Pediatr Nephrol (2008) 23:439–444
DOI 10.1007/s00467-007-0693-x

ORIGINAL ARTICLE

Pulse contour analysis: a valid assessment of central arterial stiffness in children?

**Giacomo D. Simonetti · Ute Eisenberger ·
Ivo P. Bergmann · Felix J. Frey · Markus G. Mohaupt**

Received: 14 August 2007 / Revised: 22 October 2007 / Accepted: 24 October 2007 / Published online: 21 December 2007

Abstract In adults the contour analysis of peripheral pressure waves in the upper limb reflects central aortic stiffness. Here, we wanted to demonstrate the appropriateness of pulse contour analysis to assess large artery stiffness in children. Digital volume pulse analysis, with the computation of the stiffness index and pulse wave velocity between carotid and femoral artery, were simultaneously determined in 79 healthy children between 8 years and 15 years (mean age 11.4 years, 32 girls). The stiffness index of 42 healthy adults (mean age 45.6 years, 26 women) served as control. Pulse wave velocity between carotid and femoral artery was directly correlated with systolic pressure and mean blood pressure, as well as with pulse pressure. The results from the stiffness index of children revealed the expected values extrapolated from the linear regression of adulthood stiffness index vs. age. Childhood stiffness index positively correlated with pulse wave velocity ($r^2=0.07$, $P=0.02$) but not with blood pressure parameters. The exclusion of individuals with an increased vascular tone, as indicated by a reflexion index > 90%, improved the correlation between stiffness index and pulse wave velocity ($r^2=0.13$, $P=0.001$). Our data indicate that digital volume pulse-based analysis has limitations if compared with pulse wave velocity to measure arterial stiffness, mostly in patients with a high vascular tone.

Keywords Arterial stiffness · Blood pressure · Children · Digital volume pulse · Pulse wave velocity · PWV

Introduction

At all ages, disease entities such as arterial hypertension and chronic renal or metabolic diseases are accompanied by increased stiffness of large elastic arteries. Arterial stiffness is recognised as a major determinant of cardiovascular risk [1–3]. Consequently, pulse pressure and other indices of aortic stiffness, such as pulse wave velocity (PWV), have been consistently and strongly linked to cardiovascular morbidity and mortality in patients with hypertension [4].

Recently, several non-invasive methods to assess arterial stiffness have been proposed. Most of them are difficult to be accomplished routinely in children; therefore, uncomplicated methods that are easily performed are warranted for the evaluation of arterial stiffness in childhood diseases in clinical practice. Millasseau and co-workers have demonstrated that arterial stiffness, as measured by peripheral pulse wave analysis, was correlated with the measurement of central aortic stiffness and PWV between carotid and femoral artery (PWV_{cf}), currently the gold standard in adults [5, 6].

The peripheral pulse wave, as analysed via the digital volume pulse (DVP), may be fast and simply obtained by measuring the transmission of infrared light through the finger pulp (photoplethysmography), a potentially attractive method to rapidly assess arterial stiffness in childhood.

The purpose of this study was to demonstrate whether the DVP method is appropriate to assess large artery stiffness in children via the stiffness index (SI) derived from the digital volume pulse analysis (SI_{DVP}) as compared with values of PWV_{cf} in healthy children.

G. D. Simonetti
Division of Paediatric Nephrology, Children's Hospital,
University of Bern,
Berne, Switzerland

U. Eisenberger · I. P. Bergmann · F. J. Frey · M. G. Mohaupt (✉)
Department of Nephrology and Hypertension,
Division of Hypertension, University of Bern,
3010 Berne, Switzerland
e-mail: markus.mohaupt@insel.ch

