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Pulse Wave Velocity with 4D Flow MRI: Systematic Differences and Age-Related Regional Vascular Stiffness

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ABSTRACT

Purpose: The objective of this study was to compare multiple methods for estimation of PWV from 4D flow MRI velocity data and to investigate if 4D flow MRI-based PWV estimation with piecewise linear regression modeling of travel-distance vs. travel time is sufficient to discern age-related regional differences in PWV.

Methods: 4D flow MRI velocity data were acquired in 8 young and 8 older (age: 23±2 vs. 58±2 y.o.) normal volunteers. Travel-time and travel-distance was measured throughout the aorta and piecewise linear regression was used to measure global PWV in the descending aorta and regional PWV in three equally sized segments between the top of the aortic arch and the renal arteries. Six different methods for extracting travel-time were compared.

Results: Methods for estimation of travel-time that use information about the whole flow waveform systematically overestimate PWV when compared to methods restricted to the upslope-portion of the waveforms ($p < 0.05$). In terms of regional PWV, a significant interaction was found between age and location ($p < 0.05$). The age-related differences in regional PWV were greater in the proximal compared to distal descending aorta.

Conclusion: Care must be taken as different classes of methods for the estimation of travel-time produce different results. 4D flow MRI-based PWV estimation with piecewise linear regression modeling of travel-distance vs. travel time can discern age-related differences in regional PWV well in line with previously reported data.

Key words: Pulse wave velocity, MR flow imaging, vascular stiffness, 4D flow MRI, phase-contrast MRI, ageing.

1. INTRODUCTION

Aortic pulse wave velocity (PWV) is a marker of vascular stiffness and a strong and independent predictor of cardiovascular morbidity and mortality [1-4].

Catheter-based pressure measurements are considered gold standard for PWV estimation but this method is rarely used due to its invasiveness. Clinically, a combination of tonometry or ultrasound and measuring-tape is used to assess carotid-to-femoral PWV. The invasiveness of the gold standard technique and the limitations of the current clinical approach have prompted the development of alternative means of estimating PWV [5]. Notably, MRI has evolved as a promising method [6-18] The merits of MRI for the estimation of PWV include the capabilities of obtaining: 1) angiographic images that permit accurate determination of vascular distance and 2) an arbitrary number of velocity or flow waveforms at any location in the body. MR-based PWV estimation has primarily been done with 2D cine phase-contrast (PC) MRI [6,9-11,13]. Another method that has been explored is 1D Fourier velocity encoding (FVE) MRI, which permits high temporal resolution but is limited to applications in straight vessel segments [7,8,15,16].

Most of the existing data on in-vivo PWV concerns global aortic PWV. However, vascular stiffness and thus PWV is known to vary regionally along the vasculature [19]. This may be particularly interesting with respect to focal diseases such as thoracic or abdominal aortic aneurysms. A few previous studies have addressed regional PWV invasively using catheter-based pressure measurements and non-invasively using 2D cine PC-MRI or 1D Fourier velocity encoding (FVE) MRI [10,16,20].

The traditional approach to PWV estimation is based on the distance ("travel-distance") between two locations in the vasculature and the temporal shift between velocity, flow or pressure waveforms recorded at these locations ("travel-time"). This "time to travel a fixed distance"-approach, essentially treats travel-distance as a discrete variable and therefore high (temporal) resolution is crucial for the single continuous variable travel-time. Shorter vascular distance, as used in regional PWV assessment, necessitates an even higher temporal resolution. There exist multiple methods for the estimation of travel-time and it is known that the choice of method can impact the results [18,20-22]. In principle, PWV can also be estimated in the opposite way, i.e. by locating the pulse wave at the two instances in time. In such a "distance travelled in a fixed time" approach, the spatial resolution would be crucial, as well as an appropriate algorithm for spatial pulse wave detection. The "distance travelled in a fixed time" approach could be advantageous for assessment of spatial variations of PWV.

