developed a transitory acute arterial occlusion that resolved spontaneously with no complications.[2]

Our study confirms the ability of thermodilution with continuous infusion of room-temperature saline to quantify functional parameters of intracoronary blood flow in a population of patients with no angiographically significant coronary lesions. These quantified variables are obtained by the infusion of saline solution through a specially designed catheter. This new method is the first to allow quantitative measurement of MCF and minimal vascular resistance. A recent study confirmed that intra-arterial infusion of room-temperature saline solution can induce vasodilation in the absence of adenosine.[3] However, until now there were no published data on MCF and minimal microvascular resistance in human patients. Further studies are needed to determine the normal values for these parameters and the implications of their alteration in different disease settings.

Fernando Rivero, Teresa Bastante, Javier Cuesta,
Marcos García-Guimaraes, Ramón Maruri-Sánchez,
and Fernando Alfonso*

Servicio de Cardiología, Hospital Universitario de La Princesa, IIS-IP, Universidad Autónoma de Madrid, Madrid, Spain

* Corresponding author:
E-mail address: falf@hotmail.com (F. Alfonso).

Available online 28 December 2017

REFERENCES

1. Van't Veer M, Adjedj J, Wijnbergen I, et al. Novel monorail infusion catheter for volumetric coronary blood flow measurement in humans: in vitro validation. *EuroIntervention.* 2016;12:701–707.
2. Garcia-Guimaraes M, Rivero F, Cuesta J, Alfonso F. Iatrogenic coronary artery dissection induced during invasive absolute coronary blood flow measurement: optical coherence tomography findings. *EuroIntervention.* 2017;13:364–365.
3. De Bruyne B, Adjedj J, Xaplanteris P, et al. Saline-induced coronary hyperemia: mechanisms and effects on left ventricular function. *Circ Cardiovasc Interv.* 2017. http://dx.doi.org/10.1161/CIRCINTERVENTIONS.116.004719.

https://doi.org/10.1016/j.rec.2017.10.040
1885-5857/

Pulse Wave Velocity and Central Blood Pressure: Normal and Reference Values in Older People in Spain

Velocidad de la onda de pulso y presión arterial central: valores normales y de referencia en personas mayores en España

To the Editor,

There is growing interest in pulse wave velocity (PWV) and central aortic systolic pressure (CASP) as cardiovascular disease risk markers that go beyond conventional (brachial) blood pressure (BP).[1,2] Pulse wave velocity estimates arterial stiffness, and CASP is representative of the "true" BP in major organs. Both parameters can now be reliably estimated through brachial cuff-based oscillometric methods[3]; however, their clinical usefulness is limited by the scarcity of normative data.

Two major international studies have reported pooled normative PWV and CASP values,[4,5] but neither included Spanish data. Therefore, 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 from 2008 to 2010, which has had CASP and PWV data since 2014-2015.[6] 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 cardiovascular disease. Diabetes was defined as glucose ≥ 126 mg/dL, previous diagnosis, or current treatment; dyslipidemia as total cholesterol ≥ 240 mg/dL, low-density lipoprotein cholesterol ≥ 160 mg/dL, high-density lipoprotein cholesterol ≤ 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 24 h PWA, I.E.M., Stolberg, Germany; Mediscan, Spain).[3] The mean of the last 3 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 (Figure of the supplementary material). Of these 1544, 946 were excluded for being treated for hypertension or dyslipidemia, having diabetes, or previous cardiovascular disease.[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 participants plus the untreated hypertensive patients without (n = 180) or with (n = 155) other cardiovascular risk factors formed the "reference population".

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

The participants mean age was 72.9 years (57.7%, women) (Table 1). Mean body mass index, glucose, lipids, and BP were higher in the reference population. PWV and CASP distributions were nonnormal, asymmetric to the right, and with moderate kurtosis. For the total population, median PWV was 10.2 m/s and was higher in the reference than in the normal population (10.3 vs 10.1; P = .042 with Mann-Whitney test and < .001 with Wald-Wolfowitz test), in women (10.3 vs 10.1 in men; P = .049), and in participants aged ≥ 75 years (11.6 vs 10.0 in < 75 years; p < .001) (Table 2). Median CASP was 116.6 mmHg, and was higher in the reference population (P < .001 with both nonparametric tests); this pattern remained when the analysis was stratified by age and sex. The concordance between measurements was close to good (intraclass correlation coefficients in the 3 populations for both PWV and CASP: ∼0.61-0.67).

