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Pulse wave velocity and central blood pressure: normal and reference values in older people in Spain

Short title: pulse wave velocity and central pressure reference values in older Spaniards

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There is growing interest in pulse wave velocity (PWV) and central aortic systolic pressure (CASP) as cardiovascular disease (CVD) risk markers that go beyond conventional (brachial) blood pressure (BP)^{1,2}. PWV estimates arterial stiffness and CASP is representative of the “true” blood pressure in major organs. Both parameters can now be reliably estimated through brachial cuff-based oscillometric methods³, however, their clinical utility is limited because of the scarcity of normative data.

Two major international studies have reported pooled normative PWV and CASP values^{4,5}, but none included Spanish data. Thus, this is the first study to report normative values for these parameters in older adults in Spain.

Data were taken from 1824 community-dwelling adults aged ≥ 65 years belonging to the third wave of the Seniors-ENRICA study, a cohort set up in Spain in 2008-2010, which has CASP and PWV data since 2014-2015⁶. Participants gave written consent, and the study was approved by the *La Paz* Hospital Clinical Research Ethics Committee.

Fasting lipids and glucose were analyzed in a central laboratory. Participants reported diagnosed CVD. Diabetes was defined as glucose ≥ 126 mg/dl, previous diagnosis, or current treatment; dyslipidemia as total cholesterol ≥ 240 mg/dl, LDL-c ≥ 160 mg/dl, HDL-c ≤ 40 mg/dl (men) and ≤ 50 mg/dl (women), triglycerides ≥ 250 mg/dl, previous diagnosis or current treatment.

Brachial BP, CASP, and PWV were measured under standardized conditions with a validated oscillometric device (Mobil-O-Graph 24h PWA, I.E.M., Stolberg, Germany; Mediscan, España)³. The mean of the 3 last of 4 measurements was used for analysis. Hypertension was defined as mean brachial systolic BP ≥ 140 mmHg, diastolic BP ≥ 90 mmHg, or current treatment.

Of the 1824 participants, 1544 had valid, complete data on the study variables (**Supplementary Figure**). Of these 1544, 946 were excluded for being treated for hypertension or dyslipidemia, having diabetes, or previous CVD^{4,5}. Of the 598 remaining individuals, 263 were normotensive, with 129 without cardiovascular risk factors (untreated dyslipidemia or current

smoking) forming the “*normal population*”, and 134 with other cardiovascular risk factors. These latter 134 subjects plus the untreated hypertensive patients without (180) or with (155) other risk factors form the “*reference population*”.

Normative data were expressed in percentiles, stratified by sex and age. Analyses were performed using the SPSS v.21.

Participants’ mean age was 72.9 years (57.7%, women) (**Table 1**). Mean BMI, glucose, lipids, and BPs were higher in the reference population. PWV and CASP distributions were non-normal, asymmetric to the right, and with moderate kurtosis. For the total population, median PWV was 10.2 m/s, higher in the reference than the normal population (10.3 vs 10.1, $p=0.042$ with Mann-Whitney test and <0.001 with Wald-Wolfowitz test), in women (10.3 vs 10.1 in men, $p=0.049$), and in ≥ 75 years (11.6 vs 10.0 in <75 years, $p<0.001$) (**Table 2**). Median CASP was 116.6 mmHg, higher in the reference population ($p<0.001$ with both nonparametric tests); this pattern remained by age and sex. Concordance between measurements was close to good (intraclass-correlation coefficients in the three populations for both PWV and CASP: $\sim 0.61-0.67$).

CASP values were quite lower in our study (median ~ 117 mmHg) than in older individuals of a worldwide database (median ~ 126 mmHg)⁵. Although the international pooling used tonometry-based techniques, oscillometric methods yield only smaller CASP values (~ 0.6 mmHg)³. Thus, we suggest that despite methodological standardization across studies, pooling normal/reference data do not necessarily apply to a specific country. From a physiological viewpoint, for a given brachial pulse pressure, the lower the central pulse pressure the more beneficial the effect on the cardiovascular system, because the heart and the aorta would confront lower pulsatile load¹.

Median PWV (10.1 m/s in our normal population) was comparable to that in the pooled database (median, 10.2).⁴ On average, over half the older population would have arterial stiffness (PWV >10 m/s)² and thus would be at higher cardiovascular risk.

This study's main limitation is that we did not use the gold-standard method to estimate CASP and PWV, nevertheless, oscillometric methods are as effective as using tonometry-based methods^{1,3}. Further, by using the same technique and protocol for all participants, our study avoided the strong centre/technique interaction in major pooling studies^{4,5}. Although our sample was not representative of the older population of Spain because ours is a cardiovascular health study, the sex distribution was rather comparable to that in Spain and, as expected, it had relatively lower frequency of the oldest subpopulation since we excluded additional CVD or risk factors^{4,5}. Additional exclusion of patients with renal disease did not change substantially main results. Although some differences in parameters between normal and reference populations were statistically significant, they were generally small and not necessarily clinically relevant. Lastly, our limited sample size, especially the normal population, hindered a wider stratification by age, nevertheless it allowed for precision of estimates generally <5%.

This report represents one step toward the clinical application of PWV and CASP, providing guidelines for assessing older patients' vascular status besides brachial systolic BP. However, further studies should obtain evidence for effective intervention on these parameters.

