RESEARCH ARTICLE

Accurate arterial path length estimation for pulse wave velocity calculation in growing children and adolescents [version 1; peer review: 2 approved with reservations]

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Abstract

Background: Most adult cardiovascular disease begins in childhood. Given the burgeoning obesity pandemic in children worldwide, there is a need for precise and scalable surveillance methods to detect subclinical cardiovascular disease in children and adolescents. Early detection allows early intervention and intensified primary prevention strategies in affected individuals. Carotid-femoral pulse wave velocity (PWV) directly measures arterial wall stiffness, an early feature of atherosclerosis. Calculation of PWV in growing children requires an accurate estimation of the true distance travelled by the aorto-femoral pressure wave, using surface anatomy landmarks. However, a variety of methods are used to estimate this distance, and these have not previously been investigated in growing children and adolescents. We sought to investigate this by comparing true arterial path length measured on computerized tomography (CT) scans, with a variety of estimations based on surface anatomy landmarks.
Methods: Arterial path lengths were measured using multi-planar reformation (MPR) imaging software. These measurements were then compared with the surface anatomy measurements obtained using the same MPR imaging software. The fidelity of a variety of arterial path length estimation methods was tested.
Results: The surface anatomy distance between the suprasternal notch and the angle of the mandible (PWV recording site in the neck), should be adjusted using the formula y=4.791+(1.0534*x). This value subtracted from the unadjusted distance from the suprasternal notch to the umbilicus, through the mid-inguinal crease to the femoral PWV recording site, provides the simplest reliable approximation of true intraluminal distance travelled.
Conclusions: There is high correlation between the surface anatomy

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distances and the arterial path lengths they represent; however, these are not equal. Most surface anatomy measurements require adjustment using the formulae that we have provided, to accurately estimate the true distance travelled by the pulse wave.

Keywords
PWV, arterial path length, accurate estimation, CT, MPR, Multi planar reformation, Arterial stiffness

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Introduction

Most adult cardiovascular disease begins in childhood[1]. Given the burgeoning obesity pandemic in children worldwide[2], there is a need for precise and scalable surveillance methods to detect subclinical cardiovascular disease in children and adolescents. PWV directly measures artery wall stiffness, an early feature of atherosclerosis. Early detection allows early intervention and intensified primary prevention strategies in affected individuals.

PWV measurement involves measuring the time it takes the arterial pulse to travel a specific distance, and then dividing the distance by the transit time, to calculate the velocity. Transit time is obtained by measuring the interval delay between the pulse wave arriving at a proximal and distal sensor that are placed on fiducial points, most commonly over the external carotid and femoral arteries. Arrival of the pulse wave is identified using various devices that monitor the arterial pressure waveform. These methods of measuring transit time are generally highly reproducible and accurate. However, the distance estimations used for PWV calculation are obtained using a tape measure over the body surface and are vulnerable to error. A variety of methods exist using different surface anatomy landmarks and there is no clarity on the most appropriate method for growing children and adolescents.

Previous studies have highlighted the importance of standardizing methodologies, as the use of different arterial path length estimation methods produce noticeably different results[3–5]. This makes inter-study comparisons of PWV data very difficult and creates confusion regarding normal values for PWV in children. In adult patients (who are no longer growing in height), any inaccuracy in estimating the distance traveled is irrelevant because the true distance travelled will not change between one visit and the next. Therefore, a change in transit time in adults reliably reflects a change in PWV and thereby indicates progression of arteriosclerotic vascular disease. However, in growing children and adolescents, the distance travelled by the pulse wave may well change between one visit and the next. Therefore, a change in transit time in children or adolescents does not necessarily indicate a change in PWV.

We sought to investigate the fidelity of a variety of arterial path length estimation methods by comparing true arterial path length measured on computerized tomography (CT) scans, with estimations based on a variety of surface anatomy landmarks.

Methods

Using the Picture Archiving and Communication System (PACS) at Tygerberg Academic Hospital, Cape Town, we identified all archived CT scans of paediatric and adolescent patients, excluding those with congenital abnormalities of skeleton or any disease likely to distort the gross anatomy of the large vessels. Mid-luminal arterial lengths were measured using the multi-planar reformation (MPR) imaging software Intellispace Portal version 4 (Philips: Amsterdam). Surface anatomy measurements were obtained using the same MPR imaging software. 3D Slicer[6], an open source software platform for medical image informatics, image processing, and three-dimensional visualization, with the Vascular Modeling Toolkit (VMTK) extension[7] can be used as an alternative to IntelliSpace Portal for computing vessel centerlines and to perform measurements on both surface anatomy and blood vessels.