Recently, some studies have explored PWV estimation based on 3D cine PC-MRI ("4D flow MRI") [14,17,18]. The most interesting feature of 4D flow MRI for PWV estimation is its full 4D spatiotemporal coverage of velocity data. With this 4D coverage, both travel-time and travel-distance can be treated as continuous variables. Consequently, 4D flow MRI meets the prerequisites for PWV assessment using both the "time to travel a fixed distance" and the "distance travelled in a fixed time" approach. Optimally, these approaches are combined in one estimate of the PWV. One way to exploit the 4D coverage is based on the extraction of flow waveforms at multiple locations throughout a vessel of interest. In this approach, the travel-distance variable is mapped based on 3D vascular anatomy derived from the 4D flow MRI data. The travel-time variable is calculated by conventional transit-time methods. The relationship between the variables can be modeled with piecewise linear regression, for example.

The objective of this study was to compare multiple methods for estimation of PWV from 4D flow MRI velocity data and to investigate if 4D flow MRI-based PWV estimation with piecewise linear regression modeling of travel-distance vs. travel time is sufficient to discern age-related regional differences in PWV.

2. MATERIALS AND METHODS

2.1. Study population

8 young (age: 23 ± 2 years, range 21-26 years) and 8 older (age: 58 ± 2 years, range 55-60 years) normal male volunteers were included in the study (see **Table 1**). All volunteers were normotensive and non-smokers, had no history of cardiovascular disease, and did not take any medication. The volunteers were also asked to refrain from intake of any vasoactive substances (including caffeine) at the day of the MRI study. The local ethics committee approved the study and written informed consent was obtained from all participants.

2.2. 4D Flow MRI

3D cine phase-contrast (4D flow) MRI velocity data of the aorta were acquired using a 1.5T scanner (Philips Achieva, Philips Healthcare, Best, the Netherlands) with a retrospectively electrocardiogram-gated gradient-echo sequence with interleaved three-directional velocity encoding [23]. Imaging parameters included TE = 2.8-3.1 ms, TR = 4.9-5.4 ms, flip angle = 6 degrees, velocity encoding range (VENC) = 160-200 cm/s, parallel imaging reduction factor (SENSE) = 2, k-space segmentation factor = 2, matrix size = 128-144 x 128-144, 3D field-of-view: 300-420 x 300-420 x 70 mm^3, voxel size = 2.3-2.8 mm isotropic. Respiratory motion artifacts were suppressed by navigator gating with an acceptance window of 7 mm. Nominal scan time was 896-1000 heartbeats and the respiratory navigator efficiency was around 60%.

The acquired temporal resolution was 39-43 ms and the retrospectively gated data were reconstructed into 32 time frames on the scanner. Maxwell effects were corrected on the scanner and offline processing was applied to correct for phase-wraps and background phase-errors [24,25].

2.3. Semi-automatic PWV estimation

A semi-automatic approach to PWV estimation was implemented in Matlab (Mathworks Inc., Natick, MA, United States) (**Figure 1**). The approach used here is similar to that used in previous 4D flow MRI studies in that is exploits the volumetric nature of the data and extracts complete pulsatile flow waveforms at multiple locations [14,18]. Similar methods have also been used with 2D in-plane PC-MRI and 1D FVE, where velocity-time profiles rather than complete pulsatile flow waveforms are measured [8,26]. First, a 3D segmentation of the aorta was obtained by manual delineation in angiographic images which were generated by taking the systolic time-average of the product between velocity magnitude (i.e. speed) and MR signal intensity to the power of 1.2. Next, the centerline of the aorta was extracted by using a fast-marching algorithm [27]. Based on the centerline, flow vs. time waveforms in planes perpendicular to the aorta were extracted automatically with 1 mm spacing throughout the aorta. 1 mm spacing corresponds to a finer resolution than the native spatial resolution of the source images and represents a way to avoid loss of information due to spatial undersampling of the travel-distance variable. The flow waveforms were upsampled by a factor of 40 using spline interpolation. The travel-time and travel-distance variables were calculated using transit-time algorithms and distances along the centerline, respectively. This resulted in a travel-time vs. travel-distance graph that could be interrogated for global and regional PWV estimation. Global PWV (PWV_{global}) in the descending aorta was obtained by linear fitting of travel-time vs. travel-distance from the top of the arch to the renal arteries. Further, the aortic

region between the top of the arch and the renal arteries was divided into three equally sized segments: the proximal, mid and distal suprarenal descending aorta. Regional PWV in these three segments was calculated in the same way as the global PWV.

