Normal paediatric values of arterial stiffness parameters measured by echo-tracking

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Abstract

Background: Increase in arterial stiffness (AS) has recently been recognized as a predictor of cardiovascular disease development. Aim of this study was to provide the normal range of some ultrasonographic AS indices evaluated in a paediatric population with an Echo-tracking system that accurately measures changes in arterial diameter synchronized with the ECG signal.

Method

We studied 130 healthy children, aged 3-16 years, free from cardiovascular risk factors. Echo-tracking was performed with an A10 Aloka echocardiographic machine and a linear B 8 MHz probe. The right and left common carotid arteries were approached: the common carotid bulb was identified, and the segment of the artery 2 cm proximal to the bifurcation region was scanned. A time related pressure-diameter curve of the artery was then obtained; calibration for the blood pressure permitted measurement of arterial stiffness for any given blood pressure. The following parameters were calculated: 1) Stiffness index (β); 2) Pulse wave velocity (PWVβ); 3) Elastic modulus (Ep); 4) Arterial compliance (AC). In addition, carotid artery intima-media thickness (IMT) was measured.

Results

β, PWVβ and Ep undergo a statistically significant (p<0.001) progressive age-related increase, while AC shows only a week (p<0.05) correlation with age. In contrast, no relationship between IMT and age was found.

Conclusion

In paediatric subjects, AS progressively increases with aging. The values here reported, obtained from a “normal” paediatric population, may represent a basis for detecting early AS abnormalities in children at risk for atherosclerosis and cardiovascular involvement.

Key words: Arterial stiffness, Atherosclerosis, Echo-tracking

Introduction

Arterial Stiffness (AS) and pulse wave reflection phenomenon have been recognized as determinants of systolic blood pressure and pulse wave velocity (1, 2). Studies performed in adults have demonstrated that alterations in AS parameters herald atherosclerosis, hypertension and cardiovascular CV) disease development (3-6), and show an independent predictive value for CV events in hypertension (3, 4), diabetes (coronary artery disease and renal failure) (10, 11). Although mainly affecting adults, atherosclerosis can also be demonstrated as a subclinical form in selected paediatric patients (2, 13).

Several techniques aimed at AS measurement have been proposed (14). Recently, a new ultrasonographic method, based on Echo-tracking technique, has been proposed as a valuable tool for AS evaluation. Aim of this study was to provide the normal range of some ultrasonographic AS indices, measured with this new Echo-tracking system, in a paediatric population.

Materials and Method

To evaluate arterial stiffness directly, measurements of changes in arterial diameter and pressure at the same vessel site should be performed. Recently developed non-invasive techniques aimed at evaluating arterial stiffness are based on the analysis of pulse wave configuration (15-18).

Echo-Tracking (Aloka, Japan) reconstructs a pulse wave profile from a two-dimensional (2D) vessel image using radiofrequency signals rather than video signals (2, 14, 16, 19). Two “tracking gates”, displayed as small bars on the ultrasound beam line, are placed just outside the intima-media complex, close to the edge of the adventitia side, of the near and far arterial walls.

The ultrasonic diagnostic unit receives high echo signals from the arterial walls: when the blood vessel diameter changes, the tracking gate moves following the motion of the wall. The diameter-change waveform is calculated by subtracting the distance to the near wall from that to the far wall.

The ultrasound measures arterial diameter changes at a rate of 1kHz, with a precision of 1/16 of the ultrasound wave length (0.013 mm). Internally, the tracking gate is set on the zero cross point of radiofrequency signals (time phase); the system automatically tracks the zero cross point specified by the gate on receiving the next signal, that is received in a different position. This time phase difference is converted into distance in real time, permitting the one point measurement of pulse wave velocity.

Data can be saved for 1 to 20 sec. The sphygmonomanometer-measured blood pressure data are entered, and the maximum and minimum values of the diameter-change waveform are calibrated by systolic and diastolic blood pressure.

Five consecutive beats are averaged to obtain a representative waveform, and the following arterial stiffness indices are automatically calculated.

• (Stiffness index): Ln [(Pa/Pd) / (Ds-Dd)] / Dd
• PWVβ (Pulse wave velocity): [ln(Pa/Pd) β:stiffness index; P:diastolic pressure; p: blood density (1050 Kg/m3)]
• Ep (Elastic modulus): (Ps / Pd) / [(Ds – Dd) / Dd]
• AC (Arterial compliance): (ln (Dx × Ds) – Dd x Dd) / (4 × Pa – Pd)

Stiffness index (β), resulting from the ratio of logarithm (systolic/diastolic pressures) to relative change in diameter, expresses local stiffness of the arterial wall, obtained from the relationship between vessel diameter and artery pressure values. Pulse wave velocity (PWVβ) indicates the propagation velocity of the wave (m/sec), and is dependent on stiffness index.