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Table 1. Characteristics of the study participants

	Total	Normal population	Reference population	p
N	598	129 (21.6)	469 (78.4)	
Age (years)	72.9±5.5	72.5±4.9	73.0±5.7	0.340
Sex, n (%)				
Men	253 (42.3)	43 (33.3)	210 (44.8)	0.020
Women	345 (57.7)	86 (66.7)	259 (55.2)	
Body Mass Index (kg/m ²)	26.5±4.0	25.6±3.7	26.7±4.0	0.005
Body Mass Index ≥30 kg/m ² , %	103 (17.2)	19 (14.7)	84 (17.9)	0.397
Smoking, n (%)				<0.001
Non-smoker	349 (58.4)	94 (72.9)	255 (54.4)	
Ex-smoker	193 (32.3)	35 (27.1)	158 (33.7)	
Current smoker	56 (9.4)	0	56 (11.9)	
Systolic blood pressure (mmHg)	135.8±17.2	123.3±9.5	139.3±17.2	<0.001
Diastolic blood pressure (mmHg)	81.2±10.4	74.9±7.8	82.9±10.4	<0.001
Glycemia (mg/dl)	92.2±11.4	90.1±11.4	92.7±11.3	0.019
Creatinine (mg/dl)	0.73±0.17	0.69±0.16	0.74±0.16	0.003
Dyslipidemia, n (%)	259(43.3)	0	259(55.2)	<0.001
Total cholesterol (mmol/l)	196.4±32.9	191.6±25.0	197.7±34.7	0.064
HDL-cholesterol (mg/dl)	56.7±13.6	60.8±11.8	55.5±13.8	<0.001
LDL-cholesterol (mg/dl)	119.6±27.4	113.9±21.6	121.2±28.6	0.002
Triglycerides (mg/dl)	89 (72-117)	79 (63-99)	91 (74-123)	<0.001

Values are mean±SD (or mean interquartile range) for continuous variables or percentage for categorical variables. Differences in study characteristics between groups were tested with the Student's t test for normal-distribution continuous variables or the U Mann-Whitney test otherwise, and the χ^2 for categorical variables.

Table 2. Normal and Reference values for Pulse Wave Velocity (m/seg) and Central Arterial Systolic Pressure by age and sex

	Total			Normal Population			Reference population			P*
	N	Median (p25-p75)	P10-P90	n	Median (p25-p75)	P10-P90	N	Median (p25-p75)	P10-P90	
Pulse Wave Velocity (m/seg)										
Total	598	10.2 (9.1-11.1)	7.3-12.3	129	10.1 (9.0-10.7)	7.4-11.8	469	10.3 (9.1-11.3)	7.3-12.4	0.042
Men	253	10.1 (8.8-11.0)	6.4-12.4	43	9.9 (9.0-10.5)	7.5-12.0	210	10.1 (8.6-11.1)	5.6-12.6	0.429
Women	345	10.3 (9.3-11.1)	7.6-12.2	86	10.2 (9.0-10.8)	6.7-11.6	259	10.4 (9.4-11.4)	7.8-12.4	<0.001
P		0.049			0.740			0.024		
Age (years)										
<75	410	10.0 (9.0-10.6)	7.4-11.0	90	9.8 (9.0-10.4)	7.4-10.8	320	10.0 (9.0-10.7)	7.3-11.1	0.128
≥75	188	11.6 (9.5-12.6)	7.2-13.4	39	11.0 (9.2-12.1)	5.2-12.9	149	11.8 (9.6-12.7)	7.3-13.6	0.035
P		<0.001			<0.001			<0.001		
Central Arterial Systolic Pressure (mmHg)										
Total	598	116.6 (100.0-128.0)	77.3-139.5	129	110.8 (97.5-118.7)	76.3-122.0	469	119.5 (101.3-131.9)	77.3-143.3	<0.001
Men	253	115.0 (98.8-130.3)	72.3-141.9	43	108.8 (92.5-118.3)	76.1-122.5	210	118.0 (98.9-132.5)	67.2-145.5	0.001
Women	345	117.8 (103.0-127.5)	83.9-138.5	86	112.4 (97.9-118.8)	76.8-122.0	259	120.3 (105.3-130.8)	84.3-141.3	<0.001
P		0.457			0.610			0.300		
Age (years)										
<75	410	116.4 (102.3-126.3)	81.6-137.4	90	111.7 (100.8-118.4)	83.3-122.0	320	119.1 (102.3-130.3)	79.5-139.5	<0.001
≥75	188	117.1 (97.0-131.8)	71.9-147.3	39	109.3 (91.0-118.8)	53.3-122.5	149	121.0 (99.3-135.4)	74.5-149.3	<0.001
P		0.586			0.470			0.302		

* Values of statistical significance of the PWV and CASP between normal and reference population. Comparisons between groups were done using the U Mann-Whitney test.

Supplementary material.

Figure legend

Supplementary FIGURE. Flowchart describing selection of the normal and reference value populations

HT: Arterial Hypertension; DL: Dyslipidemia; CVD: Cardiovascular disease; CVRFs: cardiovascular risk factors (untreated dyslipidemia or current smoking).