PULSE TRANSIT TIME VALUES AND PREDICTIVE MODELS IN CHILDREN AGED 5-12 YEARS

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ABSTRACT
Increased arterial stiffening can be an indication of cardiovascular disease. Pulse wave velocity (PWV) has shown to be a direct measure of this property. However, the assessment of the elastic properties of arteries is hampered by the absence of techniques to estimate arterial pulse pressure non-invasively. Pulse transit time (PTT) is a simple and non-invasive method derived from PWV that has shown potential in cardiovascular and respiratory studies. Limited knowledge on PTT is found in the present literature, especially for children. The aim of this study was to describe prediction equations for healthy children aged 5 to 12 years. 61 children (41 male and 20 female) were studied. Predictive equations for PTT were obtained by multiple regressions with age, vascular path length, blood pressure indexes and heart rate. The derived equations were compared in their PWV equivalent against 2 previously reported equations. Significant agreement was obtained with these 2 equations ($p<0.05$). The use of PTT measurement in a clinical environment is still to realise its full potential for children. The data and prediction equations here supplement the existing limited data in childhood PTT investigation.

KEY WORDS
Biomechanics, pulse wave velocity, arterial stiffness, cardiovascular diseases, and pulse transit time

1. Introduction
The mechanical properties of large arteries play an important role in the pathogenesis of cardiovascular disease, such as hypertension [1-2]. Increased arterial stiffness with an associated increase in the amplitudes of the forward and reflected pressure waves is a major determinant of increased systolic and pulse pressure [1-3]. During childhood, it is expected that arterial elastic properties may vary with changes in arterial size, maturation of the wall structure and geometry. However, limited information is available about these age-associated changes in children [3]. Arterial stiffening can be induced by a number of known cardiovascular disease risk factors raising the possibility that increased arterial stiffness may be an indicator for atherosclerotic vascular disease [1]. It is useful to identify changes in arterial properties in normal children as a reference for earlier detection of abnormalities.

Pulse wave velocity (PWV) has shown to be a direct measure of arterial stiffness that is related to adverse clinical events [2]. However, assessment of the elastic properties of arteries is impeded by the absence of techniques to estimate arterial pulse pressure non-invasively. PWV is determined largely by the elastic property of the arterial wall. The commonly used Moens-Korteweg’s equation gives PWV in terms of the incremental Young’s modulus of the arterial wall: $\text{PWV} = \sqrt{\frac{(Eh/\rho D)}{\text{area gradient}}}$. Where $E$ is the incremental Young’s modulus, $h$ is the thickness of the arterial wall, $\rho$ the blood density and $D$ the diameter of the artery. However, this equation in practice is not convenient for non-invasive measurements as $h$ is difficult to measure unless it is in vivo and $E$ is not constant but depends on arterial pressure in the subject. Hence, the derivation of the Moens-Korteweg’s equation in most PWV studies considered the pressure gradient force only and omits the area gradient force. The area gradient force term causes the derivation of a linear wave equation to be inaccessible. Some researchers have tried to take the oscillating wall as a correction factor that results in complex equations and parameters [4]. To avoid the direct use of pulse pressure, others have measured PWV by estimating the time delay between waveforms recorded simultaneously at two positions [5].

A simple and non-invasive technique derived from the principle of PWV is termed pulse transit time (PTT) [6]. From present literature, this is defined as the interval between ventricular electrical activity and the appearance of a peripheral pulse waveform [7]. For the convenience of continuous monitoring, the R-wave of the electrocardiographic (ECG) is generally used to indicate the start of the PTT estimation [8-9]. Finger and toe are the two commonly used peripheral sites. The finger is generally used on older children and adults. However, for younger children, this can be switched between the two sites depending on the suitability of the studies and cooperation of the young child. PTT has shown its potential clinical use, like respiratory sleep studies in adults [8] and
children [9]. With the established correlation between PTT and PWV, it is possible that PTT can be regarded as a simpler alternative measure of arterial stiffness. However, scanty data is available in the present literature to understand the normality of PTT in healthy children. Hence, the objectives of this study were to (1) identify independent variables for inclusion in a PTT model for healthy children aged 5 to 12 years, (2) develop PTT prediction equations based on the model with the finger or toe as the measuring periphery and (3) evaluate the predicted values in PWV equivalent against those from other studies in similar age groups.