Subjects and methods

Carotid-femoral PWV_{cf}

PWV_{cf} was determined as previously reported [5, 7]: Briefly, the "Pulse Trace PWV unit" (Micro Medical Limited, Rochester, UK) obtained the PWV by measuring the time lag between the R-wave of the ECG and the arrival of the arterial pulse at two distinct arterial sites. After application of ECG electrodes, the Doppler pencil probe was placed at the carotid and thereafter at the femoral artery. Approximately ten systolic peaks were recorded at both sites so that the mean $\Delta t_{carotid}$ and $\Delta t_{femoral}$ (Δt_{cf}) could be obtained. The distance (l_{cf}) between the two detection sites was measured and recorded. PWV_{cf} was calculated by the division of l_{cf} by Δt_{cf} ($PWV_{cf}=l_{cf}/\Delta t_{cf}$).

Determination of SI_{DVP}

The "Pulse Trace PCA unit" (Micro Medical Limited) was used to record the DVP and pulse wave by photoplethysmography, as outlined previously [5, 7]. The children were comfortably rested in a supine position with the right hand supported. A finger clip containing an infrared light emitter and receiver (940 nm) was applied to the right index finger of the child. The contour of the DVP was recorded and analysed after validation of an appropriate signal by the investigator.

The first part of the waveform (systolic component) is thought to be formed as a result of pressure transmissions along a direct path from the aortic root to the finger. The second part (diastolic component) is formed by the pressure transmitted from the ventricle along the aorta to the lower body, where it is reflected back along the aorta to the finger (Fig. 1). The timing of the diastolic component relative to the systolic component depends upon the PWV of the pressure waves within the aorta and large arteries relative to large artery stiffness. The SI_{DVP} is an estimate of the PWV in large arteries and is obtained from subject height (h) divided by the time between the systolic and diastolic peaks of the DVP (Δt_{DVP}), ($SI_{DVP}=h/\Delta t_{DVP}$).

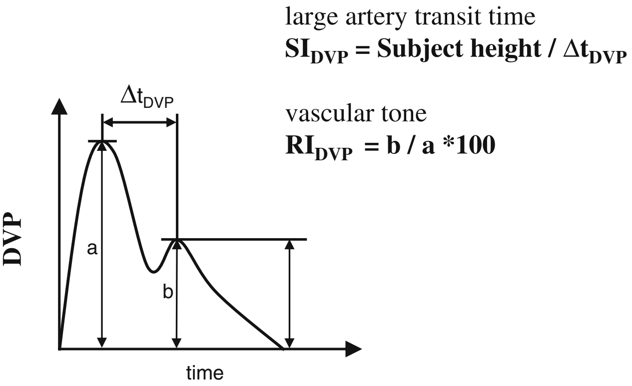

Fig. 1 Calculation of stiffness index (SI_{DVP}) and reflexion index (RI_{DVP}) by using the digital volume pulse wave-form (adapted from the users' manual of Micro Medical Limited, Rochester, UK)

The height of the diastolic component of the DVP relates to the amount of pressure wave reflection. This, in turn, relates mainly to the tone of the small arteries. The reflection index (RI_{DVP}) is the height of the diastolic component of the DVP expressed as a percentage of the systolic peak and is a measure of the tone of the small arteries (Fig. 1).

