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## ORIGINAL ARTICLE

## Arterial distensibility in children and teenagers: normal evolution and the effect of childhood vasculitis

Y F Cheung, P A Brogan, C B Pilla, M J Dillon, A N Redington

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**Background:** Polyarteritis nodosa is a necrotising vasculitis of the medium sized and small muscular arteries. The inflammatory and subsequent reparative processes may alter the arterial mechanical properties. The effect of vasculitic damage on arterial distensibility has never been explored however.

**Aim:** To determine the normal values and the effect of childhood vasculitis on arterial distensibility in children and teenagers.

**Methods:** Distensibility of the brachioradial arterial segment was studied using pulse wave velocity ( $PWV \propto 1/\sqrt{\text{distensibility}}$ ), in 13 children with polyarteritis nodosa at a median age of 11.8 (range 4.9–16) years. As a control group, 155 healthy schoolchildren (6–18 years, 81 boys) were studied. PWV was assessed using a photoplethysmographic technique; blood pressure was measured by an automatic sphygmomanometer (Dinamap). Data from patients were expressed as z scores adjusted for age and compared to a population mean of 0 by a single sample *t* test. Determinants of PWV in normal children were assessed by univariate and multivariate linear regression analyses.

**Results:** Age, height, weight, and systolic blood pressure correlated individually with the brachioradial PWV. Multivariate analysis identified age as the only independent determinant. Ten of the patients were in clinical remission, while three had evidence of disease activity at the time of study. The PWV in the patient group as a whole was significantly greater than those in healthy children (mean z score +0.99). Raised C reactive protein concentration (>2 mg/dl) in the three patients with active disease was associated with a higher PWV when compared to those in remission (z score +2.78 v +0.45). The diastolic blood pressure of the patients was higher than those of the controls (z score +1.04) while the systolic pressure was similar (z score –0.36).

**Conclusions:** PWV in the brachioradial arterial segment increases gradually during childhood independent of body weight, height, mass, and blood pressure. Increased PWV, and hence decreased distensibility, in this peripheral arterial segment occurs in polyarteritis nodosa and is amplified during acute inflammatory exacerbation.

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Vasculitis is the predominant feature of a variety of diseases in childhood.<sup>1</sup> The degree of damage to the vessel ranges from minimal with local leakage of fluid and cells to total destruction of the vessel wall with thrombosis. The acute inflammation and subsequent reparative process may lead to replacement of elastic tissue by fibrous scar,<sup>2</sup> thereby potentially altering the mechanical properties of the vessels.<sup>3</sup>

Arterial distensibility is an important mechanical property of the arterial tree. Reduction of arterial distensibility increases arterial characteristic impedance, pulse pressure, and the pulsatile cardiac workload.<sup>4</sup> Arterial distensibility can satisfactorily be assessed by measuring pulse wave velocity, which is inversely related to the square root of distensibility.<sup>5</sup> Decreased arterial distensibility, as evaluated by pulse wave velocity, is a strong predictor of cardiovascular morbidity and mortality in patients with hypertension and end stage renal disease.<sup>6,7</sup> The effect of vasculitic damage on arterial distensibility has never been explored however. Furthermore, while distensibility has been shown to decrease with aging in adults, it has not been examined in normal children. We therefore measured the pulse wave velocity in the medium sized conduit arteries in children with vasculitis affecting arteries of this calibre, namely polyarteritis nodosa, and compared it to that in normal healthy children.

## PATIENTS AND METHODS

### Subjects

Thirteen children with polyarteritis nodosa who were followed up at the Hospital for Sick Children were studied. The

diagnosis of polyarteritis nodosa was based on the American College of Rheumatology classification criteria.<sup>8</sup> As a control group, 155 healthy schoolchildren (aged 6–18 years, 81 boys) from three local schools were studied. The study was approved by the institutional ethics committee and written informed consent was obtained from the parents of all subjects.

We recorded the age, body weight, and height of all subjects. Body mass index was calculated as weight (kg)/square of height (metres). Blood pressure in the right upper arm was measured twice using an automated sphygmomanometer (Dinamap, Critikon, Inc.) with an appropriate size cuff. The clinical and laboratory indicators of disease activity were assessed concurrently at the time of the study, and medications taken by the patients were noted.