Comparisons were performed in segments, since there were no whole-body CT scans available. Segments of surface anatomy distances and arterial path lengths are presented in Table 1 and Table 2, respectively. Segment comparisons are tabulated in Table 3. On sagittal, coronal, axial and three-dimensional (3D) volume-rendered images, an experienced operator (LRW) measured the components of the sets of distances presented in Table 3.

Centerline paths of major vessels were created with the Advanced Vascular Analysis (AVA) application within Intellispace Portal, by placing serial markers along the vessel using the axial, sagittal, coronal, and 3D volume rendered images, as per Intellispace Portal operation manual. 3D Slicer with the Vascular Modeling Toolkit (VMTK) extension can be used as an alternative to AVA for computing vessel centerlines. After creating the vessel centerline, the vessel measurements were performed in the "measurement" stage of AVA application.

Table 1. Six surface anatomy distances used for pulse wave velocity calculations, with associated abbreviations.

Six surface anatomy distances	Abbreviation
Angle of the mandible to **S**uprasternal notch	AS
Suprasternal notch to **X**iphisternum	SX
Suprasternal notch to Midpoint of the right **I**nguinal crease	SI
Xiphisternum to **U**mbilicus	XU
Xiphisternum to Midpoint of the right **I**nguinal crease	XI
Umbilicus to Midpoint of the right **I**nguinal crease	UI

Table 2. Six arterial path lengths used for pulse wave velocity calculation, with associated abbreviations.

Six arterial path lengths	Abbreviation
Origin of brachiocephalic **T**runk to Origin of right **C**ommon carotid	TC
Origin of right **C**ommon carotid to Carotid **B**ifurcation	CB
Carotid **B**ifurcation to **E**xternal carotid at angle of mandible	BE
Origin of brachiocephalic **T**runk to Aorta at the **X**iphisternum	TX
Aorta at the **X**iphisternum to **A**ortic bifurcation	XA
Aortic bifurcation to Right **F**emoral artery at inguinal ligament	AF

Table 3. Comparison Sets.

	Surface anatomy distance	Arterial path length
Set 1	AS	TC+CB+BE
Set 2	SX	TX
Set 3	XI	XA+AF
Set 4	XU+UI	XA+AF
Set 5	SI	TX+XA+AF
Set 6	SX + XI	TX+XA+AF
Set 7	SX + XU +UI	TX+XA+AF

Thereafter the rendering parameters of the 3D volume rendered image were changed to display skin surface to perform the surface anatomy measurement. All distances were measured in millimeters.

An example: Measuring the arterial path length TC+CB+BE.

In the "vessel extraction" stage of the AVA application, serial markers were placed at the midpoint of the artery lumen, starting at the origin of the brachiocephalic trunk (Figure 1a, b & c) and ending at the external carotid artery at the level of the angle of the mandible (a common PWV recording site in the neck), using the axial, coronal and sagittal images. Markers were placed at approximately 10mm intervals. In the "measurement" stage of the of the AVA application, the length of the vessel centerline from the brachiocephalic trunk to the external carotid artery at the angle of the mandible was measured (Figure 2a & b).

A similar method was used to measure the arterial path length TX+XA+AF. This is illustrated in the *Extended data* (Figure 7)[8].

An example: Measuring the surface anatomy distance AS

Continuing in the "measurement" stage, the rendering parameters of the volume rendered image were changed to display skin surface. Thereafter the "magic glass window" feature was selected from the right click menu. This "magic glass window" feature is an enhanced visualizing window that can be superimposed on top of the volume rendered image of the skin surface. It is a moveable mini-window which can be set with its own windowing, image enhancement and rendering parameters to enable the operator to "look through" the skin at the anatomical structures beneath. The rendering parameters inside the active "magic glass window" were adjusted to visualize the precise position of the underlying supra-sternal notch (Figure 3a) and the angle of the mandible (Figure 3b). The surface distance between these two points was then measured with the volume rendered image rotated 45 degrees to the right as shown in Figure 4a. Thereafter the volume rendered image was turned 90 degrees (lateral) as shown in Figure 3b to check the measuring line placement on the face (angle of the mandible) and then to the antero-posterior position to check the measuring line placement on the supra-sternal notch as shown in Figure 3a.

A similar method was used to measure the other surface anatomy distances. These are illustrated in the *Extended data* (Figures 8 to 10)[8].