Elastic modulus (Ep) expresses the increase of artery pressure necessary for a (theoretical) 100% increase of vessel diameter, and is measured in kPa.

Arterial compliance (AC) expresses the vessel diameter for a given pressure, namely the relationship between pressure value and vessel volume, measured in mm²/kPa.

Population

We studied 130 healthy children, aged 3-16 years, free from cardiovascular risk factors and with a normal-for-age electrocardiogram and echocardiogram. Children with even minor conduction disturbances or arrhythmias, trivial mitral or aortic incompetence, blood pressure or body weight greater than 90° percentile for age, were excluded; subjects performing intense physical or sport activity were also excluded.

The study protocol was approved by the local ethical committee; written informed consent was obtained by parents in any case.

Examination technique

Echo-tracking was performed with a Prosound alpha-10 Aloka echocardiographic machine and a linear B 8 MHz probe. Before examination, the subjects lay down in the supine position for 10 min, and a continuous ECG trace was obtained.

The blood pressure was measured using cuffs of variable size, in relation with age; care was taken to select for any subject a cuff whose width corresponded roughly to 2/3 of the arm length. The right and left common carotid arteries were approached: the common carotid bulb was identified; in order to avoid the influence of complex flow in the carotid sinus, the segment of the artery 2 cm proximal to the bifurcation (1.5 cm for children younger than 6 years) was scanned. A time related pressure-diameter curve of the artery was then obtained; calibration for blood pressure permitted measurement of arterial stiffness, expressed by the above listed parameters (β, PWVβ, Ep, AC; Figure 1).

In addition, the intima-media thickness (IMT) was measured. In performing examinations, the ultrasonic probe was oriented according to a latero-medial, rather than antero-posterior, direction. This was because in an initial series of 12 consecutive paediatric subjects the same operator used both the antero-posterior and latero-medial approaches, obtaining results that the former resulted in values of stiffness parameters significantly higher than those obtained with the latter approach (Table I). The ultrasonographic examinations were performed by 2 experienced operators which had a training period in an adult population study.

Fifty-eight randomly selected subjects were examined independently by both investigators, during the same session, in order to calculate interobserver variability.

Statistical analysis

Children were subdivided in 14 classes according to age: class 1 (3 years), class 2 (4 years), and so on. Each class was made of 8 to 11 subjects. Mean values and standard deviations of parameters were calculated in each age class. SPSS 12.0 (SPSS Inc) was used for all descriptive and inferential statistical analyses. Pearson's analysis was used for evaluating bivariate correlations between each parameter and age.

Interobserver variability was estimated by means of Wilcoxon Matched-Pairs Signed-Ranks Test; the same was also used to compare the 2 different echographic approaches (latero-medial versus antero-posterior).

The significance level was set at p=0.01. Error bars were used for graphic display of mean plus or minus 2 standard deviations of data.

Results

Both the right and the left carotid arteries were studied in all subjects. Since no statistically significant difference was found between the 2 series of data, only the results obtained from the right carotid artery examination were used for the final analysis.

The results, expressed as mean ± 2SD, are presented in Table II and in Figure 2. Table III demonstrates that β, PWVβ and Ep undergo a statistically significant (p <0.001)
progressive age-related increase, while shows only a weak (p <0.05) correlation with age.

In contrast, no relation between IMT and age was found (Table III and Figure 2). Interobserver variability was explored in 58 subjects.

Table IV shows that no significant difference between the data obtained by the 2 operators was found.

Discussion

The reported data show that the majority of AS parameters undergo a progressive increase throughout childhood in normal subjects. This is not surprising, since the same pattern has been observed in adults (20, 21), being AS higher in elderly than in young adults.

The blood ejected from the left ventricle during systole generates, at the level of the aortic root wall, a pulse wave that is transmitted anterogradely towards the peripheral vessels. This wave is then reflected retrogradely to the aorta.

The amplitude and configuration of the pulse wave in any given point of the arterial tree depend on the relationship between the anterograde and the retrograde components. The interval between the 2 components is a function of the pulse wave velocity: whenever the arterial vessels are normally compliant, the propagation velocity of the pulse wave is low, and the reflex or retrograde component comes back from the peripheral compartment to the aorta during diastole.

