

Accuracy of a new instrument for noninvasive evaluation of pulse wave velocity: the Arterial sTiffness faitHful tOol aSsessment project

*Original*

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## Original Article

# Accuracy of a new instrument for noninvasive evaluation of pulse wave velocity: the Arterial sTiffness faitHful tOol aSsessment project

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**Background:** Large artery stiffness, assessed by carotid–femoral pulse wave velocity (cfPWV), is a major risk factor for cardiovascular events, commonly used for risk stratification. Currently, the reference device for noninvasive cfPWV is SphygmoCor but its cost and technically challenging use limit its diffusion in clinical practice.

**Aim:** To validate a new device for noninvasive assessment of cfPWV, ATHOS (Arterial sTiffness faitHful tOol aSsessment), designed in collaboration with the Politecnico di Torino, against the reference noninvasive method represented by SphygmoCor.

**Methods:** Ninety healthy volunteers were recruited. In each volunteer, we assessed cfPWV, using SphygmoCor (PWV<sub>SphygmoCor</sub>) and ATHOS (PWV<sub>ATHOS</sub>) devices in an alternate fashion, following the ARTERY Society guidelines. The accuracy was assessed by Bland–Altman plot, and reproducibility was assessed by interoperator correlation coefficient (ICC).

**Results:** Mean PWV<sub>ATHOS</sub> and mean PWV<sub>SphygmoCor</sub> were  $7.88 \pm 1.96$  and  $7.72 \pm 1.95$  m/s, respectively. Mean difference between devices was  $0.15 \pm 0.56$  m/s, with a high correlation between measurements ( $r = 0.959$ ,  $P < 0.001$ ). Considering only PWV values at least 8 m/s ( $n = 30$ ), mean difference was  $0.1 \pm 0.63$  m/s. The ICC was 97.7% with ATHOS.

**Conclusion:** ATHOS showed an excellent level of agreement with SphygmoCor, even at high PWV values, with a good reproducibility. Its simplicity of use could help increase clinical application of PWV assessment, improving patients' cardiovascular risk stratification.

**Keywords:** arterial stiffness, carotid–femoral pulse wave velocity, hypertension-mediated organ damage, noninvasive evaluation, pulse wave velocity, risk factor

**Abbreviations:** Alx, augmentation index; ATHOS, Arterial sTiffness faitHful tOol aSsessment; cfPWV, carotid–femoral pulse wave velocity; CBP, central blood pressure systolic – SBPc diastolic – DBPc mean – MBPc pulse pressure – PPc; EACVI, European Association of Cardiovascular Imaging; HMOD, hypertension-mediated organ damage; ICC, intraclass correlation coefficients; ITM algorithm,

intersecting tangent method; PPA, pulse pressure amplification index; PTT, pulse transit time; PWA, pulse wave analysis; PWVATHOS, cfPWV measured with ATHOS; PWV<sub>SphygmoCor</sub>, cfPWV measured with SphygmoCor; SPSS, Statistical Package for the Social Sciences; TTE, Transthoracic echocardiography

## INTRODUCTION

High blood pressure is a recognized risk factor for cardiovascular disease-related morbidity and mortality. Despite the extensive knowledge about the role of prevention and treatment of arterial hypertension, its prevalence is constantly increasing as the incidence of related cardiovascular complications [1].

Current International Guidelines underline the role of arterial stiffness assessment by carotid–femoral Pulse Wave Velocity (cfPWV) for the management and treatment of high blood pressure [2]. A cfPWV value greater than 10 m/s is identified as an index of hypertension-mediated organ damage (HMOD). Increased aortic stiffness showed an independent predictive value for cardiocerebrovascular events compared with other commonly used cardiovascular risk factors, such as age, smoking, obesity, dyslipidemia [3,4].

In the last years, several methods have been developed for the measurement of PWV [5]. However, this assessment is still currently seldom performed mainly because of both the cost of the required equipment and the technical expertise required.

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The aim of our study was to validate a new noninvasive tool for the measurement of the cfPWV (ATHOS, Arterial stiffness faithful Tool assessment). This device was designed in collaboration with the Politecnico di Torino, Turin – Italy (patent protocol number P3640IT00, 2020-025, dated 20 November 2020 [6]). We tested the ATHOS accuracy comparing the cfPWV values obtained by the new tool against those measured using the current gold standard for the noninvasive measurement of cfPWV (SphygmoCor System) in healthy and hypertensive participants.

## METHODS

### Population

During the initial part of this study (between April 2018 and November 2019), 90 voluntary healthy volunteers were recruited. Patients aged over 18 years and without any known cardiovascular diseases or antihypertensive therapy were enrolled. Study participants were then classified into three groups based on age: less than 30, 30–59 years, at least 60 years.

Eventually (between January 2021 and April 2021), we recruited 30 consecutive hypertensive volunteers of our Hypertension Center, in order to evaluate ATHOS reliability in patients with higher cardiovascular risk. All underwent measurement of anthropometric parameters, such as weight, height and abdominal circumference. Smoking habit, daily alcohol consumption and weekly physical activity hours were assessed. Family history of arterial hypertension, type 2 diabetes mellitus, acute coronary syndrome, ischemic or hemorrhagic stroke, atrial fibrillation, valvulopathies and aortic disease were evaluated as well. Pulse wave analysis (PWA), cfPWV (by reference instrument and ATHOS prototype) and Transthoracic echocardiography (TTE) were assessed on the same day.

The examination took place at the Molinette Hospital, AOU City of Health and Science of Turin, Internal Medicine Department, Echocardiography Laboratory. The study was approved by the local bioethics committee of the University of Turin (protocol number 155412 of 12/04/2018). All the recruited volunteers provided a written informed consent. The investigation complied with the principles outlined in the Declaration of Helsinki.