Ethical statement

Ethical approval was sought from Health Research Ethics Committee of Stellenbosch University (Ethics Reference #: S15/05/113). A retrospective collection of CT scans between January 2010 and May 2018 were used. Since the images were part of an archive database, there was no direct interaction with patients and a request for a waiver of individual informed consent was approved from the ethics committee. Personal information was kept strictly confidential and identifying demographic information was not captured.

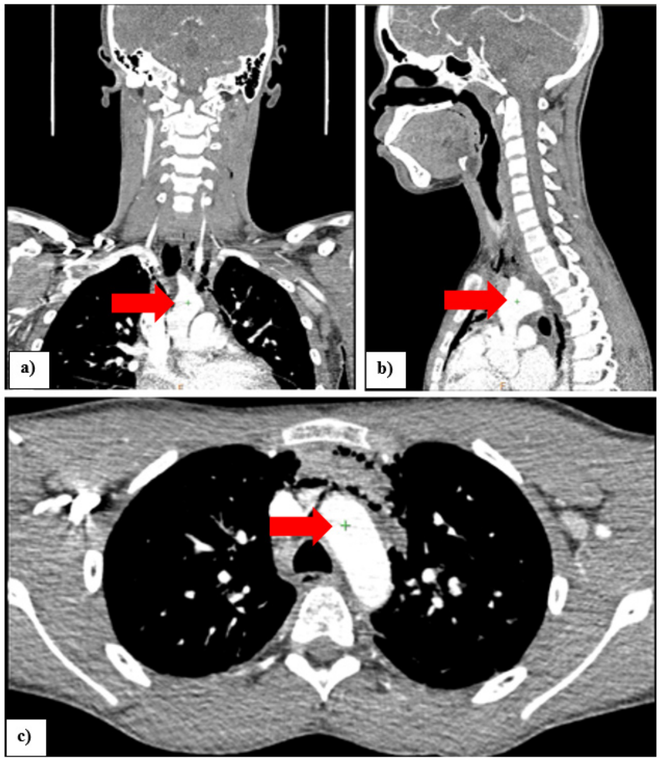

Figure 1. Seed placement at origin of brachiocephalic trunk. Illustrating the placement of the first marker (seed) on the coronal (**a**), sagittal (**b**) and axial (**c**) images, for measurements starting at the origin of the brachiocephalic trunk.

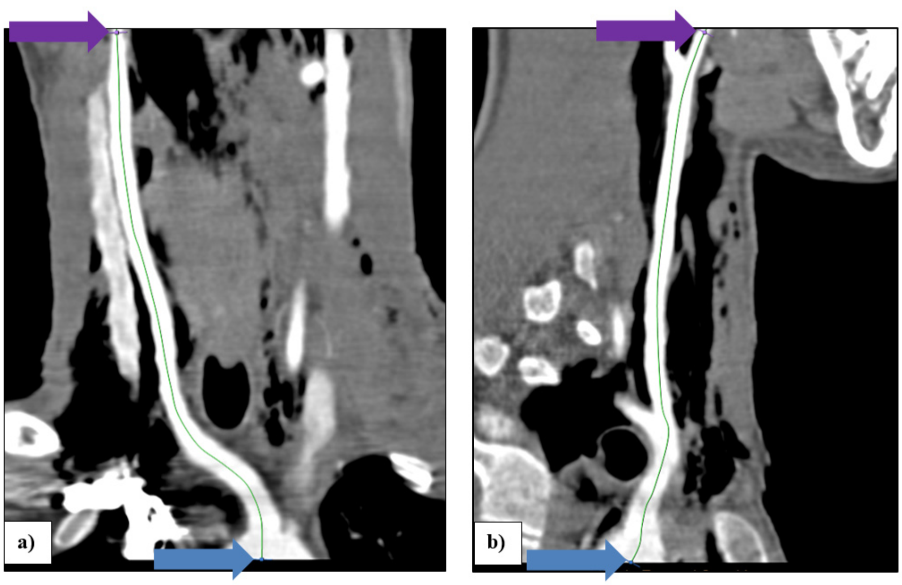

Figure 2. Arterial path length measurement TC+CB+BE on curved MPR. Illustration of vessel centerline TC+CB+BE on a curved coronal (**a**), and on a curved sagittal (**b**) MPR. The blue arrows point to the start of the vessel measurement at the origin of the brachiocephalic trunk and the purple arrows point to the end of the measurement in the right external carotid artery at the level of the angle of the mandible.