Six different methods for the estimation of the travel-time variable were included:

- *Time to foot (TTF) method*

  Tracks the point at which a line fitted to the upslope of the flow curve crosses the base of the flow waveform (i.e. foot of waveform) [20,28,29]. The upslope region of the flow waveform was defined as the region between 20% and 70% of the peak flow rate. The base of the flow waveform was defined as the average diastolic flow rate.

- *Time to peak upslope (TTU) method*

  Tracks the point of peak first derivative at the upslope of the waveform [30].

- *Time to foot method #2 (TTF2)*

  Tracks the point on the flow waveform that corresponds to 20% of the flow rate at the point of the maximum derivative of the upslope portion of the waveform [21]. The maximum derivative was obtained as for the TTU method.

- *Fourier analysis (FA) method*

  Estimates travel-time based on the phase-shift between two waveforms [31]. A line is fitted to the low frequency components of the quotient of the Fourier transforms of the two waveforms. The slope of this line gives the travel-time: travel-time = slope / 2π. In the present study, the 1-3 Hz range was considered.

- *Cross correlation (XC) method*

  Estimates the travel-time as the time-shift that results the maximum cross correlation between two waveforms [10,12]. In the present study, cross correlation was applied to the complete flow waveform.

- *Center of mass (COM) method*

  Tracks the center-of-mass of the main lobe of the flow waveform. The main lobe was defined as the portion between 20% of the peak flow rate at the upslope and 20% of the peak flow rate at the downslope. To our knowledge this method has not been previously published.

It may be noted that the first three methods (TTF, TTU and TTF2) operate on the upslope of the flow waveform. The last three methods (FA, XC, COM), on the other hand, use information about larger parts of the waveform. As pointed out in previous studies, the latter class of methods can be expected to be more sensitive to the presence of reflected waves [20,21,29].

2.4. Data analysis

Results on global and regional PWV in the descending aorta are reported for all six methods for the estimation of the travel-time variable.

Statistical evaluations of the effects of age and location (age-related regional PWV), as well as detailed inter-methods comparisons, were carried out for the TTF and XC methods. These methods were chosen because they represent two of today's most frequently used methods. The TTF method is used with multiple modalities and has frequently been considered the most accurate method. The XC method was introduced more recently and has gained popularity due to its robustness inherent to the use of the complete flow waveform. Additionally, age-related global and regional PWV in the ascending aorta were compared against corresponding data available in the literature.

Numerical results are reported as mean ± one standard deviation, unless otherwise noted. One-way analysis of variance (ANOVA) with Tukey's honestly significant difference (HSD) post-hoc analysis was used to assess the difference between the different methods for extracting travel-time. The difference between the TTF and XC methods was further assessed by linear regression and Bland-Altman analysis [32]. Two-way ANOVA was used to assess the interaction between age and location. All calculations were done in Matlab (Mathworks, Natick, MA, USA).

3. RESULTS

The PWV for the different age groups, locations and methods evaluated in this study are shown in **Table 2**. One-way ANOVA revealed a significant difference in PWV_{global} among the six different methods for extracting PWV (one-way ANOVA, $P < 0.001$. Post-hoc tests further showed that PWV_{global_FA}, PWV_{global_XC} and PWV_{global_COM} were higher than PWV_{global_TTU}, PWV_{global_TTF} and PWV_{global_TTF2}, although the difference between the XC method vs. TTU and TTF2 methods was not significant. Moreover, there were no significant differences between PWV_{global_FA} vs. PWV_{global_XC} vs. PWV_{global_COM} or PWV_{global_TTU} vs. PWV_{global_TTF} vs. PWV_{global_TTF2}, respectively, for any of the two age groups.

