, a SDC of 1.05 m/s is too large to evaluate changes over time in individual children.

This does not mean that the SphygmoCor is unsuitable for use in clinical studies. The sample size can be increased so that the PWV change in the study population can be measured reliably. For instance in a study population of 100 or, alternatively, 441 children the SDC$_{group}$ is 0.11 m/s or 0.05 m/s, respectively. A mean change in PWV$_{cf}$ over time in a study population of this size can be considered “real change”, not due to random measurement variation, if it is larger than the SDC.

We compared the results of our study with data on reproducibility in childhood conditions reported in other studies (Table 2). We found only 5 papers on ESRD$^{3,5,6,13,14}$. They report CV, ‘intra-observer variability’, ‘intra-observer reproducibility’ and ‘intra-observer error’, respectively. How these last three terms were defined is not clear. For
Table 2. Comparison reproducibility studies in children.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Device / technique</th>
<th>Condition</th>
<th>n</th>
<th>Age range (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study</td>
<td>SphygmoCor</td>
<td>ESRD</td>
<td>48</td>
<td>6-18</td>
</tr>
<tr>
<td>Aoun 2010</td>
<td>SphygmoCor</td>
<td>ESRD</td>
<td>15</td>
<td>11.1±4.8* (hemodialysis)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12.9±7.4* (renal transplantation)</td>
</tr>
<tr>
<td>Cseprekal 2009 &amp; Reusz 2010</td>
<td>PulsePen</td>
<td>ESRD / Healthy</td>
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<td>6.5-19.9</td>
</tr>
<tr>
<td>Shroff 2007</td>
<td>Applanation tonometry</td>
<td>Dialysis / Healthy</td>
<td>125</td>
<td>5-18</td>
</tr>
<tr>
<td>Covic 2006</td>
<td>SphygmoCor</td>
<td>ESRD / Healthy</td>
<td>20</td>
<td>4.1 ± 2.6*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Healthy</td>
<td></td>
<td>12.7 ± 3*</td>
</tr>
</tbody>
</table>

SDC: Smallest Detectable Change; ICC: Intraclass Correlation Coefficient; CV: Coefficient of Variation *Mean ± SD; **Median (Range); ***Mean (Range); #Calculated from reported mean and CV

the clinical interpretation of the reproducibility of a device’s measurements the LoA of Bland and Altman or the SDC give more insight. We tried to estimate the LoA from the reported data in these studies. If the grand mean and CV are presented for reproducibility studies, the SD<sub>diff</sub> can be calculated, and the LoA are estimated as ± 2 SD<sub>diff</sub>, assuming a mean difference between repeated measurements of 0. Using this approach the LoA in the study by Cseprekal et al. could be estimated as ± 1.12 m/s, which is comparable with our data. Covic et al., Shroff et al. and Aoun et al. did not report the data needed for this calculation.

We also compared the results of our study to reproducibility studies with the SphygmoCor in adults. Wilkinson et al. reported LoA of ± 2.3 m/s and Frimodt-Møller et al. reported intra-observer LoA varying from ± 2.4 m/s to ± 3.9 m/s, for a more and less experienced observer, respectively. In a recent study comparing the reproducibility of the SphygmoCor with that of a new device called the Vicorder, van Leeuwen et al. reported LoA of ± 1.62 m/s and ± 4.48 m/s, respectively. Although mean PWV<sub>c</sub> values in adults are generally higher than in children, e.g. Frimodt-Møller reports a mean ± SD PWV<sub>c</sub> value of 9.9 ± 3.3 m/s, it appears that, also in adult studies, the size of this measurement error is very large.

In a reproducibility study all factors are kept constant to estimate the measurement error specifically. This is why we performed all measurements during one visit, immediately after each other, under stable conditions to make sure that none of the possible determinants of PWV in children with ESRD would be changed between the measurements. All data were generated with the use of 1 device, which was carefully checked and installed before the study to make sure no measurement errors could be due to technical problems of the
device. The observer was thoroughly trained and had substantial experience with these measurements, which may explain the favorable results compared to other studies.

We did not evaluate the inter-observer reproducibility. Yet, when intra-observer reproducibility is low, inter-observer reproducibility can be expected to be even lower. We expected that the reproducibility in the youngest children would be lower due to anatomical reasons and because the participant must be able to lie still during the examination. However, the age sub-group results do not confirm the existence of an age-related difference in measurement error. Our study was conducted in chronically ill children. The procedure and measurements might be easier in healthy children and as a result the reproducibility might be better.

In conclusion, the SphygmoCor device may be useful for longitudinal or comparative studies including sufficiently large groups of patients, but it is not suitable to monitor PWV changes over time in individual children with ESRD because the reproducibility is insufficient.

ACKNOWLEDGMENTS

This study was performed as part of the RICH-Q project, which is mainly funded by the Dutch Kidney Foundation. Additional funding was provided by Astellas, Ferring Pharmaceuticals, Genzyme, Roche, and Shire. The funder had no role in the design and conduct of the project, data gathering or interpretation, or in the preparation of the manuscript. We are grateful to all patients and the participating centers in the RICH-Q study for their support with patient enrollment and logistics of the measurements.
REFERENCE LIST