Results

There is excellent correlation between all surface anatomy distances and the arterial path lengths they represent (see Table 4). However, the surface anatomy distances and the arterial path lengths are not equal; they require mathematical conversion using the linear regression equation shown on their respective

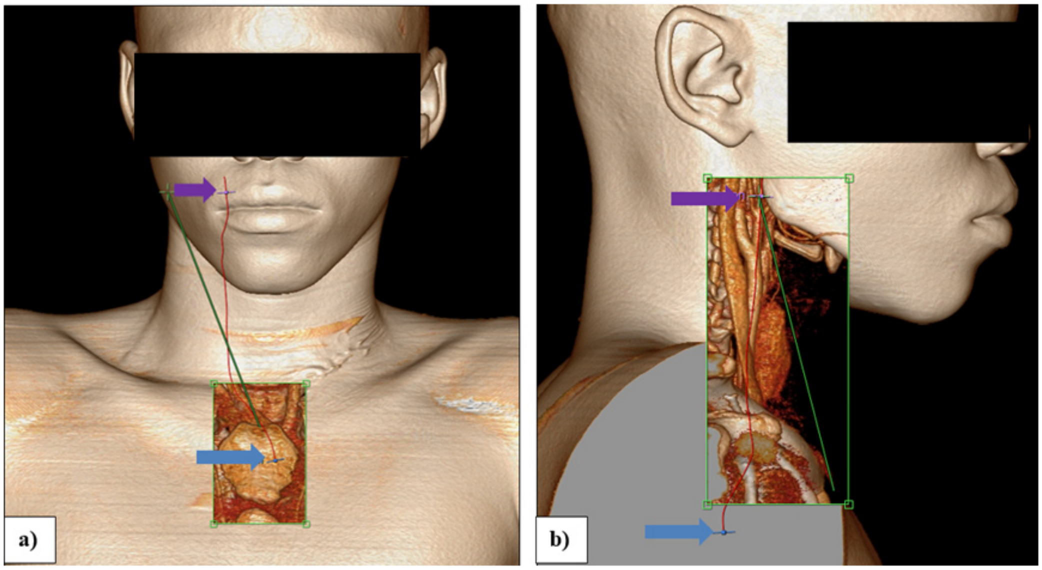

Figure 3. Surface measurement AS on 3D volume rendered image with magic glass. Illustrating surface measurement AS on an anterior-posterior 3D volume rendered image (**a**) and a lateral 3D volume rendered image (**b**), using the "magic glass window". The green line represents the surface anatomy distance between the angle of the mandible and the suprasternal notch. Also visible is the vessel centerline TC+CB+BE constructed in Figure 4: The blue arrows point to the start of the vessel measurement TC+CB+BE at the origin of the brachiocephalic trunk and the purple arrows point to the end of the measurement in the right external carotid artery at the level of the angle of the mandible.

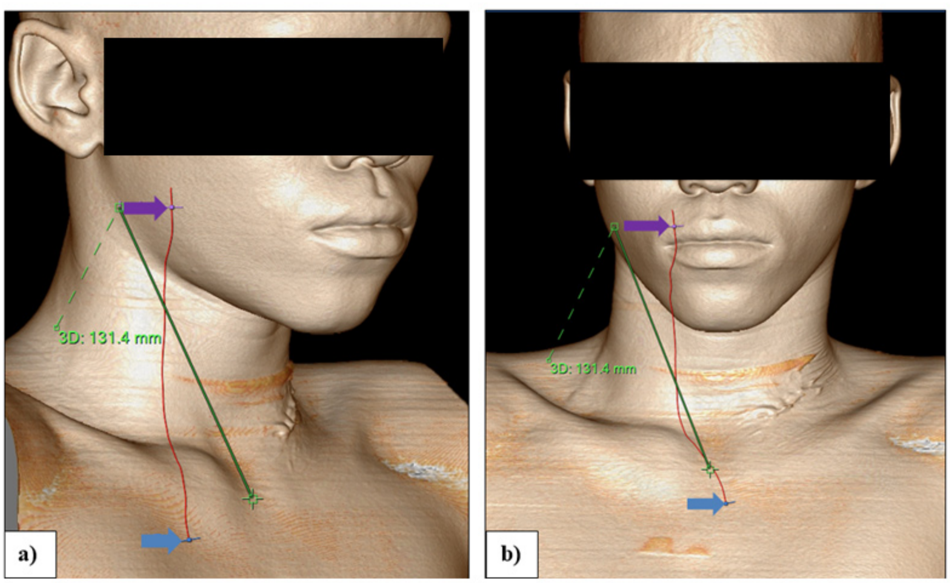

Figure 4. Surface measurement AS on 3D volume rendered images. Illustrating surface measurement AS on an oblique 3D volume rendered image (**a**) and an anterior-posterior 3D volume rendered images (**b**), after the "magic glass window" has been removed. As before, the blue arrows point to the start of the vessel measurement TC+CB+BE at the origin of the brachiocephalic trunk and the purple arrows point to the end of the measurement in the right external carotid artery at the level of the angle of the mandible.

scatterplots. Figure 5 and Figure 6 show scatterplots of Comparison Set 1 and Comparison Set 5, respectively. Scatterplots of the other Comparison Sets are provided in the *Extended data* (Figures 11 to 15)[8].