### Measurement of pulse wave velocity

Each subject rested supine for at least 10 minutes before recordings were made. The pulse wave velocity in the brachioradial arterial segment was measured by a previously described non-invasive photoplethysmographic technique.<sup>5,9</sup> Briefly, two probes, each containing an infrared emitting diode and a phototransistor, were placed over the right brachial and right radial arteries and secured without compression. As the pulse wave passes along and distends the artery under the probe, more of the infrared signal is absorbed and less reflected. The signals from the two probes were amplified, displayed in real time on the monitor, and sampled by a custom made analog-to-digital converter at a rate of 1 kHz. The recordings, each consisting of 20 seconds of data, were stored on floppy disks for subsequent analysis. The stored data were

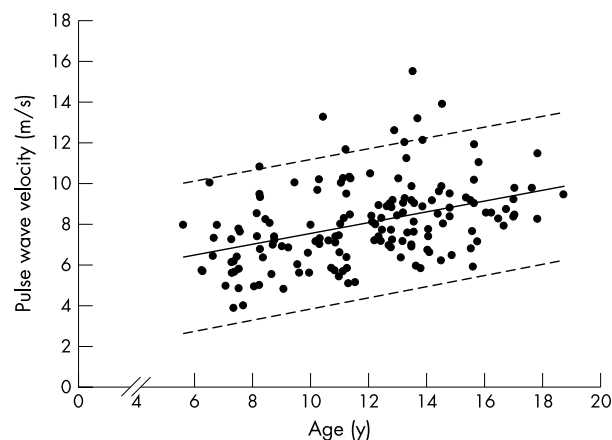
**Table 1** Univariate and multivariate analysis of variables relating to pulse wave velocity

Variables	Univariate analysis		Multiple linear regression	
	r	p	$\beta$ (standardised)	p
Age				
Whole group	0.40	<0.001	0.57	<0.001
Boys	0.46	<0.001		
Girls	0.28	0.015		
Sex (male)			0.081	0.32
Height (cm)	0.41	<0.001		
Weight (kg)	0.32	<0.001		
Body mass index (kg/m <sup>2</sup> )	0.13	0.1	-1.64	0.08
Systolic blood pressure (mm Hg)	0.16	0.047	-0.017	0.87
Diastolic blood pressure (mm Hg)	0.04	0.64	-0.11	0.31
Mean blood pressure (mm Hg)	0.14	0.09	0.16	0.20
Pulse rate (per minute)	-0.09	0.29	0.16	0.09

analysed using custom made software. A non-weighted four point running average technique was used to smooth the signal. The transit time was determined from the time delay between the foot of the corresponding brachial and radial pulse waves, as this point is relatively free of wave reflection.<sup>5</sup> The foot was determined by an algorithm that identified the point at which the second derivative of the diameter waveform is maximum. The pulse wave velocity was derived by dividing the measured distance between the two probes by the transit time.

#### Statistical analysis

Data from the healthy control subjects were analysed by univariate followed by multivariate linear regression to identify significant determinants of pulse wave velocity in childhood. Preliminary analyses identified age as the only significant determinant. The mean pulse wave velocity was therefore calculated for six age groups (6 to  $\leq 8$ , 8 to  $\leq 10$ , 10 to  $\leq 12$ , 12 to  $\leq 14$ , 14 to  $\leq 16$ , and 16 to  $\leq 18$ ). From these normal data, z scores were calculated so that for the control group, the mean value was 0 with an SD of 1. The z score results are presented as mean (95% confidence interval).<sup>10</sup> The blood pressure parameter was similarly normalised for age for comparison. The z scores of the patients were compared to a population mean of 0 by a single sample t test. A p value of <0.05 was considered statistically significant. All data analyses were performed with SPSS software (SPSS, Chicago) and all statistical tests were two tailed.



**Figure 1** Scatter plot of pulse wave velocity against age. The lines represent the mean (solid line) and the 95% prediction interval (dashed lines).