A direct comparison between the XC method and TTF method with linear regression and Bland-Altman analysis revealed that $PWV_{\_global\_XC}$ tended to be higher than $PWV_{\_global\_TTF.}$ The estimated linear regression function was $PWV_{global\_XC} = 2.37 + 0.97^* PWV_{global\_TTF}$ ($r^2 = 0.76$), where both the slope and intercept were significantly different from zero. In the Bland-Altman analysis, bias ± 2SD was 2.21 ± 1.01 m/s. The same tendency can be observed for regional PWV, as seen in Table 1.

Paired two-tailed t-tests demonstrated that PWV_{global} was significantly higher in the older compared to the younger volunteers with both the XC method and TTF method. Further, a significant interaction between age and site of increased PWV was found for both methods (two-way ANOVA, $P < 0.05$). Profile plots of PWV versus location (see **Figure 2**) demonstrate that the age-related differences in regional PWV were greatest in the proximal descending aorta and smallest in the distal suprarenal descending aorta. These age-related changes in PWV were significant for the proximal descending aorta and the mid descending aorta for both the XC and TTF methods (one-way ANOVA, $P < 0.01$). The age-related difference in distal suprarenal descending aorta did not reach significant levels for any of the methods (one-way ANOVA).

Age-related regional PWV with the TTF method in the young vs. older subjects were 3.7 ± 0.4 vs. 8.8 ± 3.5, 3.3 ± 0.5 vs. 7.0 ± 2.1, and 4.5 ± 0.8 vs. 5.2 ± 1.5 m/s for the proximal, mid and distal descending aortic segments, respectively. The corresponding numbers for the XC method were 4.2 ± 0.7 vs. 10.2 ± 3.6, 5.7 ± 1.6 vs. 10.6 ± 3.8, and 4.6 ± 0.8 vs. 6.9 ± 1.7. A comparison between these values of age-related regional PWV and those reported in previous studies is shown in **Figure 3**. The TTF method appears to match literature data better than the XC method.

4. DISCUSSION

4D flow MRI allows PWV assessment with both the traditional “time to travel a fixed distance” approach and the opposite “distance travelled in a fixed time” approach. In the present study employed a combined approach based on the extraction of flow waveforms throughout a vessel of interest. In this approach, the travel-distance variable is mapped based on 3D vascular anatomy derived from the 4D flow MRI data and the travel-time variable is

calculated by conventional transit-time methods. As the choice of method can impact the results, six different methods for estimation of travel-time were evaluated in the present study. The findings of the inter-method comparisons suggest that the six methods can be divided into two different groups. One group that operates on the upslope portion of the waveform (TTU, TTF, and TTF2) and one group that operates on larger parts of the waveform (FA, XC, and COM). As previous studies have pointed out, the latter class of methods is more sensitive to the presence of reflected waves [20,21,29]. All methods in the latter group produced PWV_{global} values that were higher than those in the former group. There were no significant differences within the groups of methods. A direct comparison between the TTF and XC methods indicated that the XC method overestimates PWV_{global} by about 2m/s compared to the TTF method. These findings indicate that care must be taken when interpreting PWV values obtained with different methods for estimation of travel-time. The age-related regional PWV obtained with the TTF method better matched the patterns of age-related regional PWV that have been reported previously [10,16,20].

To our knowledge, the present study is the first to report 4D flow MRI-based estimation of age-related regional PWV. Our results on age-related regional PWV obtained with the TTF method agree well with previously reported data and show that the PWV in the descending aorta is homogeneous in young subjects and markedly heterogeneous in older subjects [10,16,20]. We also found that the PWV increases more rapidly with age in the proximal compared to distal suprarenal descending aorta. A structural explanation for this observation may be derived from the fact that the ratio between elastin to collagen decreases towards the distal parts of the aorta, in combination with the life-long fragmentation of elastin [29]. It should be noted that this and previous studies have observed a trend towards increased PWV with age also in the distal aorta, although the studies have been too small to statistically verify this

difference [10,16,20]. However, this trend has been confirmed by larger-scale investigations of local stiffness in the distal aorta [33].