Relationship between SI_{DVP} and PWV_{cf}

SI_{DVP} and PWV_{cf} were determined in 79 healthy children (32 girls and 47 boys); mean age 11.4 years, range 8.4–14.8 recruited from the local area of Berne. All subjects were physically examined. Mean weight, height and BMI were 40.1 kg (range 21.8–69.7 kg), 146.4 cm (range 124.2–175 cm) and 18.3 kg/m^2 (range 13–27.6 kg/m^2), respectively. Of the children, 10.1% ($n=8$) were adipose [8]. Mean systolic and diastolic blood pressures were 108±11/60±6 mmHg. One child had systolic and diastolic blood pressure values above the 90th percentile. Eight children (10.1%) had isolated systolic blood pressure values between the 90th and 95th percentile, and seven children (8.9%) had isolated systolic blood pressure values above the 95th percentile. Pulse pressure was 48±11 mmHg, and mean heart rate was 77±11/min. After the children had had at least 10 min of supine rest, three consecutive measurements of PWV_{cf} and seven consecutive measurements of SI_{DVP} were made by the same investigator. To calculate PWV_{cf}, the mean of the measurements was calculated; to determine SI_{DVP}, the highest and lowest recorded values were excluded and the mean of the remaining five measurements was calculated. Office blood pressure was taken as the mean of three measurements obtained from the supine child after a 10 min rest before arterial stiffness was assessed with a calibrated oscillometric device (Dinamap); considering the altering normal values of blood pressure in the growing child, we corrected the measured blood pressure to percentiles and age-corrected z-scores for a given child's age and height [9]. Previously published values of SI_{DVP} of 42 healthy adults (mean age 45.6 years, 26 women) [7] were used for comparison with the SI_{DVP} values of these children.

Ethics

The protocol was approved by the local ethics review board and additionally by the paediatric ethics committee, and all subjects and parents gave informed consent.

Statistics

The subjects' characteristics and results are presented as mean ± SD. Associations between SI_{DVP} and PWV_{cf} or blood pressure were examined by univariate or multivariate regression analysis, as appropriate, the Bland–Altman plot or receiver operating characteristics (ROC) analysis. All the statistical analyses were performed with either GraphPad Prism, version 4.01 for Windows (GraphPad Software, San Diego, California, USA) or SYSTAT, version 10 (SPSS Inc., Chicago, IL, USA). Significance was assigned at $P<0.05$.

Results

The mean values of SI_{DVP} (5.8±0.7 m/s, range 4.8–9.6 m/s; $n=79$) and of PWV_{cf} (5.7±0.9 m/s, range 4.1–9.0 m/s) were similar. The mean coefficients of variation for individual children were 4.0±4.0% for SI_{DVP} and 7.4± 7.5% for PWV_{cf}, demonstrating good reproducibility for both methods. The mean value of RI_{DVP} was 68±12% (range 41–92%).

Both the SI_{DVP} and PWV_{cf} were independent of age and height, expressed in absolute values or in age-dependent z-scores. SI_{DVP} showed a consistent, inverse, yet weak, correlation with absolute ($r^2=0.08$, $P=0.0094$) and age-corrected ($r^2=0.12$, $P=0.002$) BMI. SI_{DVP} did not correlate with systolic, diastolic, or mean blood pressures, or with pulse pressure. In contrast, PWV_{cf} correlated with absolute ($r^2=0.1$, $P=0.006$) and age-corrected ($r^2=0.08$, $P=0.01$) [9] systolic and mean blood ($r^2=0.08$, $P=0.016$) pressures, as well as with pulse pressure ($r^2=0.06$, $P=0.028$). If the subjects were subdivided into blood pressure percentiles [9] (group 1 ≤ 50th percentile, group 2 > 50th percentile and < 90th percentile, group 3 ≥ 90th percentile), group 3 had a significantly higher PWV_{cf} than group 1 [$P<0.05$ in an analysis of variance (ANOVA); Fig. 2, upper panel]. In contrast, SI_{DVP} did not show this trend (Fig. 2, lower panel). A weak, positive, correlation between SI_{DVP} and PWV_{cf} was detectable in healthy children ($r^2=0.07$, $P=0.02$; Fig. 3, upper panel). The analysis demonstrated that low PWV levels were over-rated and high PWV levels were under-rated by SI_{DVP}. If we excluded the values with an RI_{DVP} higher than 90% (indicating elevated peripheral

