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Pulse wave velocity normal levels in a Uruguayan population: differences between 'adjusted' and measured values vary depending on age and the calculation algorithm used

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Abstract— **Carotid-femoral pulse wave velocity (PWV) has emerged as the gold standard for non-invasive evaluation of aortic stiffness. However, the absence of standardized methodologies of study and lack of normal and references values have limited wider implementation of PWV in clinical practice. In this work normal PWV levels were determined in a Uruguayan population and the obtained values were analyzed taking into account data from other populations. The differences between the ´real´ PWV levels and the PWV calculated using different wave detection algorithms and path lengths were assessed, and compared the taking into account the changes in PWV with aging. Results: The Uruguayan population showed a rate of PWV increase comparable to that reported previously in non-hypertensive European subjects, although overall, PWV values were approximately 2 m/s higher in the Uruguayan population. The different approaches used to calculate the PWV showed differences in their availability to follow aging-variations in 'adjusted' (or 'real') PWV.**

I. Introduction

Non- invasive vascular evaluation has emerged as a useful tool for cardiovascular (CV) diagnosis and risk stratification. Among other structural and functional vascular indexes used to those ends, arterial stiffness has shown to be a valuable/advantageous parameter. In turn, from the different non-invasive methods and parameters used to assess arterial stiffness, carotid-femoral pulse wave velocity (PWV) has emerged as a gold standard due to its accuracy, reproducibility, relatively easy measurement and low costs [1], [2]. Even of more importance is that the measure of aortic stiffness through PWV has yielded prognostic value beyond and above traditional risk factors [3].

Arterial stiffness increases with age [1], which is a major determinant of PWV and should be considered at the time of evaluating PWV. Furthermore, despite several factors have shown to influence the PWV, in many cases their effects would be negligible after correction for age [2].

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However, and in spite of its recognized value a wider implementation of PWV into clinical practice has been hampered, among other factors, by the absence of standardized methodologies of study, and due to the lack of established normal and reference values for different populations [2]. About this, is worth noting that PWV assessment involves measuring both, the arterial waveform transit time along the analyzed vascular region and the distance on the skin between the recording sites. Then, PWV values depend on both, the path length measurement and the algorithm used for detecting the analyzed waves 'foot'. The algorithms most frequently used are the intersecting tangent and the point of maximal upstroke during systole [2]. In turn, the pathway length can be either the direct distance between the carotid and femoral measurement sites, or the distance obtained by subtracting the carotid measurement site to sternal notch distance from the sternal notch to femoral measurement site distance. Different algorithms applied to the same waves can lead to differences in PWV of 5–15%, while differences in path length alone can result in differences in PWV values of up to 30% [4]. Normal and reference values for a European population categorized by age, and the way to convert PWV values obtained with a methodology to values for other approaches have been recently published [2], [5].

This work aims were to a) quantify PWV normal levels for a healthy Uruguayan population, b) evaluate age-associated changes in PWV and c) analyze and compare the differences between 'adjusted' or 'real' PWV values and those obtained using different wave detection algorithms and path lengths, taking into account the changes in PWV with aging. A comparison with data from other populations was done.

II. Methods

The Human Research Committee of the Republic University (Uruguay) approved all procedures. Subjects gave written informed consent. The study was carried out according to international ethic rules and the Helsinki Declaration principles.

1. *Study population and subjects groups*

Asymptomatic subjects (n=210, 164 women, age range: 20-69 years old), without known cardiovascular disease and consecutively referred for vascular evaluation in the context of the CUiiDARTE Project were included. The Project is a population-based national study designed to evaluate structural and functional vascular parameters to assess arterial aging, CV risk and sub-clinical atherosclerosis.

None of the included subjects was taking CV acting medications or had CV risk factors (other than risk related with gender and age). To obtain 'normal' PWV levels, subjects were considered for data analysis if they did not show high blood pressure levels (sistolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90mmHg). Subjects´ main characteristics are detailed in Table I.