In 4D flow MRI, high temporal resolution is costly in terms of increased scan time. Consequently, the acquired temporal resolution of 4D flow MRI is often low compared to other techniques used to estimate PWV. However, 4D flow MRI offers full 3D coverage. High temporal resolution is crucial for the conventional "time to travel a fixed distance"-approach, which aims to determine travel-time based on the timing of the pulse wave at two discrete locations. Low precision in the assessment of timing (i.e. if temporal resolution is low, or if data is noisy) directly impacts the precision of the PWV estimate. The situation becomes different when the distance in not regarded as fixed, as in the present study and previous 4D flow MRI studies [14,18]. Treating distance as a continuous variable enables the use of analysis locations along the entire aorta. Clearly, temporal resolution and noise define the precision with which the timing of the pulse wave can be determined at each specific location. However, when the timing information from all locations is combined (here using linear regression, see Figure 1C), the significance of the lack of precision of each individual observation, and thus the sensitivity to temporal resolution, is reduced. In the present study, we found that 4D flow MRI-based regional PWV closely matches regional PWV data available in the literature (see **Figure 3**). An age-based comparison of our results on global PWV in the descending aorta corresponding high-temporal resolution PWV data available in the literature provides complementary support of the promising performance of 4D flow MRI (see **Table 3**). This accord well with previous comparisons between 4D flow MRI and methods with higher temporal resolution [14,18]. Nevertheless, further studies are needed to assess the impact of temporal resolution, as well as spatial resolution, on PWV estimates. Future work should also assess the minimum vascular distance along which PWV can be

calculated for different spatial and temporal resolutions. Another intriguing aspect for future work is to improve the combination of the "time to travel a fixed distance" and "distance travelled in a fixed time" approaches. Linear regression modeling of the relationship between the travel-distance and travel-time variables, as used here, may not be the optimal way to exploit the full 4D spatiotemporal coverage.

An important limitation of the present study is that we did not have access to gold standard catheter-based PWV estimates in our normal volunteers. Neither did our imaging protocol include 1D FVE or multi-planar 2D cine PC-MRI. We are therefore unable to report on the precision of 4D flow MRI-based PWV estimation relative to the gold-standard method as well as to other MRI methods. Consequently, the comparison of different methods for the estimation of travel-time may only be valid for the type of 4D flow data and data processing used in this study.

5. Conclusion

4D flow MRI-based PWV estimation with piecewise linear regression modeling of travel-distance vs. travel time can discern age-related differences in regional PWV well in line with previously reported data. However, care must be taken as different classes of methods for the estimation of travel-time based on flow waveforms obtained by 4D flow MRI produce different results. Methods that use information from the complete flow waveform estimate higher PWV than methods that are restricted to the upslope portion of the flow waveform.

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TABLES

Table 1. Demographics

	Age (years)	Height (cm)	Weight (kg)	Blood pressure (mmHg)*	Heart rate (bpm)**
Young Normal Volunteers	23	181	69	118/70	64
	24	185	77	131/67	59
	21	182	67	134/74	68
	23	186	73	125/58	61
	24	187	72	116/73	63
	26	178	71	115/65	55
	21	188	72	125/65	65
	24	179	75	133/73	65
Older Normal Volunteers	56	187	90	121/78	50
	56	182	72	132/78	67
	55	180	87	133/82	64
	57	190	78	143/88	48
	60	167	61	128/76	60
	58	178	72	123/74	68
	58	182	85	127/78	60
	60	173	81	131/74	54

* Systolic/diastolic blood pressure measured over the left arm prior to the MRI exam.
** Heart rate during MRI

Table 2. PWV for the different age groups, locations and methods evaluated in this study.