Table 4. Summary outcome of each comparison.

Comparison		n	r^2	p-value
Set 1	TC+CB+BE compared to AS	66	0.92	<0.0001
Set 2	TX compared to SX	152	0.84	<0.0001
Set 3	XA+AF compared to XI	105	0.99	<0.0001
Set 4	XA+AF compared to XU+UI	107	0.99	<0.0001
Set 5	TX+XA+AF compared to SI	18	0.98	<0.0001
Set 6	TX+XA+AF compared to SX+XI	18	0.97	<0.0001
Set 7	TX+XA+AF compared to SX+XU+UI	17	0.97	<0.0001

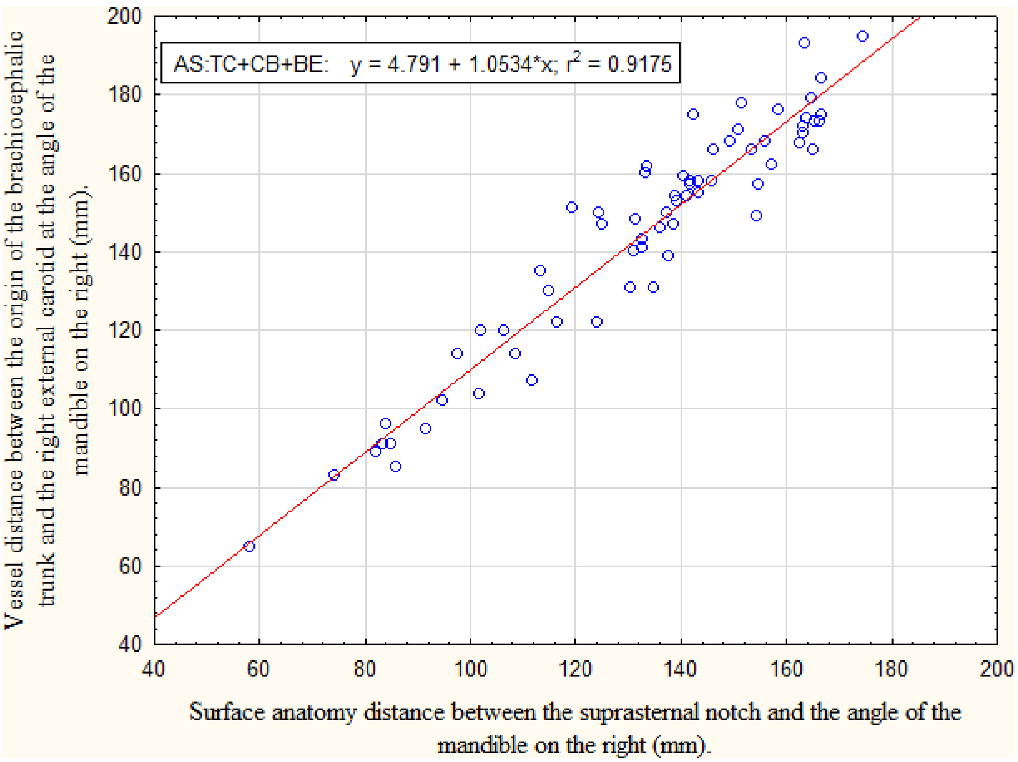

Figure 5. Scatterplot of Comparison Set 1: TC+CB+BE compared to AS. Relationship between arterial path length TC+CB+BE (origin of the brachiocephalic trunk to the external carotid at the angle of the mandible on the right) and surface anatomy distance AS (suprasternal notch to the angle of the mandible) in children younger than 18 years. Linear regression analysis showed a strong positive correlation (r^2 =0.92). The regression equation to be used for mathematical conversion is presented in the block insert.

The age range and gender split for each Comparison Set is presented in the *Extended data* (Table 5 and Figure 16)[8].