Table I Clinical characteristics of the study group (n=210)

	20-29	30-39	40-49	50-59	60-69
n, (female)	74, (57)	28, (22)	40, (29)	53, (46)	15, (10)
Age, year	22 ± 2	35 ± 3	46 ± 3	54 ± 3	64 ± 3
Height, cm	167 ± 9	165 ± 8	164 ± 9	160 ± 8	158 ± 9
Weight, kg	65 ± 13	72 ± 16	75 ± 16	73 ± 15	71 ± 15
BMI, kg/m2	22 ± 4	26 ± 5	27 ± 5	28 ± 5	28 ± 6
SBP, mm Hg	123 ± 11	126 ± 13	129 ± 10	129 ± 8	130 ± 8
DBP, mm Hg	71 ± 8	74 ± 10	77 ± 9	77 ± 11	78 ± 11
HR, bpm	72 ± 11	72 ± 8	71 ± 10	72 ± 11	69 ± 7

Values expresed as mean ± standard deviation.

BMI: Body mass index, SBP: Sistolic blood pressure, DBP: Diastolic blood pressure, HR: Heart rate

Experimental protocol

Vascular evaluation was done after 9-12 hours overnight fast. Exercise, caffeine, alcohol, and vitamin C were avoided prior (at least six hours) to the examination. Before PWV measurement, subjects rested for 5-10 minutes in supine position in a temperature-controlled, to reach physiological baseline conditions.

The carotid and femoral pulse waves were measured using mechano-transducers placed simultaneously on the skin over the arteries (Hemodyn 4-M, Buenos Aires, Argentina). From those recordings, PWV was automatically calculated as the quotient between the carotid-femoral (C-F) distance and the pulse transit time difference. To this end, the maximal upstroke (max up) algorithm and straight distance between recording sites (direct distance, cf) were considered [6]. The reported PWV value was always the average of at least 8 consecutive beats. Brachial pressure and heart rate were quantified during PWV assessment (Omron HEM-433INT Oscillometric System; Omron Healthcare Inc., Illinois, USA).

From the calculated PWV values, 'real' PWV (PWVr) was obtained. PWVr is a standardized PWV, obtained if the C-F direct distance and the intersecting tangent algorithm are used, and the obtained value is multiplied by 0.8 (to reach more realistic PWV values) [2].

From the measured PWV we obtained the PWV values for the intersecting tangent (int tang) algorithm, and PWV values obtained considering the sternum-femoral distance (sf, sf = C-F direct distance minus the suprasternal notch-carotid distance), and the substracted distance (sub, sub = suprasternal notch-femoral distance minus the suprasternal notch-carotid distance) [4], [2]. [6]. Then, for each subject seven PWV values were calculated.

The age-range was selected taking into account recent international consensus that recommends starting non-invasive arterial evaluation at ~20 years-old. To analyze age –related PWV changes, subjects were divided into the following age groups: 20-29 (n= 74), 30-39 (n= 28), 40-49 (n= 40), 50-59 (n= 53), 60-69 (n= 15) years old.

Age-related PWV profiles were constructed considering PWV values obtained using different path lengths and algorithms of calculation. The differences (absolute and relative) between PWV calculated by means of the different algorithms and path lengths, and the PWVr were determined.

Statistics: PWV values were compared using ANOVA and unpaired t tests. Significance level: $p<0.05$.

III. Results

PWV could be measured in all the included subjects. A main result of this work was the establishment of PWV normal values for a Uruguayan population (Table II).

Table II. Pulse wave velocity

	20-29	30-39	40-49	50-59	60-69
	MV ± SD	MV ± SD	MV ± SD	MV ± SD	MV ± SD
"Real" PWV	7.3 ± 1.5	8.3 ± 1.3	9.3 ± 2.3	10.3 ± 4.1	11.8 ± 3.4
PWV cf/int tang	9.1 ± 1.9	10.4 ± 1.6	11.7 ± 2.9	12.8 ± 5.1	14.8 ± 4.3
PWV cf/max up	8.4 ± 1.3	9.3 ± 1.1	10.1 ± 1.7	10.6 ± 2.7	12.0 ± 2.3
PWV sf/max up	7.2 ± 1.1	8.0 ± 1.0	8.7 ± 1.5	9.1 ± 2.3	10.3 ± 2.0
PWV sf/int tang	7.8 ± 1.6	8.9 ± 1.4	10.0 ± 2.5	10.9 ± 4.3	12.7 ± 3.7
PWV sub/max up	6.0 ± 1.0	6.7 ± 1.1	7,2 ± 1.3	7.7 ± 2.2	9.0 ± 2.8
PWV sub/int tang	6.5 ± 1.4	7.4 ± 1.3	8.3 ± 2.1	9.3 ± 3.8	11.2 ± 4.9

Values expresed as mean ± standard deviation.