	FA	XC	COM	TTU	TTF	TTF2
$PWV_{\_global\_young}$	5.7 ± 0.7	5.5 ± 0.7	6.0 ± 0.7	3.9 ± 0.4	3.6 ± 0.3	3.7 ±0.3
$PWV_{\_global\_old}$	9.3 ± 1.3	8.9 ± 1.4	9.2 ± 1.3	6.3 ± 2.3	6.4 ± 1.7	6.8 ± 2.6
$PWV_{\_prox\_young}$	4.3 ± 0.8	4.2 ± 0.7	4.6 ± 0.9	3.3 ± 0.6	3.7 ± 0.4	4.2 ± 0.7
$PWV_{\_prox\_old}$	8.8 ± 1.6	10.2 ± 3.6	9.1 ± 2.1	5.7 ± 2.2	8.8 ± 3.5	8.9 ± 4.5
$PWV_{\_mid\_young}$	6.6 ± 2.2	5.7 ± 1.6	6.3 ± 1.8	4.0 ± 0.7	3.3 ± 0.5	3.3 ± 0.6
$PWV_{\_mid\_old}$	11.2 ± 3.7	10.6 ± 3.8	10.5 ± 3.1	7.2 ± 4.5	7.0 ± 2.1	7.7 ± 4.2
$PWV_{\_dist\_young}$	5.1 ± 0.7	4.6 ± 0.8	5.8 ± 1.0	5.6 ± 1.6	4.5 ± 0.8	4.9 ± 1.3
$PWV_{\_dist\_old}$	7.3 ± 1.7	6.9 ± 1.7	7.6 ± 1.7	5.5 ± 1.7	5.2 ± 1.5	5.6 ± 2.5

Table 3. Age-related descending aortic PWV in the present study compared to previous studies with higher temporal resolution methods [13,16].

Study	**Method**	**Temporal resolution [ms]**	**Age (mean** ± 1 SD) **[years]**	**Global PWV in desc ao (mean** ± 1 SD) **[m/s]**
Present study	4D flow MRI	39-43	23 ± 2	3.6 ± 0.4
Grotenhuis et al. [13]	2D through-plane PC-MRI	6-10	29 ± 8	4.3 ± 0.6
Taviani et al. [16]	1D FVE MRI	3.5	~30*	4.2 ± 0.7
Taviani et al. [16]	1D FVE MRI	3.5	~50*	5.9 ± 0.9
Present study	4D flow MRI	39-43	58 ± 2	6.4 ± 1.7
Taviani et al. [16]	1D FVE MRI	3.5	~70*	8.0 ± 1.3

* Approximate mean age calculated as the average of the age ranges reported by Taviani et al [16].