## RESULTS

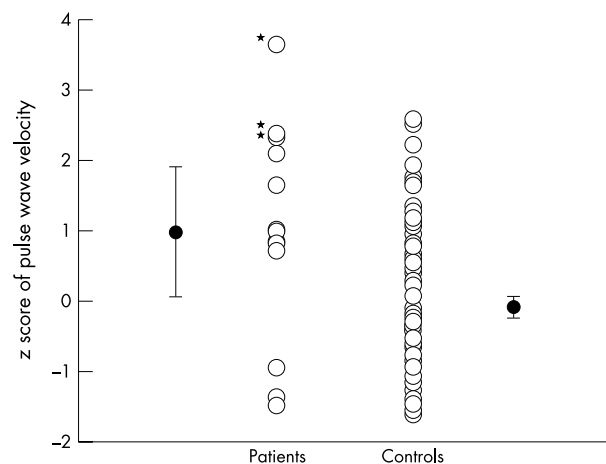
### Control subjects

Age (in both boys and girls), height, weight, and systolic blood pressure significantly and positively correlated with brachio-radial pulse wave velocity (table 1). As the height and weight variables had a strong linear relation with age (tolerance of height and weight was 0.11 and 0.17, respectively) when included in the multiple linear regression model, they were removed from the model and instead the body mass index was included. Age was identified as the only independent determinant by multivariate analysis (standardised  $\beta = 0.57$ ,  $p < 0.01$ ; table 1). Pulse wave velocity was therefore normalised for age and expressed as z score (measured value minus mean value/standard deviation) for comparison between different patient groups and controls (fig 1).

### Children with polyarteritis nodosa

Thirteen children with polyarteritis nodosa were studied at a median age of 11.8 (range 4.9–16) years. Median duration of the illness since diagnosis was 3.1 (range 0.4–11.5) years. Ten were in clinical remission, while three had clinically active disease at the time of study that coincided with an increase in C reactive protein (>2 mg/dl). Their medications included steroids (n = 11), cytotoxics (n = 10), antiplatelet agents (n = 8), cyclosporin A (n = 2), and antihypertensive drugs (n = 2).

Pulse wave velocity in children with polyarteritis nodosa was significantly greater than that in healthy children (z score +0.99 (0.92),  $p = 0.037$ ; fig 2). Diastolic blood pressure of the



**Figure 2** Vertical scatter plots of z scores of pulse wave velocity in patients and controls. The error bar represents mean (SEM); z scores of the three patients with flare of disease activity at the time of study are marked by asterisks.

patients was higher than that of the controls ( $z$  score: +1.04 (0.91),  $p = 0.028$ ), while systolic blood pressure was similar between the two groups ( $z$  score  $-0.36$  (1.08),  $p = 0.48$ ).

Raised C reactive protein concentration ( $>2$  mg/dl) in three patients with flare of disease activity at the time of study was associated with a higher pulse wave velocity ( $z$  score +2.78 (1.84), compared with those in remission (+0.45 (0.89),  $p = 0.012$ )). There was, however, no significant correlation between the  $z$  scores of pulse wave velocity and the duration of illness from diagnosis ( $r = -0.29$ ,  $p = 0.36$ ).

## DISCUSSION

Our data show that there is a gradual increase in pulse wave velocity of the brachioradial arterial segment, hence a decrease in arterial distensibility, during childhood independent of body weight, height, mass, and blood pressure. The arterial distensibility is significantly decreased in children with polyarteritis nodosa. Importantly, this abnormality is amplified during inflammatory exacerbation.

By constructing a multivariate model, we identified age as the only significant determinant that correlates positively with the distensibility of peripheral arteries in the upper limb of children and teenagers. Previous investigators have found no consistent change in distensibility of the radial or brachial arteries with age.<sup>11-14</sup> Bramwell and Hill<sup>11</sup> and Avolio and colleagues<sup>12</sup> found a linear increase in pulse wave velocity in the upper limb from 3 to 89 years of age, while Avolio and colleagues,<sup>13</sup> in another population studied, and Ho,<sup>14</sup> who studied adults  $>20$  years of age, reported little age related changes. Nonetheless, the scatter plots of Avolio and colleagues<sup>12, 13</sup> did suggest, on closer examination, a steep rise in pulse wave velocity in the upper limb from birth to 20 years of age which then plateaus off in adulthood. However, our findings, and those of the others, fail to confirm a peak in arterial compliance at around 10 years of age, as reported by Laogun and Gosling.<sup>15</sup> This is perhaps not surprising as progressive medial degeneration is probably the major underlying factor.<sup>12</sup> The rate of elastin synthesis increases to a maximum in the perinatal period and falls rapidly thereafter.<sup>16</sup> With the cyclic mechanical stress, fragmentation of the elastin fibres and transfer of the stress to much stiffer collagen fibres inevitably result in progressive reduction in vascular compliance.<sup>17</sup> Our findings echo those of Avolio and colleagues<sup>13</sup> and refute the suggestion that change in pulse wave velocity with age is entirely owing to difference in systemic blood pressure.<sup>18, 19</sup> Of importance to note, however, is that the type of blood pressure measurement is known to influence the relation between blood pressure and pulse wave velocity.<sup>20</sup> While correlation between the average of two Dinamap readings and pulse wave velocity is relatively low in this study (correlation coefficient  $r = 0.16$ ), a stronger correlation ( $r = 0.453$ ) has been shown when blood pressure was measured every three minutes for 30 minutes.<sup>20</sup> Nonetheless, the best correlation has been observed with ambulatory blood pressure reading, which gives the highest number of blood pressure measurements.<sup>20, 21</sup>