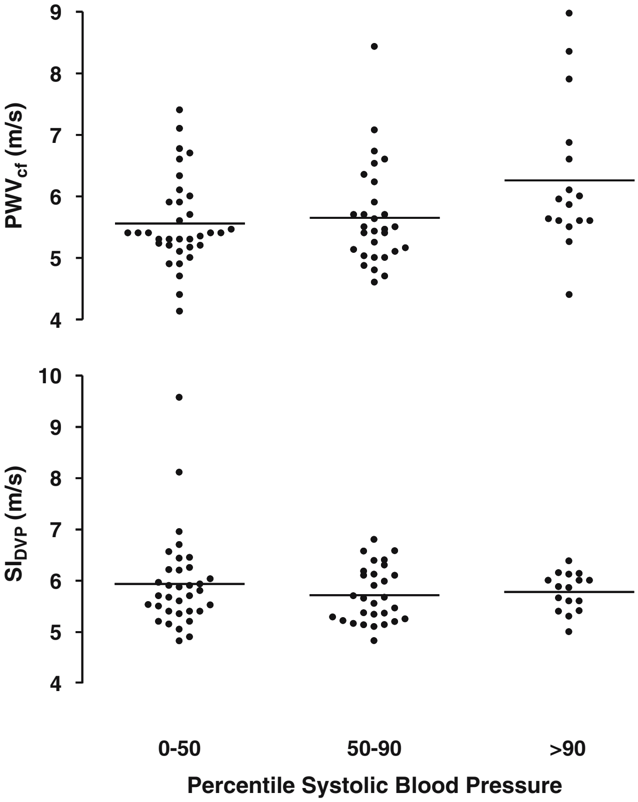

Fig. 2 Correlation between systolic blood pressure and pulse wave velocity (PWV_{cf}) (*upper panel*) and stiffness index (SI_{DVP}) (*lower panel*). Blood pressure is expressed in percentiles related to a given child's age and height. Children with systolic blood pressure ≥ 90th percentile had significantly ($P<0.05$) higher PWV_{cf} than the children with blood pressure ≤ 50th percentile; however, no differences were noted between the three groups for SI_{DVP} (ANOVA) ($n=79$ children)

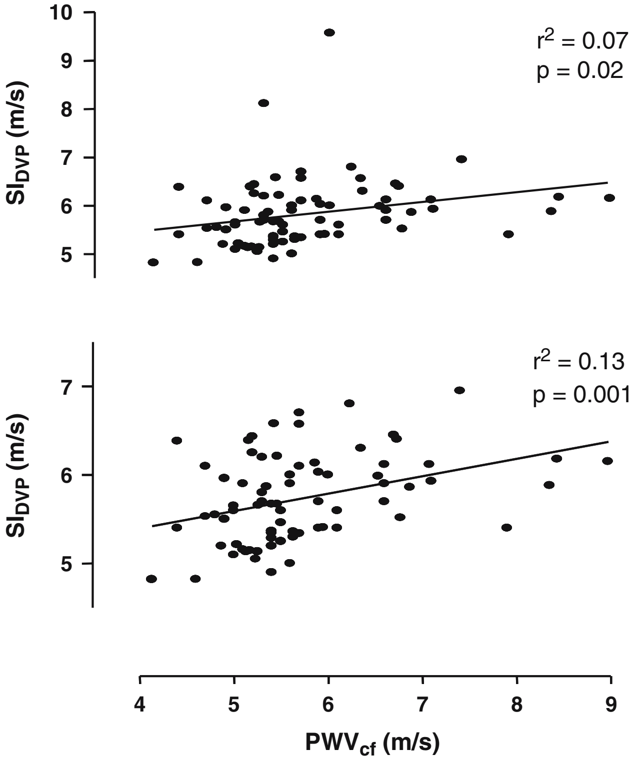

Fig. 3 Correlation between pulse wave velocity (PWV_{cf}) and stiffness index (SI_{DVP}). In the *upper panel* all values ($n=79$ children) are depicted; in the *lower panel* the values with a corresponding reflexion index (RI_{DVP}) > 90% were excluded, leaving $n=77$ children