FIGURE LEGENDS

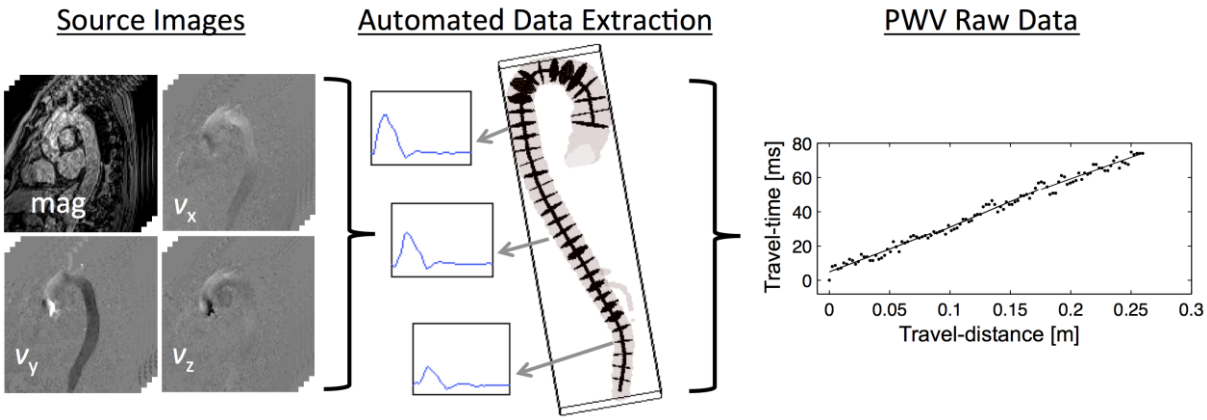

Figure 1. Schematic of semiautomatic 4D flow MRI-based estimation of regional PWV based on extraction of flow waveforms throughout a vessel of interest. Velocity and magnitude images (left) are combined to generate a PC-MR angiogram that is used for segmentation of the aortic lumen. A centerline is extracted from the segmentation and this centerline is used to define locations for extraction of pulsatile flow waveforms throughout the aorta (middle). The travel-time and travel-distance variables are calculated and subsequently combined in a 2D graph that can be interrogated for regional PWV estimation (right).

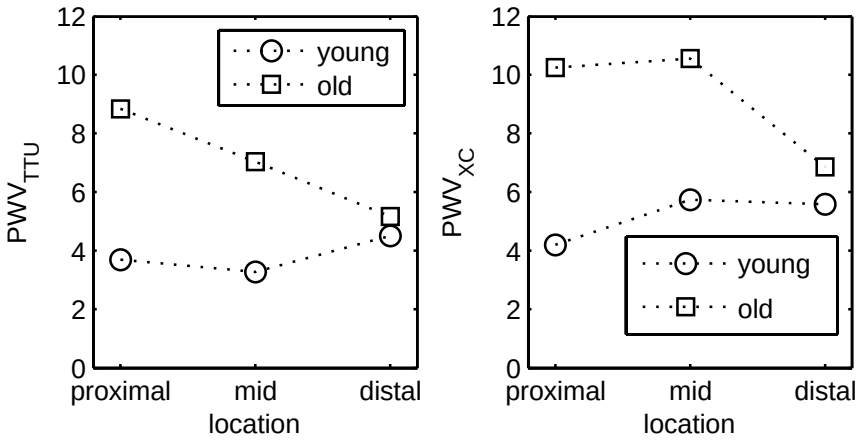

Figure 2. Profile plots of group means of regional PWV as measured with the TTF (left) and XC (right) methods in young (circles) and older (squares) subjects. For both methods, the

location-dependency of PWV is more pronounced in the older compared to younger volunteers, the age-dependency is more pronounced in the proximal compared to distal suprarenal descending aorta, and there is an interaction between age and location.

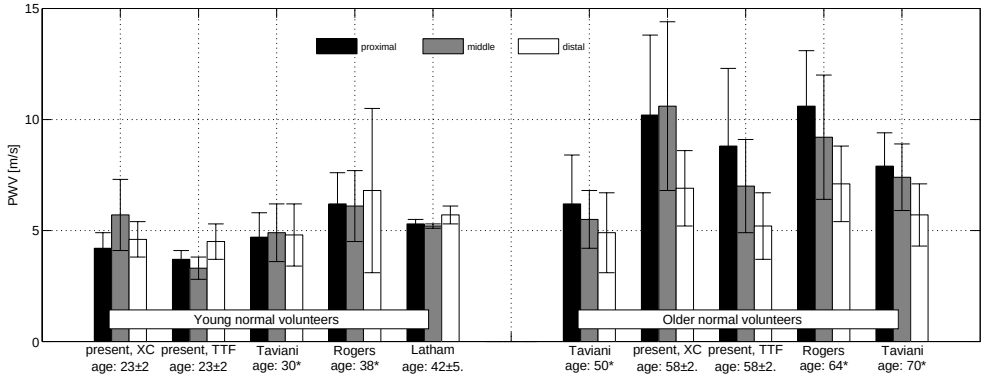

Figure 3. Age-related regional PWV in the present study as obtained with the TTF and XC methods are compared against results previously published by Latham et al [20], Rogers et al [10], and Taviani et al [16]. Left: PWV data for the proximal (black), mid (gray) and distal (white) descending aorta in younger subjects (<50 y.o.). Right: corresponding data in older subjects (>50 y.o.). The mean age (*approximated mean age) is indicated below each triplet of bars.