Superimposed on this temporal relation is the finding of significantly reduced arterial distensibility in children with polyarteritis nodosa. Polyarteritis nodosa is a necrotising vasculitis involving the medium sized and small muscular arteries. The characteristic histopathological changes of fibrinoid necrosis and notable inflammatory response occur in a segmental manner and the inflammatory cycle results in multiple stages comprising acute and healing lesions.<sup>2</sup> The acute lesions often extend to involve the full thickness of the arterial wall, while the healed lesions consist of notable fibrotic thickening. The internal elastic lamina is lost or fragmented and replaced by fibrous tissue.<sup>2</sup> Functional alteration of the arteries as a result of these pathological changes has not been investigated previously. Our finding of reduced arterial

distensibility likely represents the functional manifestation of permanent structural changes associated with replacement of the elastic tissue by the stiffer fibrous scar. It might be expected therefore that arterial distensibility should relate inversely to the duration of vasculitis, a relation that we failed to show. This is probably a result of the fact that the duration of illness as defined by the time since diagnosis does not include the inevitable and variable delay from the true onset of the disease to clinical presentation. Furthermore, the clinical variation of the disease might suggest a variable vascular response independent of the duration of the disease. Although systemic hypertension, a clinical feature of polyarteritis nodosa, may increase pulse wave velocity, all our patients had normal systolic blood pressure, including those on antihypertensive medication, at the time of study. The slightly higher diastolic blood pressure in the patients had the effect of reducing the pulse pressure, the magnitude of which is correlated directly with pulse wave velocity,<sup>4</sup> thus further supporting an intrinsic mechanism to the increased levels in these patients.

The amplification of arterial stiffness during acute inflammatory exacerbation is an interesting finding. It is possible that cellular infiltration and fluid leakage into the arterial wall may alter its physical properties, with superimposing effect on the already stiffened arteries. Furthermore, narrowing of the vessel lumen may increase the pulse wave velocity.<sup>5</sup> Of interest to note is the increasing evidence of the role of inflammation in the development of atherosclerosis, a pathological entity that is known to be associated with increased pulse wave velocity.<sup>12</sup> The acute phase protein, C reactive protein, in particular has been proposed to have an atherogenic role through an interaction with low density lipoprotein and activation of the complement system.<sup>22, 23</sup> Furthermore, a relapsing inflammatory and necrotic process within coronary intima has been suggested to be associated with coronary atherosclerosis.<sup>24</sup> It is impossible from our study, however, to suggest that early atherosclerotic changes can explain the observed reduction of arterial distensibility in patients with polyarteritis nodosa, but clearly further clarification of the relation between inflammation, relapse, atherosclerosis, and decreased arterial distensibility is required.

The significance of pulse wave velocity owes in its direct relation to characteristic impedance that has been regarded as an index of cardiac load.<sup>12</sup> The clinical relevance is illustrated by the fact that increase in aortic pulse wave velocity, and hence characteristic impedance, is a predictor of cardiovascular morbidity and mortality in patients with hypertension and end stage renal disease.<sup>6, 7</sup> Although we have studied only the peripheral artery in the upper limb, which is justified in light of the predilection of its involvement in polyarteritis nodosa, the ascending aortic input impedance is the composite of the impedance spectra of the vascular beds perfused by the ascending aorta.<sup>4</sup> The ventricular load presented to the left ventricle would inevitably increase with increased impedance in any of these vascular beds. The arterial damage in polyarteritis nodosa may therefore prejudice later cardiovascular health by decreasing arterial distensibility, increasing characteristic impedance and cardiac load.

In summary, normal aging is associated with a progressive reduction in arterial distensibility. Chronic vasculitis leads to a significantly reduced distensibility, the magnitude of which is amplified during the acute inflammatory stage of the disease.

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