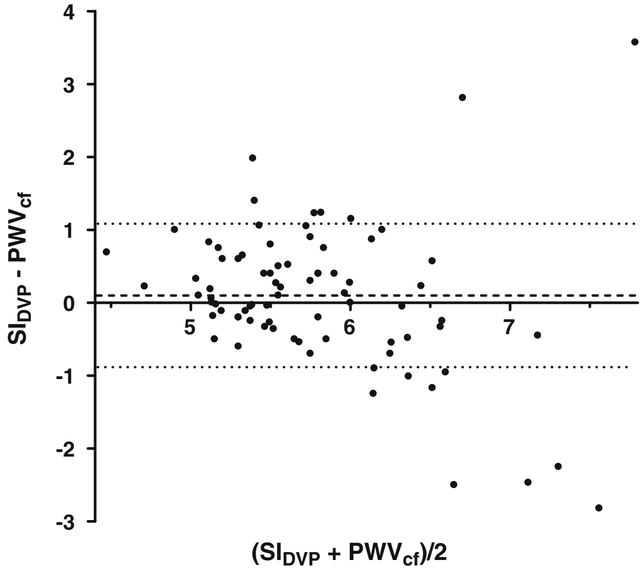

Fig. 4 Bland–Altman plot showing the difference between stiffness index (SI_{DVP}) and pulse wave velocity (PWV_{cf}) measurement as a function of the mean of both measurements. *Dashed lines* indicate mean difference ± SD (*n*=79 children)

vasoconstriction and, consequently, probably a changed pressure waves reflexion site), an improved association was found between PWV_{cf} and SI_{DVP} ($r^2=0.13$, $P=0.001$; Fig. 3, lower panel).

The Bland–Altman plot, which indicates the difference between the SI_{DVP} measurement and the PWV_{cf} measurement as a function of the mean of both measurements, showed tolerable consistency between SI_{DVP} and PWV_{cf} (mean difference 0.09±0.99 m/s) (Fig. 4). With incrementing means of PWV_{cf} and SI_{DVP}, the two methods progressively diverged, supporting the observation depicted in Fig. 3. A ROC-curve analysis between PWV_{cf} and SI_{DVP} demonstrated a limited correlation between the two methods, with an area under the curve (AUC) of 0.57.

Heart rate did not influence PWV_{cf} or SI_{DVP}, but it affected RI_{DVP} ($r^2=0.21$, $P<0.0001$). RI_{DVP} was negatively correlated with age ($r^2=0.18$, $P=0.0001$; Fig. 5, upper panel) and body length ($r^2=0.19$, $P<0.0001$), and it demonstrated a slight, though significant, inverse correlation with absolute ($r^2=0.14$, $P=0.001$; Fig. 5, lower panel) and age-corrected systolic pressure [9] ($r^2=0.06$, $P=0.03$), mean arterial blood pressure ($r^2=0.13$, $P=0.002$) and pulse pressure ($r^2=0.08$, $P=0.02$).

In this cohort of children, no differences in the values of PWV_{cf}, SI_{DVP} or RI_{DVP} with respect to gender or birth weight (i.e. low birth weight vs normal birth weight) were noticed by univariate analysis. The multivariate analysis confirmed the relationship of age-corrected BMI with SI_{DVP} ($r^2=0.148$, $P<0.002$) and of age and heart rate, yet not the weak univariate correlation of absolute and age-