Central aortic systolic pressure values were lower in our study (median ∼117 mmHg) than in older individuals from 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 does 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 deal with a lower pulsatile load.[1]

Table 1
Characteristics of the Study Participants

	Total	Normal population	Reference population	*P*
N	598	129 (21.6)	469 (78.4)	
Age, y	72.9 ± 5.5	72.5 ± 4.9	73.0 ± 5.7	.340
Sex				.020
Male	253 (42.3)	43 (33.3)	210 (44.8)	
Female	345 (57.7)	86 (66.7)	259 (55.2)	
Body mass index, kg/m²	26.5 ± 4.0	25.6 ± 3.7	26.7 ± 4.0	.005
Body mass index ≥ 30 kg/m²	103 (17.2)	19 (14.7)	84 (17.9)	.397
Smoking				< .001
Nonsmoker	349 (58.4)	94 (72.9)	255 (54.4)	
Exsmoker	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	< .001
Diastolic blood pressure, mmHg	81.2 ± 10.4	74.9 ± 7.8	82.9 ± 10.4	< .001
Glycemia, mg/dL	92.2 ± 11.4	90.1 ± 11.4	92.7 ± 11.3	.019
Creatinine, mg/dL	0.73 ± 0.17	0.69 ± 0.16	0.74 ± 0.16	.003
Dyslipidemia	259 (43.3)	0	259 (55.2)	< .001
Total cholesterol, mmol/L	196.4 ± 32.9	191.6 ± 25.0	197.7 ± 34.7	.064
HDL-cholesterol, mg/dL	56.7 ± 13.6	60.8 ± 11.8	55.5 ± 13.8	< .001
LDL-cholesterol, mg/dL	119.6 ± 27.4	113.9 ± 21.6	121.2 ± 28.6	.002
Triglycerides, mg/dL	89 [72-117]	79 [63-99]	91 [74-123]	< .001

HDL-cholesterol, high-density lipoprotein cholesterol; LDL-cholesterol, low-density lipoprotein cholesterol.
Values are mean ± standard deviation or median [interquartile range] for continuous variables or No. (%) for categorical variables. Differences in study characteristics between groups were tested with the Student *t* test for normally distributed continuous variables or the Mann-Whitney *U* test otherwise, and the chi-square for categorical variables.

Table 2
Normal and Reference Values for Pulse Wave Velocity (m/sec) and Central Arterial Systolic Pressure by Age and Sex

	Total			Normal Population			Reference population			
	N	Median (p25-p75)	P10-P90	n	Median (p25-p75)	P10-P90	N	Median (p25-p75)	P10-P90	*P**
	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	.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	.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	< .001
P		.049			.740			.024		
Age, y										
< 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	.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	.035
P		< .001			< .001			< .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	< .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	.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	< .001
P		.457			.610			.300		
Age, y										
< 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	< .001
≥ 75	188	117.1 (97.0-131.8)	71.9-147.3	39	109.3 (91.0-118.8)	53.3122.5	149	121.0 (99.3-135.4)	74.5-149.3	< .001
P		.586			.470			.302		

* Statistically significant values of the pulse wave velocity and central arterial systolic pressure between normal and reference population. Comparisons between groups were made using the Mann-Whitney *U* test.

Median PWV (10.1 m/s in our normal population) was similar 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 would thus be at higher cardiovascular risk.

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

FUNDING

This work was supported by *Fondo de Investigación Sanitaria* (FIS) grants no. PI13/02321 and 16/01460 (*Instituto de Salud Carlos III* and FEDER/FSE) and CIBERESP. The funding agencies had no role in study design, data analysis, interpretation of results, manuscript preparation or in the decision to submit this manuscript for publication.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found in the online version available at https://doi.org/10.1016/j.rec.2017.11.011.