PWV values are presented per age decade [Fig 1; Table II]. As can be seen in [Fig 1. and Table II], the studied population showed the expected increase in aortic stiffness (PWV) with age, which was evidenced with the different algorithms and path lengths used.

There were differences between PWVr levels and calculated PWV values ($p<0.05$). The differences between PWVr and calculated PWV levels varied depending on the algorithm and distance considered ($p<0.05$). About this, PWVr was overestimated if direct distance was used to calculate PWV, while the use of substracted distance resulted in an underestimation of the PWVr. When the sternum-femoral distance was considered, with dependence on the algorithm used, the PWVr was underestimated (max up) or overestimated (int tang) [Fig 1].

There were age-associated variations in the differences (absolute and relative values) between PWVr and the PWV measured [Figs 2 and 3]. Such variations depended on the approach used to calculate PWV. For instance, when $PWV_{sf/max\ up}$ was considered the differences increased with age, while they diminished if $PWV_{cf/max\ up}$ was considered. Finally, it is noteworthy that the relative differences between 'real' and measured PWV did not change with aging when $PWV_{cf/int\ tang}$ was considered.

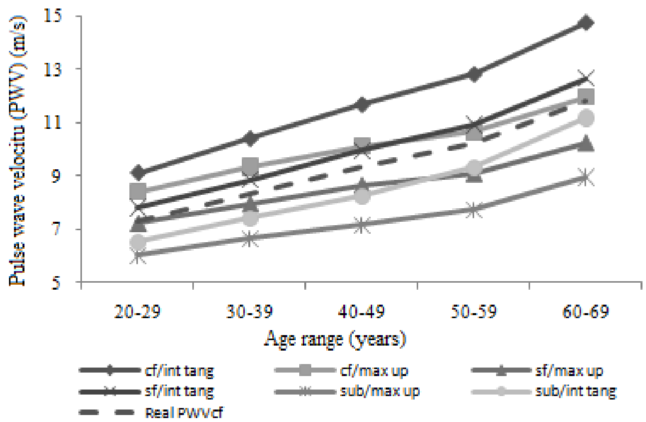

Fig 1. Age-related PWV profiles for the different approaches used. int tang: intersecting tangent; max up: maximal upstroke; cf: carotid-femoral direct distance; sub: subtracted distance; sf: sternum-femoral distance

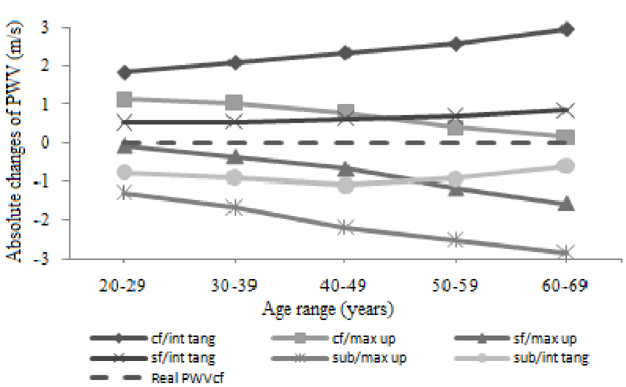

Fig 2. Differences (absolute values) between 'real' and measured PWV levels for the different age groups. int tang: intersecting tangent; max up: maximal upstroke; cf: carotid-femoral direct distance; sub: subtracted distance; sf: sternum-femoral distance.

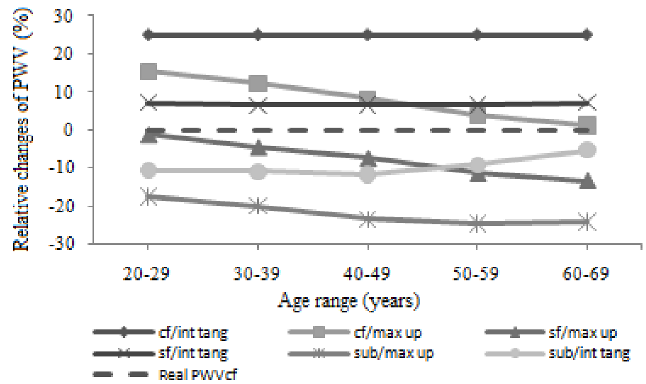

Fig. 3. Differences (relative values) between 'real' and measured PWV levels for the different age groups. See Fig 2 for abbreviations.