When, in contrast, the vessels are stiff, as it is commonly observed both in the elderly and under pathologic conditions, the pulse wave velocity is high, and the reflex component merges with the anterograde one, resulting in increased systolic, and decreased diastolic, blood pressure.

It has been observed, however, that arterial pulse morphology in infancy is similar to that observed in elderly, being characterized by a wave peak occurring in late rather than in early systole; in addition, no secondary diastolic wave is evident in children, being wave reflection from peripheral to central vessels very early (22-25).

In infancy, this phenomenon occurs despite a very distensible aorta and a relatively low pulse wave velocity, being due to the limited body length.

In the elderly, in contrast, aortic stiffness and high pulse wave velocity account for the early return of wave reflection despite normal body dimensions. With bodily growth to late adolescence, the peak of the wave moves towards early systole, and the secondary reflected wave appears in early diastole.

Since AS parameters vary with aging in normal population, age-related paediatric scales reflecting the ranges of normal values should be defined. The present study is, to the best of our knowledge, the first one reporting AS parameters in normal children; these could be assumed as an expression of "normal" AS in childhood determined by means of the Echo-tracking system we used.

This tool appears very promising, but it is still associated with some technical problems specific for infancy: we noticed that the conventional antero-posterior probe position is inadequate in children since it results in AS parameters higher than those obtained, in the same subjects, with a latero-medial position (Table I).

This is very likely to depend on the relatively small size of children neck: with the conventional "adult" approach the pressure exerted by the probe can result in a relative obstacle to systolic expansion of the artery, causing an apparent increase of AS parameters.

On the other hand, with the latero-medial position of the probe, compression of the artery is relatively less than in antero-posterior approach since the jugular vein, interposed between the probe and the carotid artery, hampers the mechanical effect of the probe on the arterial vessel.

In this sense, operators should be advised to apply the probe as gently as possible, in children examination, in order to avoid falsely high AS parameters values.

Our data suggest that carotid artery IMT does not undergo any age-related change in normal children.

It has been demonstrated that this parameter is altered in some diseases that typically affect childhood, such as Kawasaki syndrome (12); ultrasonic AS investigation in these situations is likely to provide further evidence of subclinical atherosclerosis in some affected subjects.

An increasing bulk of evidence demonstrates that abnormal AS in normal children is related to atherosclerosis, and that subjects with increased AS are at higher risk for cardiovascular disease, with respect to normal population (3-6).

Since prevention of atherosclerosis should start from infancy, it is advisable early recognition of children at risk for future cardiovascular disease.

This is particularly true in some subjects, e.g. those that have suffered from Kawasaki disease, or are affected by diabetes, hypertension, aortic coarctation or other conditions associated with potential involvement of arterial vessels.

In this respect, definition of normal limits for AS parameters is crucial in order to select children that should be followed-up and/or submitted to a prevention program.

Data contained in the present study could be a basis for further research involving a larger paediatric population.

Study Limitations

Arterial stiffness evaluation by Echo-tracking method is based on: 1) diameter change waveforms evaluated by ultrasound, and 2) blood pressure values measured by sphygmomanometry, assuming that carotid artery pressure is equal to upper arm pressure. Brachial artery pressure, however, may not exactly represent carotid artery pressure; this is a limitation shared by any non-invasive blood pressure measurement, e.g. sphygmomanometer.

Blood pressure could have been more precise although time consuming.

Figure 2: Mean ± 2 standard deviations for Stiffness index (β), Elastic modulus (Ep), Arterial compliance (AC), Pulse wave velocity (PWVβ), and Intima-Media Thickness (IMT), in the analyzed classes of age.
Table I. Latero-Medial versus Antero-posterior approach. Echo-Tracking parameters: Mean ± 2DS (N=12)

<table>
<thead>
<tr>
<th>Approach</th>
<th>β</th>
<th>EP</th>
<th>AC</th>
<th>PWV-B</th>
<th>IMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latero-Medial</td>
<td>3.22 ± 0.57</td>
<td>4.56 ± 0.63</td>
<td>0.002</td>
<td>0.002</td>
<td>0.003</td>
</tr>
<tr>
<td>Antero-posterior</td>
<td>1.67 ± 0.29</td>
<td>1.32 ± 0.36</td>
<td>0.003</td>
<td>0.003</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Table II. Analyzed Parameters (Mean +/-2DS)