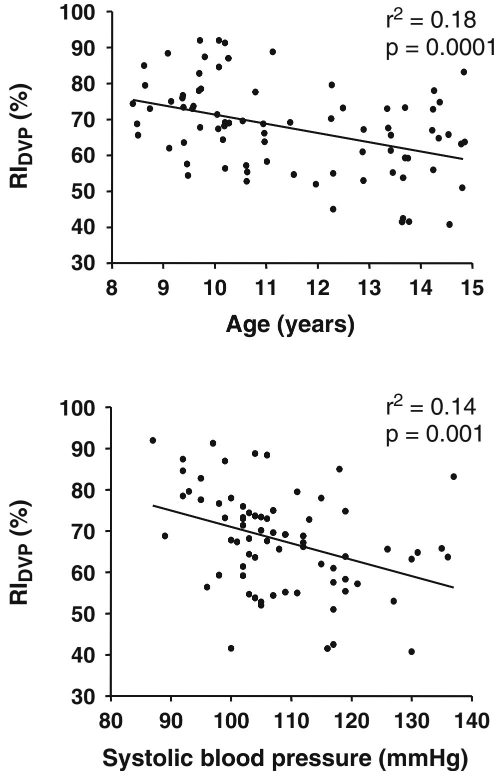

Fig. 5 Correlation between reflexion index (RI_{DVP}) and age (*upper panel*) or systolic blood pressure (*lower panel*), respectively (*n*=79 children)

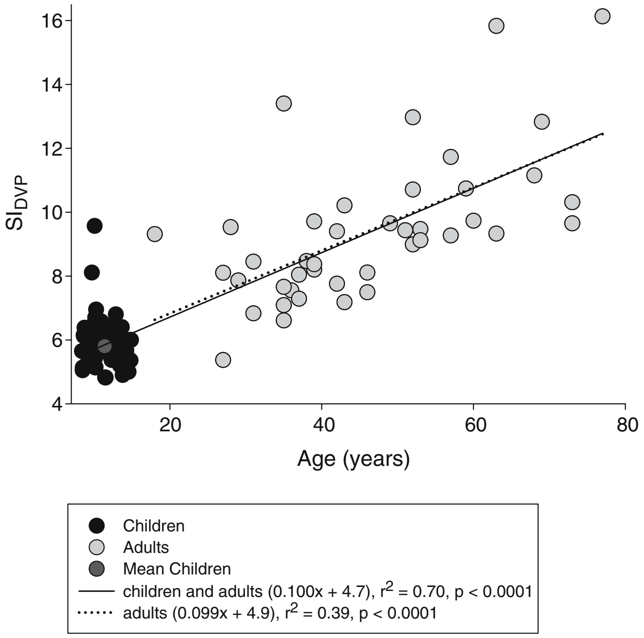

Fig. 6 Relationship between stiffness index (SI_{DVP}) and age in adults alone (*n*=42, *dotted line, grey data points*) and in adults together with children (*solid line*) (children *n*=79, represented by *black data points*, mean of all children represented by the *dark grey data point*). The two linear regressions are very similar, confirming that the measured SI_{DVP} of children reflects the expected values extrapolated from the linear regression of data from adults

corrected systolic blood pressure with RI_{DVP} ($r^2=0.493$, $P<0.0001$). Gender appeared as a determinant of PWV_{cf}, in addition to age-corrected systolic blood pressure, by multivariate analysis ($r^2=0.169$, $P<0.001$).

Previously reported SI_{DVP} values of healthy adults [7] showed a significant positive correlation with age ($0.099x+4.9$, $r^2=0.39$, $P<0.0001$). The inclusion of the SI_{DVP} values of healthy children did not alter the slope and the interception ($0.100x+4.7$, $r^2=0.70$, $P<0.0001$), a finding that confirmed that the measured SI_{DVP} in children reflected the expected values extrapolated from the linear regression of the adults' values (Fig. 6).

In addition, PWV_{cf} values in this cohort of children were similar to values previously reported [10], measured in healthy children by a comparable method and concerning the same arterial segment.

Discussion

The measurement of PWV, well established to assess large artery stiffness, is inversely correlated to arterial distensibility [11]. This non-invasive measurement at the carotid–femoral region is the most direct indicator of large artery stiffness and currently represents the gold standard to evaluate central arterial rigidity and the resulting cardiovascular risk [4]. Though reliable in children without and with chronic kidney disease [10, 12, 13], it requires time and is often displeasing, favouring more practical procedures in paediatric clinical practice.