IV. Discussion

PWV is considered the gold standard measure of the regional stiffness of an arterial pathway (territory) between two measurement sites. It depends mainly on the vascular geometry (diameter) and the arterial wall intrinsic properties (elasticity), as can be observed in Moens and Korteweg equation [1]. Although different in nature, waves such as pressure, distension or flow waves are theoretically in phase early in the cardiac cycle, and can be used alternatively to calculate PWV. Anyway, pressure wave is the signal most frequently used to evaluate PWV. It is noteworthy that PWV depends on the arterial blood pressure levels, which have to be considered at the time of analyzing PWV values. In addition, since the arterial stiffness depends on pressure, PWV would vary within the cardiac cycle. Then, a critical issue is the reference point in the wave ('foot'), for which the time delay is calculated to determine the PWV. Related with this, different algorithms have been used to determine the wave transit time. It has been demonstrated that they provide proportional results [2]. In this work we used the maximal upstroke algorithm and the direct C-F distance to calculate, automatically the PWV. Then, PWV values were converted to those obtained using the intersecting tangents algorithm and considering different distance paths [2].

The obtained PWV values were compared with the PWVr and the differences between 'real' and calculated PWV values were analyzed taking into account the PWV variations with aging. About this, we found that the different approaches proposed to assess PWV approximate PWVr, which was underestimated or overestimated depending on the way PWV was calculated. Furthermore, it is noteworthy that there were age related-variations in the differences between 'real' and calculated PWV, for the different approaches. This could not be a minor finding, since age is a major PWV determinant and aging associates changes (increase) in PWV. Related with this it should be noted that frequently a unique value is used to describe the way the calculated PWV overestimates or underestimates the real PWV. In this context, looking at our results it could be said that if age-related variations in ‘real’-calculated PWV differences are not taken into account, depending on the approach used to calculate PWV, the aging-related changes in PWV could not be adequately identified. About this, it should be remarked that aging associates, respectively, a reduction and an increase in PWV_{real}-$PWV_{cf/int\ tang}$ and PWV_{real}-$PWV_{sf/max\ up}$ differences. Anyway, it should be mentioned that the role of age in determining PWV should be carefully considered since, as it has been discussed for blood pressure; it is not clear whether normality should be defined according to age [2].

As was stated, PWV also depends on blood pressure, and it has been demonstrated that aging-associated PWV variations show differences depending on blood pressure levels. In this work, so as to obtain and analyze normal PWV levels none of the subjects showed high pressure levels. This group of subjects has shown the lower PWV values and the weakest aging-related changes in PWV [6].

Looking at our findings related with the differences among the PWV approaches to follow aging associated changes in PWVr, it would be of interest to analyse the differences between ‘real’ and calculated PWV for different ages in hypertensive subjects.

Finally, it is worth analyzing our results taking into account normal and reference PWV values recently published for a European population [2]. From the authors’ data, regression lines for mean PWVr, considering the subjects blood pressure levels were: PWV (m/s) = 0.97*decade + 4.26 (Optimal Pressure, <120mmHg and <80mmHg, systolic and diastolic blood pressure respectively), PWV (m/s) = 1.20*decade +4.02 (Normal Pressure, systolic blood pressure 120-129mmHg and/or diastolic blood pressure 80-84mmHg). Optimal and normal blood pressure values were taken from the 2007 European Hypertension guidelines.

In our population of non-hypertensive patients, the relationship was: PWV (m/s) = 1.10*decade + 6.12. Then, our population showed a rate of PWV increase comparable to that found by Boutouyrie et al. in non-hypertensive subjects. On the other hand, it is to note that in average, subjects included in our study showed higher PWV levels than those included in Boutouyrie et al. work [2]. The meaning of the differences in PWV, and the mechanisms that could explain them should be analyzed in future works. Anyway, those differences, add support to that mentioned above related with the importance of obtaining population based normal/reference values to perform a correct interpretation of a subject vascular evaluation.

V. Conclusion

In this work, the PWV levels were obtained for a Uruguayan population. The aging-associated changes in PWVr were analyzed and the capability of the PWV calculated using different algorithms and path lengths to follow the variations in PWVr with aging was evaluated.

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