| Table III: Pearson Correlation between age and analyzed parameters

<table>
<thead>
<tr>
<th>YEARS</th>
<th>β</th>
<th>EP</th>
<th>AC</th>
<th>PWV-B</th>
<th>IMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>2.19 ± 0.10</td>
<td>22.4 ± 5.3</td>
<td>1.12 ± 0.59</td>
<td>2.90 ± 0.33</td>
<td>0.35 ± 0.03</td>
</tr>
<tr>
<td>4</td>
<td>2.25 ± 0.12</td>
<td>23.1 ± 10.7</td>
<td>1.84 ± 0.96</td>
<td>2.98 ± 0.36</td>
<td>0.34 ± 0.03</td>
</tr>
<tr>
<td>5</td>
<td>2.30 ± 0.99</td>
<td>24.4 ± 8.6</td>
<td>2.23 ± 1.06</td>
<td>3.03 ± 0.45</td>
<td>0.33 ± 0.03</td>
</tr>
<tr>
<td>6</td>
<td>2.56 ± 1.19</td>
<td>27.1 ± 13.2</td>
<td>1.97 ± 1.04</td>
<td>3.14 ± 0.78</td>
<td>0.35 ± 0.04</td>
</tr>
<tr>
<td>7</td>
<td>2.60 ± 1.30</td>
<td>26.1 ± 14.7</td>
<td>2.06 ± 1.25</td>
<td>3.08 ± 0.92</td>
<td>0.32 ± 0.02</td>
</tr>
<tr>
<td>8</td>
<td>2.64 ± 1.44</td>
<td>29.1 ± 15.6</td>
<td>2.21 ± 1.65</td>
<td>3.24 ± 0.97</td>
<td>0.33 ± 0.04</td>
</tr>
<tr>
<td>9</td>
<td>2.69 ± 1.30</td>
<td>33.1 ± 12.7</td>
<td>1.71 ± 0.89</td>
<td>3.40 ± 0.56</td>
<td>0.35 ± 0.03</td>
</tr>
<tr>
<td>10</td>
<td>3.01 ± 1.29</td>
<td>32.3 ± 12.5</td>
<td>2.12 ± 1.15</td>
<td>3.46 ± 0.74</td>
<td>0.34 ± 0.04</td>
</tr>
<tr>
<td>11</td>
<td>3.09 ± 1.23</td>
<td>33.3 ± 11.8</td>
<td>1.60 ± 0.62</td>
<td>3.60 ± 0.59</td>
<td>0.31 ± 0.02</td>
</tr>
<tr>
<td>12</td>
<td>2.98 ± 1.35</td>
<td>34.2 ± 17.9</td>
<td>2.03 ± 1.56</td>
<td>3.55 ± 0.86</td>
<td>0.35 ± 0.05</td>
</tr>
<tr>
<td>13</td>
<td>3.02 ± 1.41</td>
<td>35.0 ± 15.2</td>
<td>2.02 ± 0.83</td>
<td>3.57 ± 0.84</td>
<td>0.36 ± 0.06</td>
</tr>
<tr>
<td>14</td>
<td>3.33 ± 1.18</td>
<td>39.0 ± 10.1</td>
<td>1.58 ± 0.41</td>
<td>3.76 ± 0.75</td>
<td>0.36 ± 0.03</td>
</tr>
<tr>
<td>15</td>
<td>3.35 ± 1.30</td>
<td>40.3 ± 10.2</td>
<td>1.68 ± 0.81</td>
<td>3.90 ± 0.56</td>
<td>0.33 ± 0.03</td>
</tr>
<tr>
<td>16</td>
<td>3.00 ± 1.45</td>
<td>44.1 ± 15.2</td>
<td>1.58 ± 0.49</td>
<td>4.02 ± 0.64</td>
<td>0.30 ± 0.04</td>
</tr>
</tbody>
</table>

Table IV: Comparison between Echo-Tracking parameters obtained by 2 operators (Mean ± 2DS)

<table>
<thead>
<tr>
<th>Operator 1</th>
<th>Operator 2</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>β</td>
<td>2.48 ± 0.58</td>
<td>2.54 ± 0.58</td>
</tr>
<tr>
<td>EP</td>
<td>25.9 ± 6.42</td>
<td>27.6 ± 7.95</td>
</tr>
<tr>
<td>AC</td>
<td>2 ± 0.6</td>
<td>1.9 ± 0.5</td>
</tr>
<tr>
<td>PWV-B</td>
<td>3.1 ± 0.34</td>
<td>3.16 ± 0.42</td>
</tr>
</tbody>
</table>

References
5) Demelis J, Panaretou M. Aortic stiffness is an independent predictor of progression to hypertension in nonhypertensive subjects. Hypertension 2005; 45:426-431.