The indirect measurement of central arterial stiffness by analysis of the DVP, an established method in the adult population, is technically simple, inexpensive and rapid. This method has not yet been evaluated in children. In a small number of children, only changes of RI_{DVP} with salbutamol to study endothelial function have been tested, though with rather negative results [14].

The SI_{DVP} values measured in children were found to be exactly on the extended linear correlation between SI_{DVP} and age of healthy adults [7]. The limits of the positive correlation of childhood SI_{DVP} with PWV_{cf} were perceptible by an inadequate correlation in the ROC analysis. In addition, and in contrast to PWV_{cf}, we did not find a correlation between SI_{DVP} and systolic pressure, office mean arterial blood pressure or pulse pressure [9]. These results were confirmed by multivariate analysis, yet excluding the weak univariate correlation of absolute and age-corrected systolic blood pressure with RI_{DVP}.

The missing correlation of SI_{DVP} and blood pressure might be explained by the close dependency of childhood blood pressure upon the tone of the small peripheral arteries, as indicated by RI_{DVP}, which negatively correlates with age, body length and blood pressure, is influenced by the heart rate, and which tends to be higher, as has been reported in adults [5, 15]. This is supported by the Bland Altman plot for mean averages of PWV_{cf} and SI_{DVP}, which showed tolerable consistency of both measurements at an intermediate level, but which progressively diverged with incrementing means of the two methods. Following the exclusion of patients with $RI_{DVP}>90\%$, improved correlation between SI_{DVP} and PWV_{cf} was found, allowing us to conclude that the peripheral vascular tone compromises the measurement of SI_{DVP} in children. Factors contributing are a change of the reflection sites of the pressure waves and dampening of the registered digital pulse curve.

For the narrow age range investigated, no relationship with age or body size, either for SI_{DVP} or for PWV_{cf}, was found. The number of subjects was unlikely to be limiting, since the expected association between PWV_{cf} and pulse pressure, both indicators of arterial stiffness, was present in our cohort [16, 17].

SI_{DVP} does not provide information identical to that of PWV_{cf}, since the contour of the peripheral pulse is complex. SI_{DVP} is influenced by factors in addition to PWV, including cardiac ventricular ejection and the distribution of major sites of pressure wave reflection distal to the femoral arteries. SI_{DVP} is influenced by the distensibility of these arteries in addition to that of the aorta. Furthermore, it is important to note that age-related changes seen in elastic arteries (stiffening) are not seen in muscular arteries [18]; the characteristics of the vascular tree in children are different from those of adults, due to the differences in height and proportions, the diameters of the central and peripheral arteries, and the divergence between the peripheral vascular tone and the distensibility of the central arteries [12, 19, 20].

In interpreting these results and considering the data from the literature, we strongly feel that, although DVP analysis could be an attractive technique for the assessment of arterial stiffness in childhood, the characteristics of the vascular tree in children could complicate the exact interpretation of the DVP and its relationship with central arterial stiffness.

In conclusion, this study compared DVP and PWV_{cf} to assess arterial stiffness in children: The DVP method is promising, but it is limited by factors such as high peripheral resistance and only a weak correlation with the PWV_{cf}, the standard for the assessment of central arterial stiffness. The method appears to be acceptable in those children with an $RI_{DVP}\leq 90\%$, as the SI_{DVP}/age ratio was exactly as predicted from the results in a cohort of adults.

Acknowledgements Grants support: Fondazione Ettore e Valeria Rossi (to G.D.S.), Swiss Renal Foundation (to G.D.S and M.G.M) and SNF grant nos. 3200B0-113902/1 (to M.G.M.) and no. 3100A0-102153/2 (to F.J.F).

References

1. Blacher J, Asmar R, Djane S, London GM, Safar ME (1999) Aortic pulse wave velocity as a marker of cardiovascular risk in hypertensive patients. Hypertension 33:1111–1117
2. Boutouyrie P, Tropeano AI, Asmar R, Gautier I, Benetos A, Lacolley P, Laurent S (2002) Aortic stiffness is an independent predictor of primary coronary events in hypertensive patients: a longitudinal study. Hypertension 39:10–15
3. Glasser SP, Arnett DK, McVeigh GE, Finkelstein SM, Bank AJ, Morgan DJ, Cohn JN (1997) Vascular compliance and cardiovascular disease: a risk factor or a marker? Am J Hypertens 10:1175–1189
4. Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, Ducimetiere P, Benetos A (2001) Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. Hypertension 37:1236–1241
5. Millasseau SC, Kelly RP, Ritter JM, Chowienczyk PJ (2002) Determination of age-related increases in large artery stiffness by digital pulse contour analysis. Clin Sci (Lond) 103:371–377
6. Millasseau SC, Ritter JM, Takazawa K, Chowienczyk PJ (2006) Contour analysis of the photoplethysmographic pulse measured at the finger. J Hypertens 24:1449–1456
7. Sollinger D, Mohaupt MG, Wilhelm A, Uehlinger D, Frey FJ, Eisenberger U (2006) Arterial stiffness assessed by digital volume pulse correlates with comorbidity in patients with ESRD. Am J Kidney Dis 48:456–463
8. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH (2000) Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ 320:1240–1243
9. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents (2004) The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics 114:555–576
10. Covic A, Mardare N, Gusbeth-Tatomir P, Brumaru O, Gavrilovici C, Munteanu M, Prisada O, Goldsmith DJ (2006) Increased arterial stiffness in children on haemodialysis. Nephrol Dial Transplant 21:729–735
11. Bramwell JC, Hill AV (1922) Velocity of transmission of the pulse and elasticity of arteries. Lancet i:891–892
12. Avolio AP, Chen SG, Wang RP, Zhang CL, Li MF, O'Rourke MF (1983) Effects of aging on changing arterial compliance and left ventricular load in a northern Chinese urban community. Circulation 68:50–58
13. Schack-Nielsen L, Molgaard C, Larsen D, Martyn C, Michaelsen KF (2005) Arterial stiffness in 10-year-old children: current and early determinants. Br J Nutr 94:1004–1011
14. Donald AE, Charakida M, Cole TJ, Friberg P, Chowienczyk PJ, Millasseau SC, Deanfield JE, Halcox JP (2006) Non-invasive assessment of endothelial function: which technique? J Am Coll Cardiol 48:1846–1850
15. Millasseau SC, Kelly RP, Ritter JM, Chowienczyk PJ (2003) The vascular impact of aging and vasoactive drugs: comparison of two digital volume pulse measurements. Am J Hypertens 16:467–472
16. Benetos A, Lacolley P (2006) From 24-hour blood pressure measurements to arterial stiffness: a valid short cut? Hypertension 47:327–328
17. Li Y, Wang JG, Dolan E, Gao PJ, Guo HF, Nawrot T, Stanton AV, Zhu DL, O'Brien E, Staessen JA (2006) Ambulatory arterial stiffness index derived from 24-hour ambulatory blood pressure monitoring. Hypertension 47:359–364
18. van der Heijden-Spek JJ, Staessen JA, Fagard RH, Hoeks AP, Boudier HA, van Bortel LM (2000) Effect of age on brachial artery wall properties differs from the aorta and is gender dependent: a population study. Hypertension 35:637–642
19. Aggoun Y, Szezepanski I, Bonnet D (2005) Noninvasive assessment of arterial stiffness and risk of atherosclerotic events in children. Pediatr Res 58:173–178
20. Senzaki H, Akagi M, Hishi T, Ishizawa A, Yanagisawa M, Masutani S, Kobayashi T, Awa S (2002) Age-associated changes in arterial elastic properties in children. Eur J Pediatr 161:547–551