Mercedes Sánchez-Martínez,[a,b,◇] Juan J. Cruz,[b,◇] Auxiliadora Graciani,[b] Esther López-García,[b,c] Fernando Rodríguez-Artalejo,[b,c] and José R. Banegas[b,*]

[a]*Facultad de Ciencias y Artes, Universidad Católica "Santa Teresa de Jesús", Ávila, Spain*
[b]*Departamento de Medicina Preventiva y Salud Pública, Facultad de Medicina, Universidad Autónoma de Madrid/IdiPAZ y CIBER en Epidemiología y Salud Pública (CIBERESP), Madrid, Spain*
[c]*Instituto de Alimentación IMDEA (Instituto Madrileño De Estudios Avanzados), Campus de Excelencia Internacional, Universidad Autónoma de Madrid + Consejo Superior de Investigaciones Científicas (UAM + CSIC), Madrid, Spain*

* Corresponding author:
E-mail address: joseramon.banegas@uam.es
◇Both authors contributed equally to this work. (J.R. Banegas).

Available online 7 December 2017

REFERENCES

1. Laurent S, Cockroft J. *Central aortic blood pressure. Issy-les-Moulineaux*. France: Elsevier; 2008:35–90.
2. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Practice Guidelines for the Management of Arterial Hypertension. *Blood Press.* 2014;23:3–16.
3. Weiss W, Gohlisch C, Harsch-Gladisch C, Tölle M, Zidek W, van der Giet M. Oscillometric estimation of central blood pressure: validation of the Mobil-O-Graph in comparison with the SphygmoCor device. *Blood Press Monit.* 2012;17:128–131.
4. Reference Values for Arterial Stiffness' Collaboration. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'. *Eur Heart J.* 2010;31:2338–2350.
5. Herbert A, Cruickshank JK, Laurent S, Boutouyrie P; Reference Values for Arterial Measurements Collaboration. Establishing reference values for central blood pressure and its amplification in a general healthy population and according to cardiovascular risk factors. *Eur Heart J.* 2014;35:3122–3133.
6. Banegas JR, Cruz JJ, Graciani A, et al. Impact of ambulatory blood pressure monitoring on reclassification of blood pressure prevalence and control. *J Clin Hypertens.* 2015;17:453–461.

https://doi.org/10.1016/j.rec.2017.11.011
1885-5857/

Effect of Early Treatment With Ivabradine Plus Beta-blockers on Long-term Outcomes in Patients Hospitalized With Systolic Heart Failure

Resultados a largo plazo del tratamiento precoz con ivabradina más bloqueadores beta en pacientes hospitalizados por insuficiencia cardiaca sistólica

To the Editor,

Heart rate (HR) is a parameter with prognostic value in patients with heart failure (HF), reduced ejection fraction and sinus rhythm, showing an inverse relationship with cardiovascular outcomes.[1] The ESC Heart Failure guidelines[2,3] included the achievement of a HR < 70 bpm and a specific drug for HR slowing (ivabradine) in their treatment algorithm.

This indication is based on the SHIFT study[4] (stable chronic HF patients). However, in our recently published ETHIC-AHF study,[5] we demonstrated the safety and efficacy of early coadministration of ivabradine and beta-blockers (IV + BB) during hospitalization in patients with acute systolic HF and sinus rhythm. There are no other randomized data on ivabradine use in acute HF.

The ETHIC-AHF study, whose protocol and results at 4 months have been recently published,[5] compared the strategy recom-

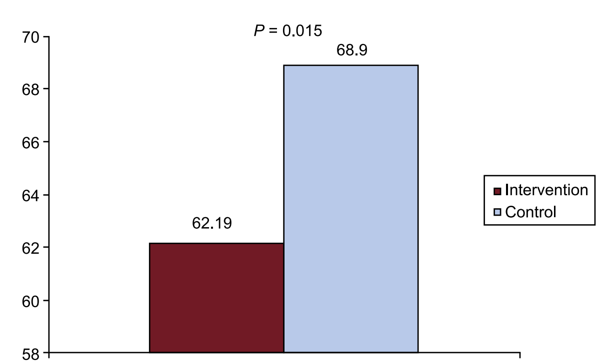

Figure 1. Heart rate in both groups at long-term follow-up.