2. Materials and Methods

2.1. Subjects

61 children (41 male and 20 female) were recruited from the community. The number of children in each age group were 5 years \((n=9)\), 6 years \((n=9)\), 7 years \((n=9)\), 8 years \((n=9)\), 9 years \((n=6)\), 10 years \((n=8)\), 11 years \((n=10)\) and 12 years \((n=7)\). The parent and they were given the study information verbally. Only those with no clinically apparent arterial were recruited. Their mean arm and leg length were 611.6 \(\pm\) 84.1mm and 1043.9 \(\pm\) 138.7mm respectively. Mean systolic blood pressure (SBP) were 107.1 \(\pm\) 8.9mmHg, diastolic blood pressure (DBP) were 65.8 \(\pm\) 8.0mmHg, mean arterial pressure (MAP) were 80.6 \(\pm\) 8.8 mmHg and heart rate (HR) were 85.7 \(\pm\) 12.4bpm. Informed consent and institutional ethical approval were obtained for this study.

2.2. Experimental Protocol

The child was asked to rest for 5 minutes first. Measurements were performed in a typical clinical environment. PPG was measured on an index finger and then on a toe using the same PPG probe. The PPG recordings were measured in conjunction with ECG signals. Both examinations were performed for 2 minutes with the child sitting on a chair and arm resting horizontally on the chair. This sitting procedure was adopted to minimise the possible effects hydrostatic pressure has on blood pressure at the measured arm [10].

A minimum of 30 PTT measurements free from motion artefacts was obtained from each examination. After these examinations, the child was asked to relax for 1 minute. The HR, MAP, SBP and DBP were measured with an appropriate arm cuff as recommended [11]. The child was then asked to stand up for the arm and leg peripheral path length to be recorded with the sterno mammary notch as the reference. A stand-alone PTT system using a micro-controller to acquire physiologic data from a single-lead ECG (S&W Medico, Teknik, Denmark) and PPG signal from a pulse oximeter (Novametrix Medical Systems Inc, Wallingford, USA) was developed. This system has an accuracy of 1ms and its detection algorithm is given in Figure 1. SBP, DBP, MAP and HR were recorded manually from an auto-oscillometric sphygmomanometer (Dinamap, Critikon Inc, Florida, USA).

2.3. Comparisons and Statistical Modelling

There is no known PTT study conducted on children for cross comparison. Hence, all obtained PTT data were derived as an equivalent PWV based on the measured peripheral path length. PWV comparisons were made with equations derived by Avolio et al [12] and Cheung et al [13]. Each equation derived in these previous studies was used to calculate the predicted PWV values in each age group and whether the prediction was regressed linearly. Another basis for comparison was the level of agreement between the derived PWV and the predicted PWV values according to age group.

For the convenient measurement of PTT, additional delay was induced to the time taken for the pulse wave to travel from the aortic valve to the periphery. By using the ECG R-wave as the starting point, left ventricular isometric contraction time or the time delay between the R-wave and opening of the aortic valve was added to the measured PTT. Pitson et al [8] suggested this delay is approximately 160ms. In order to compensate for this intrinsic time differences between the opening of the aortic valve and measured R-wave, the method suggested by Nitzan et al [14] and Okada et al [15] was employed. This can be achieved by taking the differences in path length and transit time between the two measured peripheral sites. In this way, the intrinsic time delay can be minimised since this delay is inclusive in both the transit time measurements. Due to the complexity of the arterial route in the circulation system, this method may not fully compensate the differences. However, this was done due to the present lack of childhood PTT data.

Independent variables and their combinations thereof considered for inclusion in the models were as follows: age, age², age³, peripheral path length, peripheral path length², peripheral path length³, SBP, SBP², SBP³, DBP, DBP², DBP³, MAP, MAP², MAP³, HR, HR² and HR³. The effect of logarithmic and exponential transformations of these variables prior to modelling was also examined. In the multiple linear regression analysis, predictor variables were retained only if their addition significantly improved the fraction of explained variability. Other
aspects explored included residual standard deviation (RSD), changes in the distribution of the residuals and the homogeneity of the variance over the predictors. Statistical analysis was performed using SPSS version 10 (SPSS, North Chicago, Illinois, USA) and Microsoft Excel XP package. Two-way analysis of variance or paired Student’s t-test assuming equal variance was used to test for significant differences and correlation for the derived PWV values in this study against values predicted by the equations of others. Statistical significance was assumed to be \( p<0.05 \) here.

3. Results

From the data obtained, the normal range of PTT using finger and toe as the periphery is presented in Figure 2 and 3 (with 95% confidence interval) respectively. Linear regressive models were applied to the series by treating PTT as the dependent measure. The best fit of the data was determined by the \( r^2 \) value. Including expression of either DBP or MAP in the regression did not increase the explained variance that is the \( r^2 \) value, by more than 0.02. Furthermore, it was found that the addition of transformations did not significantly improve the predictability of the regression equations. The PTT predictive equations for finger or toe as the measuring periphery were given in Table 1.