### Pulse wave velocity

cfPWV assessment by both validated SphygmoCor (SphygmoCor System, Atcor Medical, Sydney, Australia) reference instrument, and by ATHOS (Politecnico di Torino, Turin, Italy) were performed. After illustrating how to acquire the cfPWV with the two devices, each volunteer lied supine for about 15 min in a quiet room. During this period, the arterial pulse was palpated at the carotid and femoral levels, marking with the dermatographic marker the points considered the most appropriate based on the operators' experience.

For each participant, three measurements by ATHOS and three measurements by SphygmoCor were performed. The device-operator alternation was performed respecting the indications provided by the ARTERY Society guidelines for the validation of noninvasive tools for estimating the PWV [7].

### Pulse wave velocity by SphygmoCor

SphygmoCor System is a validated instrument equipped with a transcutaneous applanation tonometer on a pen holder. Being equipped with a single sensor, cfPWV recording require two sequential 10–20 s readings: first the pulse profile at the carotid level is acquired, followed by the registration at the level of femoral artery. As the sampling is not simultaneous, ECG trace is taken, with the R wave used as a reference point. The foot of the wave was obtained using the intersecting tangent method (ITM) algorithm [8]. Average time delay between the two waves foots (pulse transit time, PTT) is then calculated. The inputted distance between recording sites  $d$  can be estimated by superficial measurement and calculated with the '80% method' (direct carotid–femoral distance multiplied by a corrective factor of 0.8) as underlined in international guidelines [2,9,10]. The cfPWV is then calculated as follows:

$$\text{cfPWV (m/s)} = d/\text{PTT}$$

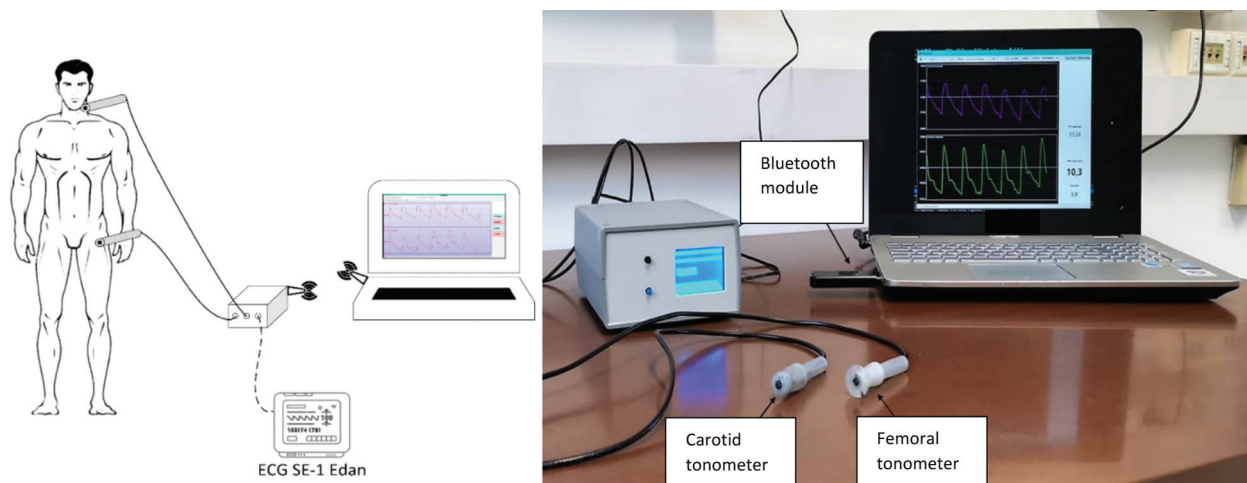
If the percentage standard deviation (SD, %) of the acquisition was greater than 10, a further measurement was carried out (always by the same operator), discarding the previous one. After each measurement, blood pressure and heart rate were measured with a validated semiautomatic sphygmomanometer (Omron Matsusaka, Kyoto, Japan), to verify the hemodynamic stability of the test volunteer. In the statistical analysis, the average of the three measurements was considered.

### Pulse wave velocity by ATHOS

The development of the new device [6] was the result of numerous preliminary tests to determine: the most accurate sensor; the correct shape of the supports for the tonometers in terms of ergonomics; the correct pressure to be exerted. The purpose was to obtain a facilitated and simultaneous acquisition of an accurate and stable signal. ATHOS is a research device compliant with the European regulation for the safety of medical devices (IEC 60601).

As shown in Fig. 1, the device is composed of a main unit that collects the signals from two tonometric sensors (developed by STMicroelectronics, Geneva, Switzerland), capable of detecting changes in surface tension, and an external diagnostic device for the acquisition of the electrocardiographic signal. Considering the simultaneous acquisition of carotid and femoral signals, ECG trace is not required for PTT calculation, making ATHOS independent from it. Nevertheless, electrocardiographic recording was used for clinical purposes, in order to evaluate heart rate data and detect any arrhythmias (e.g. extrasystoles, atrial fibrillation. . .). These signals, after being acquired synchronously, are sent via Bluetooth to a laptop, where a Graphic User Interface (GUI) allows their processing and display.

To facilitate their handling and use, both sensors have been inserted into two specifically created distinct pen-shaped supports using a 3D printer with biocompatible resin. They have different shapes leading to a better positioning and the best signal-to-noise ratio, in order to better detect pulse waves in the two different sites, femoral and carotid. The probes (Figure 1S, Supplementary Digital Content 1, <http://links.lww.com/HJH/B689>) are ergonomically designed to assure the



**FIGURE 1** Athos device summing scheme (a) and iconographic representation (b). It is composed by the main device unit (that collects the two pulse waves), the electrocardiogram, and the data processing software interface, running on the operator laptop. The two tonometers allow the simultaneous acquisition of the pulse waves at the carotid and femoral levels. The device and the computer are connected by low-energy v4.1 Bluetooth.

best performance for their application site. Lastly, dimensions of the final device are strongly reduced leading to an improved portability.

Eventually, after identifying the sites for the pulse wave detection and positioning the two sensors, the operator verifies the quality of the signals acquired by the GUI. An immediate and real-time feedback allows both repositioning and modulation of the pressure to be exerted on the probes.

ATHOS, just like the SphygmoCor device, is designed to be used by a single operator. After identifying a stable signal with adequate quality, the operator can stop the examination by pressing the space bar on the control console: the software will delete from the analysis the last 3 s beats exactly as in the SphygmoCor device. The final report will display the two traces of the pulse signal (one for each acquisition site), recorded in the last 10 s of stable signal, obtaining the individual PTTs for each beat (through the implementation of the ITM) and the final cfPWV values, applying a criterion of discarding the values extracted in the 10 s considered.

### Pulse wave analysis

PWA was recorded radially with a validated instrument equipped with a transcutaneous applanation tonometer (SphygmoCor System) after about 15 min of supine rest. Two consecutive recordings were made. The average value of the two measurements was used in the statistical analysis. If one of the two measurements did not meet the accuracy standards (see below), a third measurement was performed, and the two acquisitions meeting quality standard were considered in the statistical analysis. After each acquisition, blood pressure and heart rate were measured with a validated semiautomatic sphygmomanometer (Omron Matsusaka), equipped with an adequately sized cuff and operated by a healthcare professional. The central blood pressure values (systolic – SBPc; diastolic – DBPc; mean – MBPc; pulse pressure – PPc) were obtained from the pulse wave profile at the radial level.

The central augmentation index (AIx) was calculated as follows:

$$AIx = [\text{augmentation pressure}/(\text{SBP} - \text{DBP})] \times 100$$

where SBP and DBP are the systolic and diastolic blood pressure values respectively, while augmentation pressure is the increase in pressure because of the reflex component of the pulse wave (corresponds to the wave profile from the inflection point up to the maximum value systolic).

The pulse pressure amplification index (PPA) was also calculated, as follows:

$$PPA = [(PPp - PPc)/PPc] \times 100$$

where pulse pressure is the difference between the SBP and DBP values, measured at the brachial (peripheral pulse pressure, PPp) or central level by PWA (central pulse pressure, PPc).

### Echocardiography

A complete two-dimensional echocardiogram (TTE) was performed by commercially available ultrasound systems equipped with tissue Doppler imaging software (iE33, Philips Medical System, Andover, Massachusetts, USA). Multiple frequency phased array transducers (2–4 MHz) were used. The TTE was performed by EACVI (European Association of Cardiovascular Imaging)-accredited personnel. Patients were examined at rest in left lateral decubitus, with ECG monitoring and continuous respirometer. Standard 2D and Doppler images were acquired and archived in a continuous loop format (cine-loop), and measurements were performed offline. Measurements of the heart chambers, left ventricular mass, systolic and diastolic function were performed according to current international recommendations [11].

### Statistical analysis

The statistical analysis was performed with dedicated software (SPSS – Statistical Package for the Social Sciences, v22 for Microsoft Windows, SPSS Inc. Chicago, Illinois, USA). The normal distribution of the variables was verified by graphical evaluation and Shapiro–Wilk test. Descriptive statistics are reported as ‘mean ± standard deviation’. The categorical variables are reported as ‘frequency (percentage)’. A two-sided Student’s *t* test for continuous

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variables was performed to verify presence of a significant difference with a threshold of  $P$  less than 0.05. The groups of participants were compared by ANOVA, whereas the post hoc analyses were performed by Bonferroni tests. For the analysis of the correlation between cPWV and anthropometric and hemodynamic parameters, the average of three measurements performed for each participant was used. The accuracy of the instrument being validated was assessed by Bland–Altman plot and linear regression analysis. The correlation coefficient was evaluated by Pearson correlation coefficient, using a cut off value of more than 0.8 for identifying a strong correlation.

The reproducibility was assessed as coefficient of repeatability ( $1.96 \times$  standard deviation of differences of the measurements), whereas the within-patient coefficient of variation was calculated as the square root of the mean standard deviation/average of the measurements. Significant results were considered with  $P$  value less than 0.05.

Intra-observer agreement for cPWV for SphygmoCor compared with ATHOS was analyzed by intraclass correlation coefficients (ICC) estimates and their 95% confidence interval, based on a single-rating, absolute-agreement, two-way mixed-effects model.

In the same group, 10 patients were randomly selected and measurements of two independent blinded observers were compared. Inter-observer agreement for PWV<sub>ATHOS</sub> was analyzed by ICC based on a mean-rating ( $k=2$ ), absolute-agreement, two-way mixed-effects model. Values less than 0.5 are indicative of poor reliability, values between 0.5 and 0.75 indicate moderate reliability, values between 0.75 and 0.9 indicate good reliability, and values greater than 0.90 indicate excellent reliability [12].

Any difference between the measurements obtained with the gold standard technique (SphygmoCor) and experimental approach tested in the present study (ATHOS) was considered as an error; independent variables that could be associated with such an error were searched for and used to perform a multivariate linear regression analysis.

## RESULTS

### Study population

Ninety healthy volunteers were involved in the study. The clinical and anamnestic characteristics of the participants are summarized in Table 1 whereas echocardiographic parameters in Table 1S, Supplementary Digital Content 2, <http://links.lww.com/HJH/B692>. Population's mean age was  $45.6 \pm 17.8$  years, ranging from 18 to 86 years. They were divided into three groups depending on age: age less than 30, 30–59, and at least 60 years (mean of  $24.5 \pm 2.8$ ,  $47.3 \pm 8.3$ ,  $65.1 \pm 6.5$  years, respectively).

### Validation of the ATHOS instrument

The PWV and PTT values of the examined population, measured with the reference instrument SphygmoCor and with ATHOS are summarized in Table 2.

The average cPWV measured with ATHOS (PWV<sub>ATHOS</sub>) and with SphygmoCor (PWV<sub>SphygmoCor</sub>) was  $7.88 \pm 1.96$  and  $7.72 \pm 1.95$  m/s, respectively ( $P=0.013$ , Figure 2S – Supplementary Digital Content 3, <http://links.lww.com/HJH/B690>).

The correlation between the two measurements showed a  $R$  of 0.959 ( $P<0.001$ ). The mean difference was  $0.15 \pm 0.56$  m/s.

The coefficient of repeatability for ATHOS and SphygmoCor were 0.96 and 1.04 m/s, respectively, whereas the coefficient of variation for ATHOS was significantly lower than SphygmoCor (3.5 vs. 4.3%, respectively,  $P=0.01$ ). Analyzing the intra-observer agreement between the evaluations with the same device, ICC were 96.5% (95–97.5) and 95.7 (94.0) for ATHOS and SphygmoCor, respectively.

The Bland–Altman plot and the linear regression for PWV and PTT are showed in Figs. 2 and 3, respectively.

Considering the cases with PWV at least 8 m/s (30 participants), a difference between the measured PWV values of  $0.1 \pm 0.63$  m/s was demonstrated while considering the cases with PWV at least 9 m/s (18 participants) the difference was  $0.04 \pm 0.67$  m/s.

**TABLE 1. Anthropometric and anamnestic parameters of the study population (whole and age-based groups)**

Variable (mean $\pm$ SD)	General population (n = 90)	Group <30 (n = 30)	Group 30–59 (n = 30)	Group $\geq$ 60 (n = 30)	P value ANOVA
Age	45.6 $\pm$ 17.8	24.5 $\pm$ 2.8 <sup>#</sup>	47.3 $\pm$ 8.2 <sup>§</sup>	65.1 $\pm$ 6.5*	<0.001
Gender (male, %)	48 (53.3%)	17 (56.7%)	15 (50%)	16 (53.3%)	0.878
Weight (kg)	68.2 $\pm$ 13.6	65.2 $\pm$ 10.5	68.3 $\pm$ 15.2	70.9 $\pm$ 14.5	0.271
Height (m)	1.70 $\pm$ 0.1	1.71 $\pm$ 0.1	1.71 $\pm$ 0.1	1.68 $\pm$ 0.1	0.480
BMI (kg/m <sup>2</sup> )	23.4 $\pm$ 3.5	22.1 $\pm$ 1.8	23.2 $\pm$ 4	24.8 $\pm$ 3.9*	0.007
Waist (cm)	87.1 $\pm$ 11.4	80.5 $\pm$ 7.9	87 $\pm$ 10.9 <sup>§</sup>	94.1 $\pm$ 10.9*	<0.001
BSA (m <sup>2</sup> )	1.79 $\pm$ 0.2	1.77 $\pm$ 0.2	1.79 $\pm$ 0.23	1.80 $\pm$ 0.21	0.778
SBP (mmHg)	116 $\pm$ 13	113 $\pm$ 12	114 $\pm$ 13 <sup>§</sup>	120 $\pm$ 13*	0.053
DBP (mmHg)	72 $\pm$ 8	68 $\pm$ 7 <sup>#</sup>	73.1 $\pm$ 9	75 $\pm$ 8*	0.004
PP (mmHg)	44 $\pm$ 9	45 $\pm$ 8 <sup>#</sup>	41 $\pm$ 9 <sup>§</sup>	46 $\pm$ 9	0.039
MAP (mmHg)	86.6 $\pm$ 9.0	83.2 $\pm$ 8.0	86.6 $\pm$ 9.2	89.9 $\pm$ 8.7*	0.014
HR (beats/min)	66 $\pm$ 12	68 $\pm$ 12	65.5 $\pm$ 11	66 $\pm$ 12	0.674
Smoke	27 (30%)	4 (13.3%) <sup>#</sup>	11 (36.7%)	12 (40%)*	0.049
Alcohol	25 (27.8%)	1 (3.3%) <sup>#</sup>	11 (36.7%)	13 (43.3%)*	0.001
Sport	68 (75.6%)	19 (63.3%)	25 (83.3%)	24 (80%)*	0.159
Fam_CV	53 (58.9%)	22 (73.3%)	18 (60%)	13 (43.3%)*	0.061

BSA, body surface area; Fam\_CV, family history for cardiovascular diseases; HR, heart rate; PP, pressure pulse; waist, abdominal circumference.

<sup>#</sup> $p < 0.05$  between group <30 and group 30–59;

<sup>§</sup> $p < 0.05$  between group 30–59 and group at least 60;

\* $p < 0.05$  between group <30 and group at least 60.

**TABLE 2. Pulse wave velocity parameters of the study population (whole and age-based groups)**

Variable (mean ± SD)	General population (n = 90)	Group <30 (n = 30)	Group 30–59 (n = 30)	Group ≥ 60 (n = 30)	p value ANOVA
PTT <sub>ATHOS</sub> (ms)	64.99 ± 13.6	77.40 ± 9.65 <sup>#</sup>	64.58 ± 8.39 <sup>§</sup>	53.00 ± 9.65*	<0.001
PWV <sub>ATHOS</sub> (m/s)	7.88 ± 1.96	6.30 ± 0.96 <sup>#</sup>	7.79 ± 1.10 <sup>§</sup>	9.54 ± 2.06*	<0.001
PTT <sub>S</sub> (ms)	66.4 ± 14.77	80.13 ± 12.24 <sup>#</sup>	64.5 ± 8.89 <sup>§</sup>	54.57 ± 9.83*	<0.001
PWV <sub>S</sub> (m/s)	7.73 ± 1.95	6.12 ± 1.04 <sup>#</sup>	7.81 ± 1.11 <sup>§</sup>	9.25 ± 2.07*	<0.001
ΔPWV (m/s)	0.15 ± 0.56	0.18 ± 0.48	-0.02 ± 0.58	0.29 ± 0.59	0.104
ΔPTT (ms)	-1.40 ± 5.56	-2.73 ± 6.93	0.09 ± 5.13	-1.57 ± 4.08	0.143

ΔPTT, difference between PWV<sub>ATHOS</sub> and PWV<sub>S</sub>; ΔPWV, difference between PTT<sub>ATHOS</sub> and PTT<sub>S</sub>; PTT, pulse transition time; PTT<sub>ATHOS</sub>, PTT by ATHOS; PTT<sub>S</sub>, PTT by Sphygmocor; PWV, pulse wave velocity; PWV<sub>ATHOS</sub>, PWV by ATHOS; PWV<sub>S</sub>, PWV by Sphygmocor.

<sup>#</sup>p < 0.05 between group <30 and group 30–59;

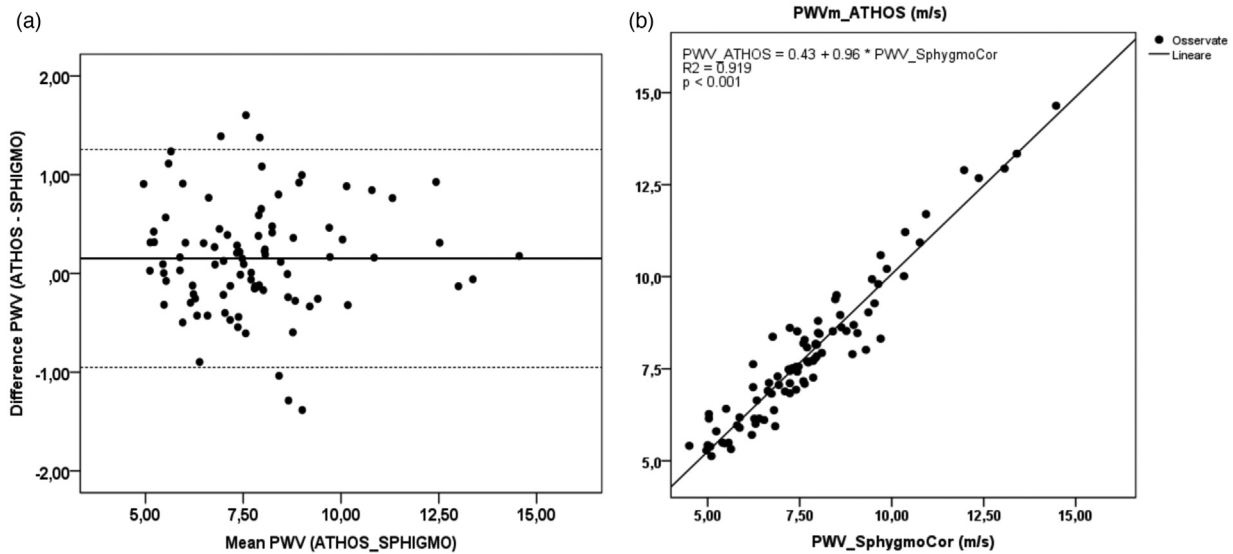
<sup>§</sup>p < 0.05 between group 30–59 and group at least 60;

\*p < 0.05 between group <30 and group at least 60.

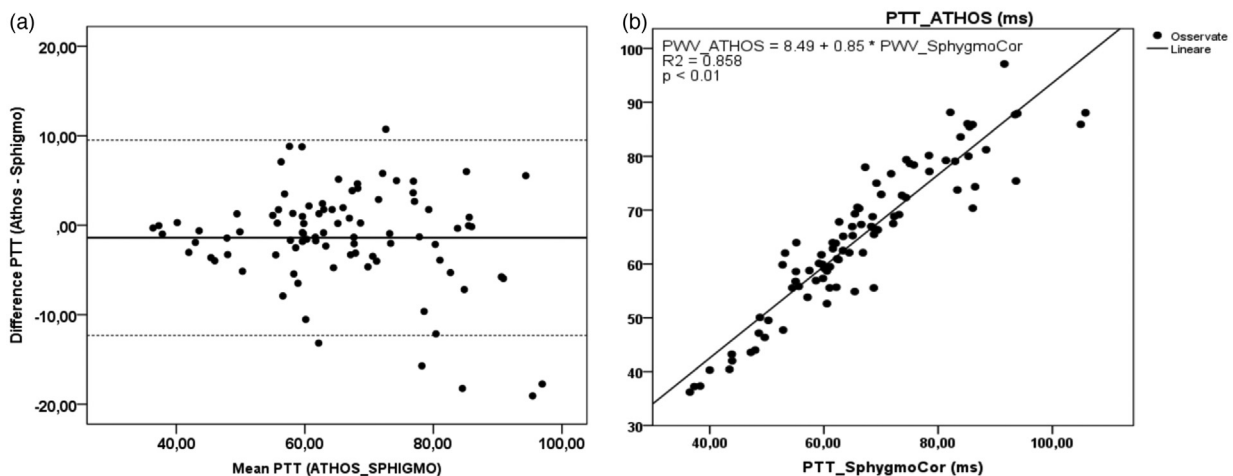
There was no statistically significant difference between the mean differences for both PWV and PTT in the three groups ( $P = 0.104$  and  $0.143$ , respectively). Considering the three groups separately, the two measurements correlated

significantly in each group ( $r = 0.889$ ,  $P < 0.001$ ;  $r = 0.857$ ,  $P < 0.001$ ;  $r = 0.959$ ,  $P < 0.001$ , respectively).

Analyzing possible variables related to the difference between PWV<sub>Sphygmocor</sub> and PWV<sub>ATHOS</sub>, no anatomic,



**FIGURE 2** Comparison of pulse wave velocity from Sphygmocor device and the new ATHOS device. (a) Bland–Altman plot of the difference. (b) Scatter plot with linear regression (solid line).



**FIGURE 3** Comparison of pulse transit time from Sphygmocor device and the new ATHOS device. (a) Bland–Altman plot of the difference. (b) Scatter plot with linear regression (solid line).

Leone *et al.***TABLE 3. Pulse wave analysis parameters of the study population (whole and age-based groups)**

Variable (mean ± SD)	General population (n = 90)	Group <30 (n = 30)	Group 30–59 (n = 30)	Group ≥ 60 (n = 30)	P value
SBP <sub>p</sub> (mmHg)	118 ± 13	113 ± 12	117 ± 13 <sup>§</sup>	124 ± 11*	0.003
DBP <sub>p</sub> (mmHg)	73 ± 7	69 ± 6 <sup>#</sup>	73 ± 8	76 ± 6*	0.001
SBP <sub>c</sub> (mmHg)	106 ± 13	98 ± 9 <sup>#</sup>	108 ± 12 <sup>§</sup>	115 ± 11*	<0.001
DBP <sub>c</sub> (mmHg)	73 ± 8	69 ± 6 <sup>#</sup>	74 ± 8	77 ± 6*	0.001
MAP <sub>c</sub> (mmHg)	85 ± 9	79 ± 6 <sup>#</sup>	86 ± 9	89 ± 7*	<0.001
PP <sub>c</sub> (mmHg)	33 ± 9	28 ± 8 <sup>#</sup>	34 ± 8 <sup>§</sup>	38 ± 10*	<0.001
Alx (%)	19.31 ± 15.8	4.58 ± 10.98 <sup>#</sup>	23.73 ± 10.52	29.60 ± 13.42*	<0.001
PPA	139.83 ± 21.02	28.21 ± 7.80 <sup>#</sup>	132.90 ± 15.51	127.10 ± 16.14*	<0.001

SBP<sub>p</sub>, peripheral SBP; SBP<sub>c</sub>, central SBP; DBP<sub>p</sub>, peripheral DBP; DBP<sub>c</sub>, central DBP; MBP<sub>c</sub>, central mean blood pressure; PP<sub>c</sub>, central pulse pressure; Alx (%), augmentation index; PPA, pulse pressure amplification.

<sup>#</sup>*p* < 0.05 between group <30 and group 30–59;

<sup>§</sup>*p* < 0.05 between group 30–59 and group at least 60;

\**p* < 0.05 between group <30 and group at least 60.

demographic, echocardiographic, or hemodynamic variables resulted to be significant predictors of such a discrepancy (data not shown).

### Reproducibility

Reproducibility of results between two operators using ATHOS was excellent, with ICC of 98% (91–99). Furthermore, the averages of the acquisitions made by the two operators were 6.61 ± 1.1 and 6.68 ± 1.16 m/s, respectively, with no statistically significant difference (*P* = 0.397).

It was also assessed reproducibility of PWV measurements obtained by ATHOS compared with SphygmoCor over heart rate span, dividing general population in terciles of heart rate. It was observed a nonsignificant reduction in the mean cfPWV value with increasing heart rate (8.18 ± 2.38, 7.92 ± 1.88, and 7.49 ± 1.48 for ATHOS; 8.07 ± 2.37, 7.68 ± 1.82, and 7.39 ± 1.54 for SphygmoCor, respectively, *P* > 0.05). Difference between ATHOS and SphygmoCor was not significantly different in the three terciles (0.11 ± 0.52, 0.24 ± 0.59, and 0.10 ± 0.58, respectively, *P* > 0.05).

### Pulse wave analysis

The PWA values of the total population and the three age groups are shown in Table 3.

cfPWV<sub>ATHOS</sub> direct correlation to Alx was present (*r* = 0.611; *P* < 0.001) and showed a significant inverse linear correlation with PPA (*r* = −0.610; *P* < 0.001). Moreover, cfPWV<sub>ATHOS</sub> was significantly related to central hemodynamic parameters (SBP<sub>c</sub> (*r* = 0.688; *P* < 0.001); DBP<sub>c</sub> (*r* = 0.357; *P* < 0.001); MBP<sub>c</sub> (*r* = 0.552; *P* < 0.001); PP<sub>c</sub> (*r* = 0.650; *P* < 0.001)).

### ATHOS device in hypertensive patients: a pilot study

Thirty hypertensive patients of our Hypertension Center were included in the second part of the study. The clinical and echocardiographic parameters are summarized in Table 2S – Supplementary Digital Content 4, <http://links.lww.com/HJH/B693>. Population's mean age was 63 ± 10.9 years, ranging from 34 to 91 years, 56.7% men, everyone treated with antihypertensive drugs. In hypertensive patients, average PWV<sub>ATHOS</sub> and PWV<sub>SphygmoCor</sub> were significantly higher than in general population (9.31 ± 2.28

and 9.27 ± 2.69 m/s, respectively, *P* < 0.001). The PWV measured by ATHOS compared with SphygmoCor device was similar: both ΔPWV and ΔPTT were not significantly different (Table 2S, <http://links.lww.com/HJH/B693>). The correlation between the two measurements showed an *R* of 0.964 (*P* < 0.001) and an ICC of 97.5%. The mean difference was 0.05 ± 0.78 m/s. The Bland–Altman plot and linear regression for PWV are showed in Figure 3S – Supplementary Digital Content 5, <http://links.lww.com/HJH/B691>.

### DISCUSSION

In this study, a new ATHOS instrument for the noninvasive evaluation of arterial stiffness and its correlation with SphygmoCor were tested. The ATHOS device was born from the collaboration between the Politecnico di Torino and STMicroelectronics [6]. It showed an excellent level of agreement with SphygmoCor, even at high PWV values, with a good reproducibility.

Arterial stiffness is an important determinant and a recognized risk factor for the development of cardiovascular disease [13–15]. The gold standard for noninvasive measurement of arterial stiffness is PWV recorded between the carotid and the femoral sites (cfPWV) [9]: higher cfPWV value means higher arterial stiffness. In the latest guidelines for the management of arterial hypertension [2] a cfPWV value greater than 10 m/s was indicated as an index of hypertension-mediated organ damage, leading to an increase in overall cardiovascular risk. In addition, cfPWV showed an independent predictive value for fatal and nonfatal cardiovascular events [16,17]. Its routine assessment would, thus allow a better stratification of intermediate-risk patients.

To implement the use of PWV in clinical practice, it is necessary to have accurate and easy-to-use tools validated according to current guidelines [7]. At the moment, there are a number of commercially available devices for aPWV evaluation that use different technologies, such as applanation tonometry (PulsePen, DiaTecne, Milan, Italy [18], SphygmoCor, AtCor Medical [19], and the newly developed SphygmoCor Excel [20]), piezoelectric transducers (Complior, Alam Medical, Paris [21] and Aortic, Exxer, Argentina [22]) and oscillometric sensors (Mobil-O-graph, IEM, Germany [23], Arteriograph, TensioMed, Hungary) [24] and Vicorder, Skidmore Medical [25]). SphygmoCor is

considered at present the reference standard for noninvasive assessment of cfPWV because of the large amount of data in prognostic studies and proven reliability [7,26–28].

Compared with the devices currently available, ATHOS features several advantages and technologic innovations. In particular, compared with Complior, which uses a piezoelectric mechanical transducer, ATHOS uses standard electronics and a modified commercial pressure sensor instead of traditional force sensors. Both determine the foot of the wave through ITM. Although SphygmoCor has a sampling rate of 128 Hz and Complior reach 1 kHz, in ATHOS device, the tonometer maximum sampling frequency is 170 Hz. Thanks to the implemented signal processing algorithm, to better synchronize both the digital output of pressure sensors and the analog ECG signal, all the signals have been resampled at 680 Hz, which ensures a temporal resolution of 1.5 ms. It allows the simultaneous acquisition of two impulse waves, the real-time display of the acquired signals, the instant cfPWV parameter and the quality factors to improve their estimation, as better explained in the technical paper [6].

Our population included healthy normotensive individuals, within a wide age range, an equal distribution between genders and a wide range of PWV values, factors that have been shown to cause a poor correlation when comparing different devices [29].

The ARTERY Society guidelines for the validation of tools for PWV measurements defines three classes of accuracy (poor, acceptable, and excellent) based on the mean difference and the corresponding standard deviation [7]. An excellent accuracy is defined as mean difference less than 0.5 m/s and standard deviation 0.8 m/s or less. In our study, we found an excellent level of accuracy, with an average difference of  $0.15 \pm 0.56$  m/s: in fact, ATHOS slightly overestimated the values compared with the SphygmoCor. We did observe a significant difference in mean cfPWV values between the two devices, probably because of the different way it was assessed. Although SphygmoCor use sequential recordings of the waveform with ECG gating, ATHOS allows the noninvasive recording of the pulse wave simultaneously at the level of the carotid and femoral sites, providing a real-time acquired PWV value (obtained from the last 10 cardiac cycles recorded). Nevertheless, there was a strong correlation between the measurements ( $r = 0.959$ ,  $P < 0.001$ ) and furthermore, this difference did not hinder the excellent accuracy of the ATHOS readings.

In addition, the accuracy between the two methods remained 'excellent' also considering the different age groups ( $<30$ ,  $30-59$ ,  $\geq 60$  years, Table 3). This is particularly important as the strong independent predictive value of PWV as a measure of aortic rigidity and cardiovascular events has led to the identification in a large European study of age-specific reference values in healthy individuals as well as in presence of cardiovascular risk factors. Results obtained in the current study with the ATHOS device are very close to the reference values identified for healthy volunteers [30] (Table 1). Of note, our study used the same methodology for foot of the wave identification and carotid-femoral distance.

A recent review, comparing validation studies of devices for the noninvasive measurement of PWV, showed that the

accuracy between the methods under examination significantly decreased in volunteers with cfPWV values greater than 8 m/s [5,21,31]. In this study, for values above this threshold and also in hypertensive patients, the average difference between ATHOS and SphygmoCor was not significantly different and remained in the 'excellent' range, assuming that this new instrument would maintain its signal recording quality even for extreme PWV values. It was also observed an excellent repeatability of measurements with the ATHOS instrument, even in hypertensive patients. It was slightly better than for SphygmoCor (coefficient of variation was 3.5% with ATHOS and 4.3% with SphygmoCor). ATHOS allows the simultaneous acquisition of the carotid and femoral pulse waves, while with SphygmoCor, the acquisition is sequential, which represents a potential source of measurement variability, although available data in literature are controversial. Under perfectly controlled hemodynamic conditions, it has been demonstrated that the simultaneity acquisitions or lack thereof does not affect the reproducibility of the measurement [18]. Moreover, in a study conducted to evaluate the short-term repeatability of six devices, simultaneous acquisition did not prove to be a source of greater repeatability [32]. Despite this, in a validation study that compared SphygmoCor and Complior Analyze (which allows simultaneous acquisition), a slightly greater variability was found in the measurements performed with SphygmoCor [21]. In our study, hemodynamic conditions were correctly monitored and controlled, to reduce possible sources of variability.

Since the evidence of an effect of heart rate on PWV [33,34], it was assessed the reproducibility of PWV measurements obtained by ATHOS over heart rate span, dividing our population in terciles of heart rate. It was observed a mean cfPWV decrease for increasing heart rate but it was not significantly different. This seems to be in apparent contrast with what was previously reported by Bikia *et al.* [33]; however, this study evaluated the impact of heart rate on PWV on an in-silico model, not *in vivo*. Furthermore, the heart rate effect on the BP-corrected cfPWV was higher in the case of low compliance, exactly as previously pointed out [34]. It was observed a positive association between heart rate and cfPWV but it was significant only for patients with increased aortic stiffness ( $PWV > 8.6$  m/s) and not for those with PWV 8.6 m/s or less. Therefore, it can be hypothesized that the differences between our results and what was previously reported are mainly because of the fact that we studied a selected population of healthy patients with normal cfPWV values, where this phenomenon is less pronounced. Furthermore, the low sample size of our study does not allow to reach a statistically significant difference between the three different terciles. Further studies designed for this purpose, with an adequate population, are needed to reach conclusions.

Other sources of variability can be identified in the method used to identify the foot of the pressure wave and measure the carotid-femoral distance to be used in the calculation. The same algorithm (ITM) for identification of the foot of the pressure wave identification was used in both devices in the present study, basically removing this issue. The ITM algorithm, in fact, has been considered the most accurate and least dependent on changes in reflection



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of waveform [8,35], and for this reason, its use is recommended by the Artery Society for PTT calculation [7]. As for the carotid–femoral distance, two methods are currently recommended by the guidelines, a ‘subtraction method’ (distance from the femoral site to the sternal notch – distance from the carotid site to the sternal notch), and the ‘80% method’ (direct carotid to femoral distance  $\times$  0.8) as they both demonstrated a high level of correlation with the invasive method in a study conducted in 915 patients [36]. However, the former requires two separate measurements, thus increasing the level of inaccuracy. Moreover, the ‘80% method’, which involves a single measurement, demonstrated the best correlation with the measurement of the aortic length performed by MRI [37] and it was the method used in studies that identified the cfPWV 10 m/s cut-off for the management and treatment of high blood pressure [2]. For the above reasons, the latter method was preferred in our study. Furthermore, distance is measured superficially, and therefore, may not be representative of the true aortic length. For this, to further reduce the possibility of error, the acquisition sites were marked on the skin of the voluntary participants after careful palpation of the pulse by expert operators.

In our study, AIx and PPA were also measured with the validated SphygmoCor instrument as additional parameters for the measurement of arterial stiffness [38]. The linear regression analysis showed a significant correlation between the AIx and PPA values obtained from the pulse wave analysis recorded radially with SphygmoCor and the cfPWV values measured with ATHOS. Although AIx and PPA have shown a limited predictive value in terms of cardiovascular events or mortality compared with cfPWV measurement [28,39], the correlation with cfPWV<sub>ATHOS</sub> represents an added value in the evaluation of the accuracy of the new instrument for the viscoelastic arterial vessel property assessment.

### Limits of the study

This study has some limitations. Firstly, the ATHOS instrument was validated against the SphygmoCor, an instrument that allows a transcutaneous, noninvasive assessment, while the current gold standard is represented by the invasive measurement of the PWV. The intrinsic characteristics of the invasive measurement, however, preclude its applicability. In addition, the SphygmoCor tool is considered by the guidelines to be an alternative gold standard in validation studies and has recently been invasively validated in a very large number of participants [36].

The BMI value represents a potential confounding in the surface measurement of PWV. The guidelines recommend exclusion from validation studies for individuals with BMI greater than 30 kg/m<sup>2</sup> [7]. In our study, four participants with BMI greater than 30 kg/m<sup>2</sup> were included. Despite the increased BMI, the physical constitution did not prevent an accurate path length measurement between the two sites, and therefore, they were considered in the final statistical analysis. Although this could represent a possible limitation of our study, the comparison of the transit times in these four participants (which are not affected by the distance measurement) proved to be comparable with the two devices.

### Future perspectives

Validation of the ATHOS device will have to be confirmed in patients with cardiovascular diseases, and patients with a broader range of PWV should be assessed. Furthermore, validation of the instrument with invasive methods or with noninvasive methods that determine an accurate measurement of the aortic length, such as MRI, will be necessary.

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### Conflicts of interest

There are no conflicts of interest.

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