Summary of the results

The aim of the current study was to estimate the true intraluminal distance travelled by the pulse wave, which is equal to:

(TX+XA+AF) minus (TC+CB+BE)

This may be estimated using the following component surface anatomy distances:

- (TC+CB+BE) is accurately estimated by (AS), provided the surface anatomy distance (AS) undergoes mathematical conversion using the linear regression equation presented in the block insert on the Figure 5 scatterplot. Without the mathematical conversion, the surface anatomy distance (AS) consistently underestimates the true arterial path length (TC+CB+BE) by -8% to -12%.

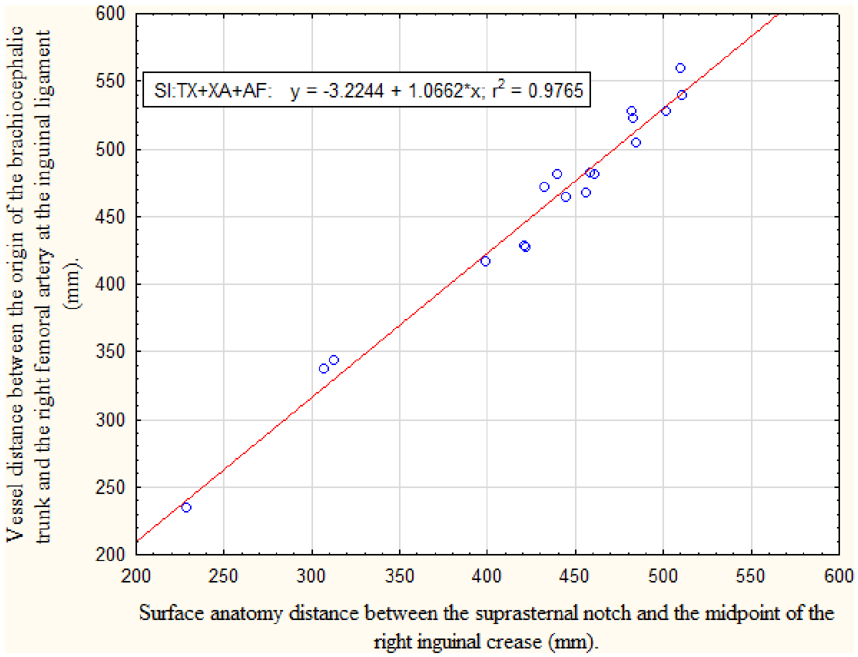

Figure 6. Scatterplot of Comparison Set 5: TX+XA+AF compared to SI. Relationship between arterial path length TX+XA+AF (origin of the brachiocephalic trunk to the right femoral artery at the inguinal ligament) and the surface anatomy distance SI (suprasternal notch to the midpoint of the right inguinal crease) in children younger than 18 years. Linear regression analysis showed a very strong positive correlation (r^2 =0.98). The regression equation to be used for mathematical conversion is presented in the block insert.

- (TX+XA+AF) is accurately estimated by the sum of the surface anatomy distances (SX) plus (XU+UI). Without the mathematical conversion using the linear regression equations presented in the block inserts on Figures 11 and 13, this combination of surface anatomy distances minimally over- or under-estimates the arterial path length (TX+XA+AF) by +2% to -1%.
- (TX+XA+AF) is less accurately estimated by the sum of the surface anatomy distances (SX) plus (XI). Without the mathematical conversions using the linear regression equations presented in the block inserts on Figures 11 and 12, this combination of surface anatomy distances underestimates the arterial path length (TX+XA+AF) by -1% to -3%.
- (TX+XA+AF) is even less accurately estimated by the surface anatomy distance (SI). Without the mathematical conversion using the linear regression equation presented in the block insert on Figure 6, the surface anatomy distance (SI) consistently underestimates the arterial path length (TX+XA+AF) by -5% to -6%.

Therefore, the true intraluminal distance travelled by pulse wave is most simply and reliably estimated by subtracting the adjusted surface anatomy distance between the suprasternal notch and the angle of the mandible (PWV recording site in the neck), from the unadjusted distance from the suprasternal notch to the umbilicus, through the mid-inguinal crease to the femoral PWV recording site. Substitution using the surface anatomy distances (SI), or (SX) plus (XI) may require mathematical conversion to retain reasonable accuracy.

Discussion

The issue of accurate PWV measurement in growing children and adolescents is a crucial one, given the burgeoning obesity pandemic in children worldwide[2] and the corresponding need for precise and scalable surveillance methods to detect subclinical cardiovascular disease in that population group. The present study was designed to investigate the most accurate method of estimating the true distance travelled by the aorto-femoral pressure wave, using surface anatomy landmarks in growing children, allowing accurate calculation of carotid-femoral PWV.

PWV directly measures increasing arterial wall stiffness, a valuable precursor to atherosclerosis[9]. Identifying progressive vascular disease early in its pathogenesis allows for early intervention to prevent progression. Automated PWV offers affordable and scalable surveillance for monitoring and identifying the early stages of arteriosclerosis.

The main finding of our study was that, although there is excellent correlation between the surface anatomy distances and their respective arterial path lengths, surface anatomy measurements require adjustment using the conversion formulae that we have provided, to accurately estimate the true distance travelled by the pulse wave. An exception may be the surface anatomy distances (SX) and (XU+UI), which differ minimally from the arterial path lengths they represent.

The combination that most accurately estimates the true distance travelled by the aorto-femoral pressure wave are the surface anatomy distances (SX) plus (XU+UI) minus (AS). The distance (AS) needs to be mathematically converted (using the linear regression equation presented in the block insert on the Figure 6 scatterplot) since the arterial path in the neck is more tortuous than the aorta. The correlation between SX and TX was not as strong as the other comparisons (r^2 = 0.84 versus 0.92 – 0.99); the reason for this may be related to morphological variability in aortic arch anatomy or the different age range of participants (median 6 versus 13 – 15 years of age). When this distance is combined with others into longer sections (such as SX+XI and TX+XA+AF), the magnitude of the error is reduced and correlations improve.

Our study is entirely novel in that, to the best of our knowledge, it is the first published attempt at investigating this question in growing children and adolescents. It is not surprising that our results are inconsistent with previous studies performed in adults[4,5,10–12], since the bodies of growing children and adolescents are different in proportion and shape to adults.

Our data will result in more reliable PWV calculation in growing children and adolescents. More robust and accurate measurement of PWV will in turn enable healthcare workers to detect arterial stiffness in its early stages and allow for early interventions to prevent vascular events such as strokes and heart attacks later in life. Finally, our findings will enable more robust inter-study comparisons of carotid-femoral PWV data in children and adolescents.

Note that the surface distances obtained in the current study are equivalent to the distances one would find when using a sliding caliper. Therefore, the exaggerations of surface anatomy measurements caused by morbid obesity may be overcome by using a sliding caliper instead of a tape measure[13].

Limitations

Our study had several limitations. First, although our results showed a very strong correlation between the surface anatomy measurements and their respective arterial path length measurement, the sample size was limited, particularly for comparisons requiring long scans stretching from the neck to the pelvis. We overcame this by comparing subsections of arterial path length (e.g. SX compared to TX; and XI compared to XA+AF).

Second, the surface anatomy measurements were performed using 3D volume rendered images. In a future study, the surface anatomy measurement could be performed on actual patients face-to-face, and then compared to the arterial path length obtained from CT imaging.

Third, we were unable to determine whether there were any systematic ethnic differences in the measurements, because ethnicity information was not available.

Fourth, although we measured the length of the centerline of large vessels, we did not measure the internal diameter of the vessel, which may confound the speed at which the aorto-femoral pressure wave travels. The latter was beyond the scope of the present study.

Conclusion

There is high correlation between the surface anatomy distances and the arterial path lengths they represent; however, these are not equal. Most surface anatomy measurements require adjustment using the formulae that we have provided, to accurately estimate the true distance travelled by the pulse wave.

Data availability

Underlying data

Due to the large number of CT scans used (n=483) in this study and the size of these DICOM files that can be as big as 2.5 Gigabytes per scan. It is not feasible to share these data sets.

A reader/reviewer can request a copy of the data sets by submitting an application to the Tygerberg hospital research committee, specifically to Mrs. Dawn Marwood (Dawn.Marwood@westerncape.gov.za Tel: +27 21 938 5966). In addition, an online application to the National Health Research Database (https://nhrd.health.gov.za/) is also required.

Figshare: DATA: Accurate arterial path length estimation for pulse wave velocity calculation in growing children and adolescents. https://doi.org/10.6084/m9.figshare.12783980[14].

This project contains underlying path length measurements in the following files:

- TC_CB_BE to AS.xlsx
- TX to SX.xlsx
- TX_XA_AF to SI.xlsx
- TX_XA_AF to SX_XI.xlsx
- TX_XA_AF to SX_XU_UI.xlsx
- XA_AF to XI.xlsx
- XA_AF to XU_UI.xlsx

Extended data

Figshare: EXTENDED DATA: Accurate arterial path length estimation for pulse wave velocity calculation in growing children and adolescents. https://doi.org/10.6084/m9.figshare.12783848.v1[8].

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Carotid-femoral pulse wave velocity (PWV) is a surrogate marker of arterial wall stiffness. Calculation of PWV in growing children requires an accurate estimation of the true distance travelled by the aorto-femoral pressure wave, using surface anatomy landmarks.

The authors compared the arterial path length measured on computerized tomography (CT) scans, with a variety of estimations based on surface anatomy landmarks using the same multi-planar reformation MPR imaging software as for the path length measurements.

They concluded that there is high correlation between the surface anatomy distances and the arterial path lengths they represent; however, most surface anatomy measurements require adjustment using formulae provided by the authors, to accurately estimate the true distance travelled by the pulse wave.

Questions and remarks:

1. The authors are stating, "a variety of methods are used to estimate this distance, and these have not previously been investigated in growing children and adolescents”.
   In fact, several studies have been conducted to standardize childhood distance measurement of PWV. Some of these were based solely on surface distance measurements (Kracht *et al.*, 2011[1], Kis *et al.*, 2011[2]), but intraluminal distance measurement using MRI has already been used as well (Reusz *et al.*, 2020[3]). Please cite these publications and discuss the results.

2. The agreement between the results of the two methods (intraluminal and surface measurements) should be evaluated using Bland-Altman plots. A good linear correlation does not necessarily mean that there is no bias in the estimates. Please use this analysis for comparison.

3. In adults, the recommended distance measurement is the direct measure between the carotid tonometry site to femoral tonometry site, applying a systematic correction for

accurate values of PWV (factor 0.8). This question was also recently addressed by ref 3. Please comment.

4. Has the surface distance data obtained by CT and the data measured with a tape measure been compared? It would be worthwhile to examine this aspect of possible bias in a few subjects.

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Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Pediatric hypertension, pediatric CKD, pediatirc pransplantation, cardiovascular consequences of CKD in childhood

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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In the present study:

In the present study, the authors investigated different methods to assess pulse wave path distances for measuring carotid to femoral PWV, an important marker of early cardiovascular disease, in growing adolescents. They used computerised images from hospital CT scans in adolescents to reconstruct body anatomy and measure surface distance, and correlate them with vascular paths.

They come with equations using fiducial anatomic landmarks such as mandible angle, sternal notch, Xiphisternum, inguinal crease etc., and combination of measures between those points, correlated with true vascular path length.

The main finding is that all anatomical distances correlate well with corresponding arterial paths, but one equation is preferred: the true intraluminal distance travelled by a pulse wave is reliably estimated by subtracting the adjusted surface anatomy distance between the suprasternal notch and the angle of the mandible (PWV recording site in the neck), from the unadjusted distance from the suprasternal notch to the umbilicus, through the mid-inguinal crease to the femoral PWV recording site. Additional calibration is necessary by mathematical conversion to retain adequate accuracy.

The paper is very well constructed and written, the methodology is impressive and very well adapted to the aim of the authors. The results are convincing. I have, nevertheless, some remarks which would help, I hope, in applying the present findings to clinical research.

My main concern is about cumulated errors when measuring distances. Measuring distances on the skin using tape meters is associated with random errors which can reach +/- 1 cm, i.e. 5% when measuring once. If three measures are done (mandible to suprasternal notch to umbilicus then to inguinal crease then the error can be made 3 times and therefore cumulate. This then makes a potential error of 3 cm for 50 cm, i.e. 12% error, which is kind of a problem. This is why, in adults, we recommend to measure only one direct measure (carotid tonometry site to femoral tonometry site), and apply a systematic correction for accurate values of PWV (factor 0.8). In the present case, I would love to see estimations of error using the proposed combinations of distances, and how a direct skin measure (for instance mandible to inguinal crease), performs in terms of accuracy, precision, and expected errors. That could be done by duplicate the datasets (5 or 10), generate Gaussian noise with 0.5 cm SD on each distance measure, calculate paths using noisy distances, then re-estimate the correlations with true vascular paths.

Another point is to estimate the influence of anatomical variants on the measurements, especially obesity, but also developmental age.

Minor points:

In adults, distance measurement is also a problem, when comparing populations and estimating normal values. The authors should quote and use the paper in adults for reference values (Mattace-Raso *et al.*, 2010 [1]), and justification for the 0.8 correction factor (Van Bortel *et al.*, 2012 [2])

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Is the work clearly and accurately presented and does it cite the current literature?
Partly

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Are sufficient details of methods and analysis provided to allow replication by others?
Yes

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Partly

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Arterial stiffness in adults, especially hypertension

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.