<table>
<thead>
<tr>
<th>Periphery</th>
<th>Equations</th>
<th>( r^2 )</th>
<th>RSD</th>
</tr>
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<tbody>
<tr>
<td>Finger</td>
<td>( 0.129(age)^2 + 0.0000000933(arm)^2 - 0.000332(SBP)^2 - 0.00131(HR)^2 + 222.789 )</td>
<td>0.74</td>
<td>8.94</td>
</tr>
<tr>
<td>Toe</td>
<td>( 0.101(age)^2 + 0.0000000218(leg)^2 - 0.00304(HR)^2 + 290.073 )</td>
<td>0.65</td>
<td>12.88</td>
</tr>
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</table>

Table 1: Prediction equations for PTT using the 2 different peripheries for healthy children aged 5 to 12 years

Table 2 shows the PWV values derived from the observed PTT obtained from the children in the present study and the values calculated from 2 prediction equations. The two-way analysis of variance for significant differences and correlation showed close agreements (\( r^2=0.99 \) and \( p<0.05 \)) between the 2 PWV equations by Avolio et al [12] and Cheung et al [13]. To compare the present equations, it can be observed that the relationship regressed proportionally when the PWV values from the present study were compared with those from Cheung et al (\( r^2=0.84 \) and \( p<0.05 \)). In contrast, this relationship was not as well proportional to those from Avolio et al. However, the \( r^2 \) and \( p \) values showed that the PWV values from this study were still significantly correlated (\( r^2=0.83 \) and \( p<0.05 \)). The study conducted by Cheung et al was on a better comparison age of 6 to 18 years while Avolio et al did on a wider age range from 3 to 89years.

<table>
<thead>
<tr>
<th>Studies</th>
<th>PWV (m/s)</th>
<th>( r^2 )</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avolio</td>
<td>6.61 6.70 6.79 6.89 6.98 7.07 7.16 7.25</td>
<td>0.83</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Cheung</td>
<td>6.22 6.48 6.74 7.00 7.27 7.53 7.79 8.05</td>
<td>0.84</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Present</td>
<td>6.22 7.02 6.86 7.59 7.30 7.87 8.05 8.00</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 2: Comparison between derived PWV values and predicted values from 2 different studies

4. Discussions and Conclusions

The current study provides equations for predicting PTT values in a population of healthy children. This equation should not be extrapolated, in general, for ages beyond those covered by the data that generated them. For children of 5 to 12 years of age, the current study showed that their normal PTT values, regardless of using the finger or toe as the measuring periphery, have an incremental trend with age. The predictive values for PTT provided in this study are not widely available in the present literature. Only the previous studies by Avolio et al [13] and Cheung et al [14] can be used as a derived comparison. In contrast to the scarce reference equations for PTT, this parameter can be a potential surrogate for PWV in those situations where convenient and prolong monitoring are impractical or unwarranted, particularly on
younger or severely disturbed children. The age, arm, SBP and HR characteristics of the currently studied children have a great influence on the normal range of PTT when finger was used as the measuring periphery. All these variables except for SBP when finger was used as the measuring periphery.

Generally, prediction equations derived from cross-sectional data are primarily used as a screening tool to identify individuals beyond the expected range. The utility of any particular reference equation depends upon its ability to correctly identify individuals beyond the limits of normal. In practice, the limits are set at the results of 95% of the normal population lie, working under the assumption that larger values have larger variances. Table 2 shows the comparison between the present studies against 2 other studies. It is evident that the differences in age range or ethnicity of the sample can explain some of the differences that were observed. However, from the results obtained here, differences in the derived PWV can be considered negligible against the studies by Avolio et al [13] and Cheung et al [14].

It is acknowledged that there are some limitations to this study. The number of children recruited in each age group in this study is small and it is recognised that this study be conducted with a larger sample of children as a continual investigation. However, the comparable PWV values obtained in this study against 2 other studies with a larger sample population ascertained the findings here. Secondly, the exact definition of a "healthy" group varies which comparisons may be drawn for any future studies. The inclusion criteria for this study then become important when future investigations of similar nature were to be performed.

The values presented herein provide a framework from which comparisons may be drawn for any future studies using PTT or PWV as a measured parameter. It is hoped that these data and models will supplement the existing scanty data in childhood pulse transit times. The attraction of PTT measurement due to its non-invasive nature and revealing properties will only increase. The study of cardiovascular and respiratory disease in children using such a technique in a clinical environment is still to realise its full potential.

References:


