Noninvasive Estimation of Aortic Stiffness Through Different Approaches

Comparison With Intra-Aortic Recordings

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Abstract**—**Aortic pulse wave velocity is a worldwide accepted index to evaluate aortic stiffness and can be assessed noninvasively by several methods. This study sought to determine if commonly used noninvasive devices can all accurately estimate aortic pulse wave velocity. Pulse wave velocity was estimated in 102 patients (aged 65±13 years) undergoing diagnostic coronary angiography with 7 noninvasive devices and compared with invasive aortic pulse wave velocity. Devices evaluating carotid-femoral pulse wave velocity (Complior Analyse, PulsePen ET, PulsePen ETT, and SphygmoCor) showed a strong agreement between each other ($r>0.83$) and with invasive aortic pulse wave velocity. The mean difference ±SD with the invasive pulse wave velocity was −0.73±2.83 m/s ($r=0.64$) for Complior-Analyse: 0.20±2.54 m/s ($r=0.71$) for PulsePen-ETT: −0.04±2.33 m/s ($r=0.78$) for PulsePen ET; and −0.61±2.57 m/s ($r=0.70$) for SphygmoCor. The finger-toe pulse wave velocity, evaluated by pOpmètre, showed only a weak relationship with invasive aortic recording (mean difference ±SD =−0.44±4.44 m/s; $r=0.41$), and with noninvasive carotid-femoral pulse wave velocity measurements ($r<0.33$). Pulse wave velocity estimated through a proprietary algorithm by BPLab (v.5.03 and v.6.02) and Mobil-O-Graph showed a weaker agreement with invasive pulse wave velocity compared with carotid-femoral pulse wave velocity (mean difference ±SD =−0.71±3.55 m/s, $r=0.23$; 1.04±2.27 m/s, $r=0.77$; and −1.01±2.54 m/s, $r=0.71$, respectively), revealing a negative proportional bias at Bland-Altman plot. Aortic pulse wave velocity values provided by BPLab and Mobil-O-Graph were entirely dependent on age-squared and peripheral systolic blood pressure (cumulative $r^2=0.98$ and 0.99, respectively). Thus, among the methods evaluated, only those assessing carotid-femoral pulse wave velocity (Complior Analyse, PulsePen ETT, PulsePen ET, and SphygmoCor) appear to be reliable approaches for estimation of aortic stiffness.

Key Words: arteriosclerosis ■ cardiac catheterization ■ coronary angiography ■ coronary artery disease ■ hemodynamics ■ pulse wave velocity ■ vascular stiffness

Aortic pulse wave velocity (PWV) is an indirect, well-established index of arterial stiffness.[1] The pulse wave is transmitted through the arterial system, and its speed is inversely related to the distensibility of the arterial wall itself: the higher the velocity, the lower the vascular distensibility.[1] Aortic intraarterial PWV is a reliable measure of the global aortic viscoelastic properties, but its invasive assessment makes this approach not feasible in clinical practice. Hence, noninvasive carotid-femoral PWV (cf-PWV) is considered the reference method for its estimation in a clinical setting,[2,3] given the large number of studies showing cf-PWV as a strong independent predictor of total mortality and major cardiovascular events.[4–6]

In recent years, numerous devices have been made available on the market, based on original operating principles, which claim to offer automated and operator-independent measurements of central PWV. Aim of this study was thus to investigate if true invasive aortic PWV, measured invasively through a specially designed catheter, is accurately estimated by a number of noninvasive methods proposed for its indirect assessment. To answer this question, we have considered 7 different noninvasive devices, commonly used in a clinical setting, either measuring cf-PWV or providing other surrogate estimates of aortic PWV, and we have compared them with each other as well as with aortic PWV obtained from catheter recordings.

Methods

To minimize the possibility of unintentionally sharing information that can be used to reidentify private information, a subset of the data that support the findings of this study are available from the corresponding author on reasonable request.

Subjects

All suitable consecutive patients undergoing angiography at the Interventional Cardiology Unit of the Monza Polyclinic Hospital (Monza, Italy) were recruited in this study over a 2-month period. The exclusion criteria were age <18 years; body mass index >35 Kg/m^2; emergency hospitalization, heart failure with unstable hemodynamic conditions, atrial fibrillation or paced cardiac rhythm, low ejection fraction, severe valvular disorders, and known significant carotid or femoral artery stenosis. The protocol was approved by Local Ethics Committees and was conducted in accordance with the Helsinki Declaration. All participants gave their written informed consent to study procedures.

Protocol of the Study

PWV was estimated by 7 noninvasive devices: BPLab, Complior Analyse, Mobil-O-Graph, pOpmètre, PulsePen ETT, PulsePen ET, and SphygmoCor. This was followed by direct PWV assessment through gold standard intraarterial catheter recordings. For each patient, measurements were sequentially performed in random order, with the exception of pOpmètre. Since the pOpmètre low-intensity infrared sensors are extremely sensitive to multiple environmental and clinical conditions, recordings with this device were performed in the end, following all manufacturer's recommendations. Seven skilled operators performed all the measurements (further details concerning inter-operator repeatability are shown in Table S1 in the online-only Data Supplement).

Patients already prepared for angiographic examination were transported to a hospital wheeled bed in a room opposite the angiographic room, where noninvasive examinations were performed. Measurements were performed in the morning, in a quiet and comfortable environment, with soft natural lighting and controlled temperature (21.5±0.5°C). Patients had been fasting for 8 hours at the time of the test and had abstained from caffeine, tobacco, large meals, or intense physical activity since the day before. Subjects had refrained from taking any vasoactive medication for at least 2 hours before the procedures. Tests started after a resting period of at least 15 minutes in supine position, during which the anthropometric data and medical history were collected from medical records.

Manufacturer's instructions have been strictly followed for each of the applied devices. Before the beginning of the measurement session, the operator marked on the patient's skin the point of maximum pulsation of carotid and femoral artery, where the pressure waves would be recorded. At that point, the researchers positioned the probes to record the pressure curves for each measurement of the cf-PWV. Thus, the same distance was used in all the cf-PWV measurements. The distance was measured with a steel tape measure, avoiding tape curves. Where indicated (in obese subjects), rigid rods at the 2 edge of the tape were used. Measurements of 3 distances were recorded: (1) the direct distance between carotid and femoral site, (2) the distance between carotid artery and suprasternal notch, and (3) the distance between suprasternal notch and femoral artery.

Brachial blood pressure (BP) measurements were assessed simultaneously with the pulse wave recordings, through a brachial cuff of suitable size, by a validated Omron 705IT oscillometric device (Omron Corporation, Kyoto, Japan). Brachial BP was measured 14 times for each work session, that is, with one measurement every about 2 minutes.

Immediately after the end of the measurements, the patient was transferred, lying down, wheeled on the same hospital bed, to the angiographic room, where invasive measurements were performed. Invasive aortic PWV was measured before performing diagnostic tests. Thus, no drugs were administered before or during the invasive measurements. The time interval between the last noninvasive PWV acquisition and the invasive procedure was 18±6 minutes.

Reference Invasive Method

FS-Stiffcath (Flag Vascular, Monza, Italy) is a fluid-filled 8Fr angiographic catheter conceived to simultaneously record pulse waves on 2 separate sites. Details of technical characteristics of FS-Stiffcath catheter and the method used to measure invasive transit time are described in the Figures S1 and S2. A graduated scale allows direct reading of the distance between the 2 catheter openings. In all the patients, the proximal catheter port was advanced through the right femoral artery up to the ascending aorta and positioned, under fluoroscopic guidance, at 2 cm above the aortic valve. The distal port, corresponding to the distal opening of the second lumen, was positioned just above the aortic bifurcation.

Pulse wave transit time was estimated by a custom-designed software (SPEGL, Milan, Italy), using foot-to-foot method[3] and intercept tangent algorithm.[7] Throughout the cardiac catheterization procedure, peripheral BP measurements were performed with an Omron 705IT oscillometric device. All invasive parameters were monitored, quantified, and reviewed off-line by operators blinded to noninvasive recordings. Likewise, investigators performing noninvasive recordings were blinded to invasive data.

In all patients undergoing coronary angiography, the complexity of coronary artery disease was graded by Syntax score,[8,9] a lesion-based angiographic scoring system, considering coronary involvement with stenosis ≥50%. In this study, we used a classification of severity of the coronary artery disease taking into account the Syntax Score, the number of coronary arteries with stenosis ≥30% and previous coronary artery bypass grafting, as follows:

1. Stage 1: Syntax score =0 and one-vessel coronary disease (stenosis <50%); or angiographically undamaged coronary arteries
2. Stage 2: Syntax score ≥1, <23; or Syntax score =0 and 2 to 3 vessel coronary disease (stenosis <50%)
3. Stage 3: Syntax score ≥23; or history of coronary artery bypass graft.

Noninvasive Methods

Cf-PWV was measured by recording the arterial pulse wave at common carotid and femoral artery sites. Since cf-PWV is calculated as the distance traveled by the pressure wave divided by the time delay between the detection of the pulse wave at the carotid and femoral sites, the definition of real wave travel distance is perhaps the most important methodological problem in the accuracy of cf-PWV measurement. Different approaches have been proposed to determine the distance for cf-PWV. In this study, the 2 methods recommended by the American Heart Association scientific statement[2] were both used: (1) subtraction of suprasternal notch to carotid site distance from suprasternal notch to femoral site distance[10,11] and (2) multiplication of the total directly measured distance between carotid and femoral recording site by 0.8.[12] Cf-PWV measures obtained using both these methods were analyzed and compared.

In this study, we evaluated 4 different noninvasive devices assessing cf-PWV. Complior Analyse[13] (Alam Medical, Vincennes, France) and PulsePen ETT (DiaTecne, San Donato Milanese, Italy) measure cf-PWV by simultaneously recording carotid and femoral pulse waves. Complior Analyse does this by means of 2 piezoelectric sensors and PulsePen ETT by using 2 arterial tonometers. PulsePen ET[14] (DiaTecne, San Donato Milanese, Italy) and SpygmoCor Px/Vx (AtCor Medical, West Ride, Australia) both assess cf-PWV at 2 times, separated by a short interval, using the R wave of the QRS complex of the ECG as a reference.

The pOpmètre (Axelife, Saint-Nicolas-de-Redon, France) is an original instrument that detects the pulse both at the index finger and at the second toe through 2 photodiode infrared light sensors. In the estimation of the finger-toe PWV, for the setting of the distance, the pOpmétre uses the formula height (mm) multiplied by 0.336. The transit time between pulse waves is used to calculate the finger-toe PWV. To verify the possible bias in measurements related to the algorithm implemented in this device,[15] finger-toe transit time was also evaluated analyzing the waves recorded by pOpmètre with the same software used for invasive PWV assessment (foot-to-foot method using intersect tangent algorithm).

This study also included the BPLab (Petr Telegin, Nizhny Novgorod, Russia) and the Mobil-O-Graph (I.E.M., Stolberg, Germany) devices that are automated oscillometric arm cuff-based ambulatory BP monitoring devices, estimating aortic PWV by proprietary algorithms. According to the statements by the producers, the ARCSolver algorithm (Austrian Institute of Technology, Vienna, Austria) inbuilt in Mobil-O-Graph is based on age, systolic BP, and pulse waveform characteristics,[16] whereas the Vasotens Office 6.02 version used by BPLab is based on age, systolic BP, length of aorta (as derived from the distance between the suprasternal notch and pubic symphysis), and the transition time between forward and reflected components of pulse wave. This recent 6.02 software version was implemented in BPLab only in June 2018. In our study, the previous version of BPLab analysis software (Vasotens Office 5.03) was also evaluated. The method for assessing aortic PWV implemented in the first BPLab software was based on the identification of the reflected wave in the oscillometric pressure waveform and on the estimation of PWV from the reciprocal of reflected wave transit time.

Comparative technical specifications of the noninvasive devices used in this study are summarized in Table S2. Further details concerning post-measurement quality controls of recordings for all the mentioned devices are shown in the online-only Data Supplement. Data concerning the repeatability of the PWV measurements of the present study have been detailed in a previous report.[17]

Statistical Analysis

The estimation of the sample size of this study was based on data available in published articles.[7] Data are reported as mean±SD or 95% CI where appropriate. The relationship between measurements provided by any couple of noninvasive devices as well as between measurements provided by each noninvasive device and the intraarterial recording was assessed (r or r^2 were used where appropriate). The relationship between PWV and age was analyzed by exponential regression. The agreement between the invasive aortic PWV or PWTT and the corresponding parameters obtained from noninvasive devices was evaluated using the Bland-Altman plots,[18] assessing the limits of agreement (±1.96 SD) both for the entire population and for low and high PWV groups. The latter were identified with reference to the median (11 m/s) of the entire population PWV values. A multivariate analysis was performed to evaluate the role of age, peripheral systolic BP, and heart rate in affecting PWV for each device. Normal distribution of variables entering multivariate analysis was confirmed by Shapiro-Wilk test. A further analysis of the differences between noninvasive devices and the gold standard method was accomplished by stratifying the population for PWV and age quartiles. After discarding the Gaussianity hypothesis in single quartiles, data were compared by the Wilcoxon rank-sum test for independent data. Results were reported with P values on a box plot. The relationship between PWV estimated by noninvasive methods and severity of the coronary artery disease was analyzed by ANOVA with posterior contrasts. For multiple comparisons, the algorithm which controls the expected rate of false-positive results for all positive results (false discovery rate) was used. In the presence of either residual not normally distributed or heteroscedasticity, analysis was done after logarithmic transformation of PWV variables.

Results

One hundred two patients (30% female) with a mean age of 65±13 years were enrolled in the study. Angiography procedure was performed for overt or suspected coronary artery disease (92 patients), to evaluate a peripheral artery disease (4 patients), or for renal sympathetic denervation due to resistant hypertension (2 patients). Thus, 96 patients underwent coronary angiography. The anthropometric, clinical and hemodynamic characteristics of patients are presented in Table S3. Nine patients did not undergo catheterization for refusal or contraindications to femoral access, and one patient was excluded because of the poor quality of the invasive pressure waveforms. Thus invasive aortic PWV measurements were available for analysis in 92 patients.

Technical problems or low quality of recordings led to the exclusion of some patients for noninvasive methods: 2 patients excluded for Complior, 3 for PulsePen ETT, 1 for BPLab, and 44 for pOpmètre (further details in the online-only Data Supplement).

Figures 1 and 2 show the relationship between PWV values acquired by invasive and noninvasive methods. In Figure 1, cf-PWV was measured using 80% of the direct carotid-femoral tape measure distance. Similar results were obtained when cf-PWV was calculated using subtracted distance-based method (Figure S3).

Difference in PWV estimates between invasive and noninvasive propagative methods showed heteroscedasticity in Bland-Altman plots, which disappeared when the inverse values of PWV (1000/PWV, in ms/m) were considered (Figure S4).

No significant difference was found between finger-toe PWV provided by pOpmètre and that obtained analyzing the finger-toe transit time with the software used for invasive aortic PWV (ie, foot-to-foot method using intersect tangent algorithm). For both cuff-based methods (BPLab and Mobil-O-Graph), Bland-Altman plot highlighted a negative proportional bias, showing a systematic underestimation of measured PWV at the highest PWV values.

Figure 3 shows the relationship between SphygmoCor (currently the most used device in the world for assessing PWV) and the other noninvasive method for assessing aortic PWV. Other correlations between noninvasive methods are shown in Figures S5 through S7 and summarized in Tables S4 and S5.

The sample stratification by age (Figure 4A) showed a significant overestimation of the true aortic PWV in the younger population (<55 years old) by all noninvasive methods, excepted for the pOpmètre and Mobil-O-Graph. Mobil-O-Graph significantly underestimated PWV in the 55 to 64 range age group. In the stratifying the population by PWV quartiles (Figure 4B), a tendency toward the overestimation of aortic PWV for lower values was present for all devices. A significant underestimation of aortic PWV in the group with higher PWV values was found for Complior, SphygmoCor, and Mobil-O-Graph.

Severe coronary artery disease was associated with higher values of PWV estimated by all the evaluated systems (white columns in Figure 5). However, when analysis was performed adjusting data for age and mean arterial pressure (gray columns in Figure 5), aortic PWV estimated by BPLab and Mobil-O-Graph totally lost their association with the degree of coronary involvement. Higher PWV values provided by cf-PWV systems remained associated with most severe coronary damage, although only PulsePen ETT and ET reached levels of statistical significance.

The role of BP and heart rate changes during data recording in determining differences in PWV values between invasive and noninvasive methods was also investigated (Tables S6 and S7 and Figures S8 through S11). Weak but significant increases in heart rate and systolic BP and decreases in diastolic BP values were observed during the invasive

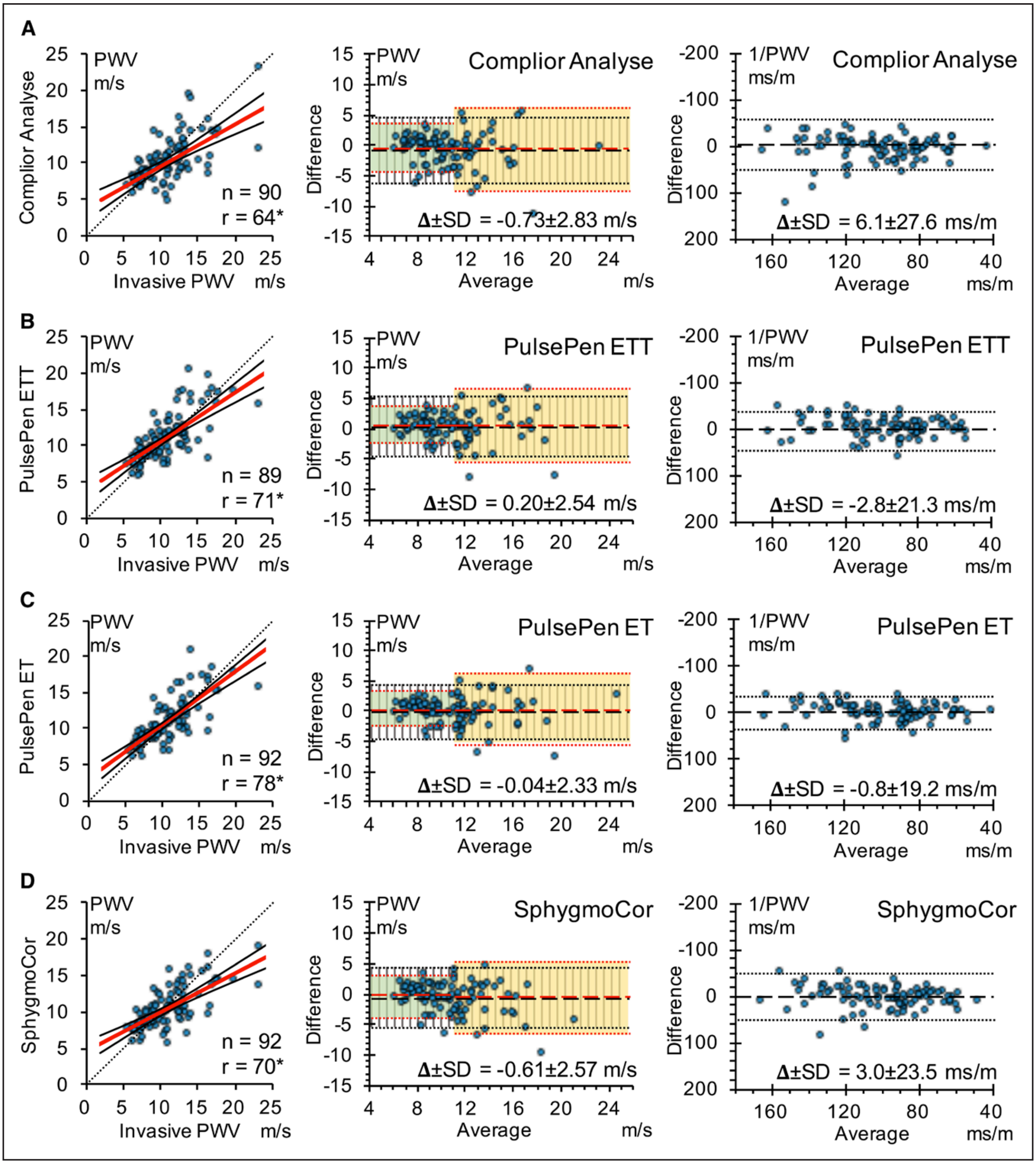

Figure 1. Relationship between pulse wave velocity values acquired by invasive and noninvasive methods (I). Carotid-femoral pulse wave velocity (PWV) was measured using 80% of the direct carotid-femoral tape measure distance. **A**, Complior Analyse; (**B**) PulsePen ETT; (**C**) PulsePen ET; and (**D**) SphygmoCor. On the **left**, the scatter plots show linear correlation between PWV values measured by the invasive reference method vs PWV measured by noninvasive devices. A linear regression line (red solid line), the 95% CIs and the identity line (dotted line) are also shown in each panel. In the middle, Bland-Altman plot shows differences observed between invasive and noninvasive measurements of PWV according to the average values. The area characterized by vertical lines and delimited by black dotted lines shows the mean values of differences (black dashed line) ±1.96 SD of pooled data. The area delimited by red dotted lines shows the mean values of differences (red dashed lines) ±1.96 SD of mean PWV values <11.0 m/s (green area, on **left** side) and >11.0 m/s (yellow area, on the **right** side); 11.0 m/s is median of invasive aortic PWV. On the **right**, Bland-Altman plot is shown using the inverse values of PWV (1000/PWV, in ms/m). The area delimited by black dotted lines shows the mean values of differences (black dashed line) ±1.96 SD of pooled data.

procedure compared with the noninvasive data acquisition, without any change in mean arterial pressure. Univariate and multivariate analyses performed on heart rate, systolic and diastolic BP as variables potentially affecting PWV differences between invasive and noninvasive methods showed a weak influence of systolic and diastolic BP, which reached

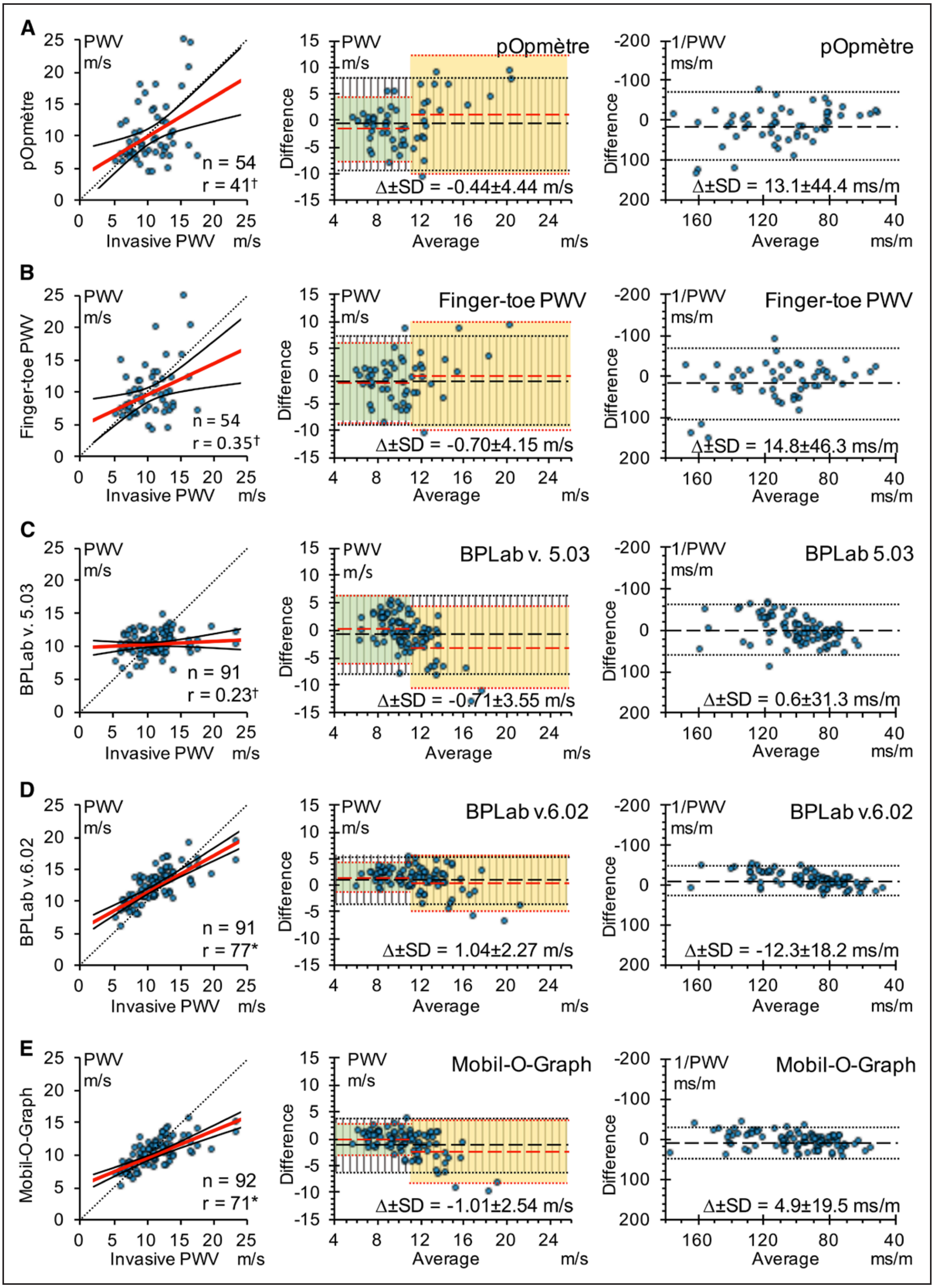

Figure 2. Relationship between pulse wave velocity values acquired by invasive and noninvasive methods (II). **A**, pOpmètre; (**B**) finger-toe pulse wave velocity (PWV), evaluated analyzing the waves recorded by pOpmètre with the same software used for invasive PWV assessment (foot-to-foot method using intersect tangent algorithm); (**C**) BPLab, using Vasotens Office 5.03 software version; (**D**) BPLab, using Vasotens Office 6.02 software version, available from June 2018; and (**E**) Mobil-O-Graph. Further explanations in Figure 1.

statistical significance only for PulsePen ET (diastolic BP; *P*=0.019), pOpmètre (systolic BP; *P*=0.008), and Mobil-O-Graph (systolic BP; *P*=0.048).

The mean running times required for measurements with all devices assessing cf-PWV and with Mobil-O-Graph were <3 minutes, while they were almost 5 minutes for BPLab and 14 minutes for the pOpmètre (Table S8).

Table shows the results of the multivariate analysis evaluating the role of the main physiological determinants of PWV, for each device. Age, peripheral systolic BP, and heart rate significantly affected aortic PWV measured by invasive method and by noninvasive methods assessing cf-PWV, with an r^2 of the model of about 0.50. Age was the only factor affecting PWV measured by pOpmètre. The relationship between age and estimated aortic PWV is shown in Figure S12.

PWV values provided by Mobil-O-Graph and BPLab were very strongly dependent on age-squared and systolic BP (cumulative r^2=0.973 and 0.990, respectively). The formula (age^2/1000 + 0.034 × systolic BP) explained 99% of the central PWV values provided by Mobil-O-Graph. The algorithm used by BPLab (0.62 software version), in addition to systolic BP and age-squared, also includes the relationship

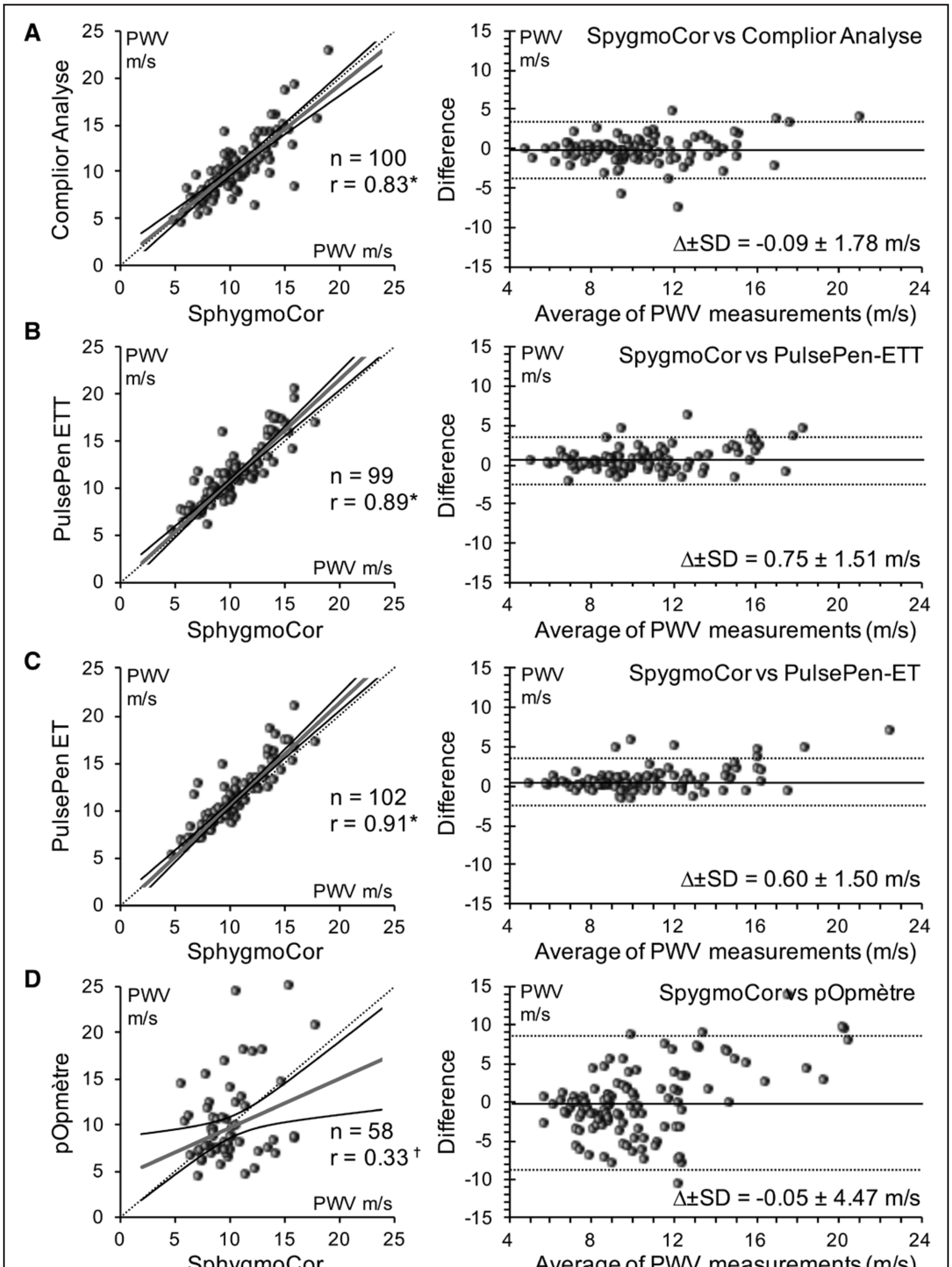

Figure 3. Relationship between pulse wave velocity values acquired by SphygmoCor and the other noninvasive methods. On the **left**, the scatter plots show linear correlation between pulse wave velocity (PWV) values measured by the SphygmoCor vs PWV measured by the other noninvasive devices. A linear regression line (solid gray line), 95% CI (solid black lines) and the y=x line (dotted line) are also shown in each panel. (*Continued*)

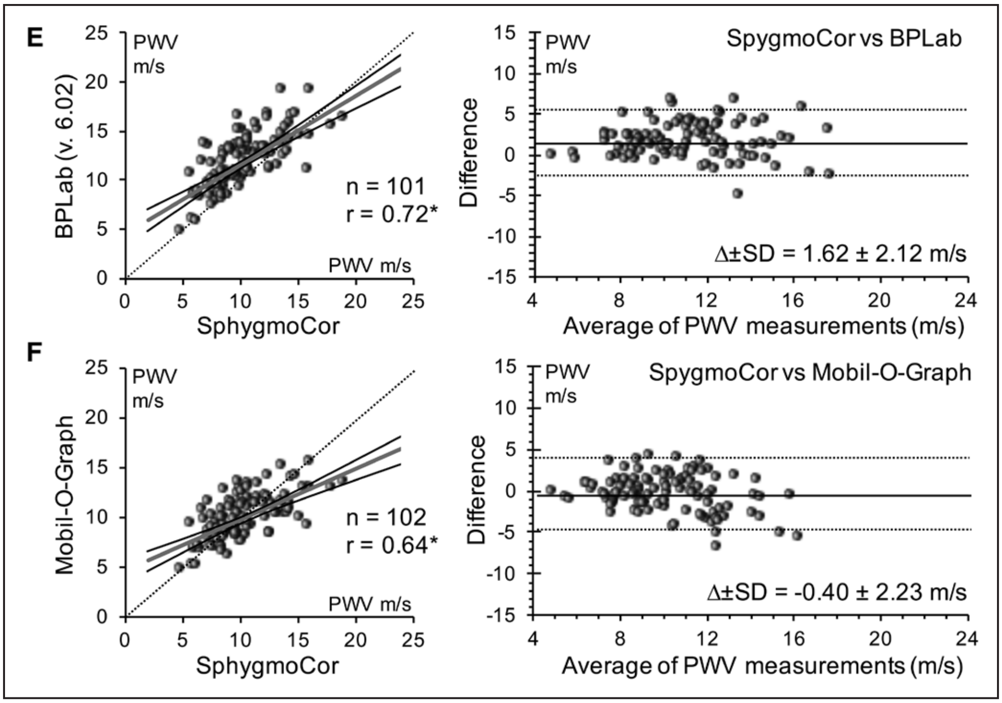

Figure 3 Continued. On the **right**, Bland-Altman analysis shows differences observed between SphygmoCor and other noninvasive measurements of PWV according to the average values. The mean values of differences (solid lines) ±1.96 SD (dotted lines) are shown.

of the distance between the suprasternal notch and the pubic symphysis and the delay of the reflected wave (spDist/rwTT). This last parameter plays a secondary role in the definition of PWV, justifying only 2.46% of the PWV measurement. In our studied sample, the formula (age^2/1000 + 0.06 × systolic BP + 6.43 × spDist/rwTT -3.78) explained 99.7% of the central PWV values provided by BPLab. This feature of close dependence on the age-squared and systolic BP of both these algorithm-based devices is clearly shown also in Figures S13 and S14.

Discussion

This is the first study comparing a true aortic PWV assessed invasively through the gold standard approach based on an intraaortic catheter, with that derived from several noninvasive methods available on the market to estimate aortic stiffness. Such a rigorous methodological approach yielded important findings, allowing us to demonstrate that: (1) All the evaluated methods assessing cf-PWV showed a strong agreement with the aortic invasive measurements. (2) The further addition of muscular arterial districts to PWV estimation (as with pOpmètre) markedly weakened the correlation with the true aortic PWV. (3) The cuff-based methods assessed in our study allow to estimate PWV through algorithms mainly including in the equation age and systolic BP, thus providing no further direct information on subclinical organ damage.

Our study has thus contributed to highlight strengths and weaknesses of these different devices, which should be separately discussed.

Propagative Methods

Currently, cf-PWV is considered the reference method for noninvasive estimation of aortic stiffness.[2] Several epidemiological studies have shown the ability of high cf-PWV values to predict incidence of cardiovascular diseases, over and above other traditional major risk factors.[4,6]

Our study demonstrates a very strong agreement between the 4 selected methods which measure cf-PWV, confirming data obtained in previous comparative studies.[19–21] Differences in sensors and algorithms used by these devices did not seem to cause significant differences in the assessment of cf-PWV. As a result, in our study, we found a strong linear positive relationship between cf-PWV and aortic PWV invasively measured. In spite of this, cf-PWV did not exactly match true aortic PWV, and this can be attributed to at least 3 possible factors, as clearly shown in Figure S15. First, cf-PWV does not include the ascending aorta in the pulse travel path. Second, brachiocephalic trunk and common carotid artery are included in the cf-PWV measurement, even if in this arterial district the pulse waves travel in an opposite direction and at different speed as compared with thoracic aorta. Third, the iliac artery and the initial segment of the femoral artery are included in the evaluation of cf-PWV. However, a reduction in elastic component and an increase in muscular component in the tunica media of their arterial wall characterize these arteries. While PWV in the aorta shows a considerable exponential increase with age, in the muscular arteries of the lower limbs PWV increases only weakly and linearly with age.[1,22] Thus, while PWV through muscular arteries is higher than in elastic arteries in younger individuals, with advancing age this difference is reversed, with PWV in muscular arteries being significantly lower than in the aorta.[1] Indeed, whereas invasive and noninvasive PWV measurements were very close in patients from 55 to 75 years, in younger adults cf-PWV values tended to be higher than aortic PWV. On the contrary, in the elderly, cf-PWV tended to underestimate the true invasive aortic PWV,

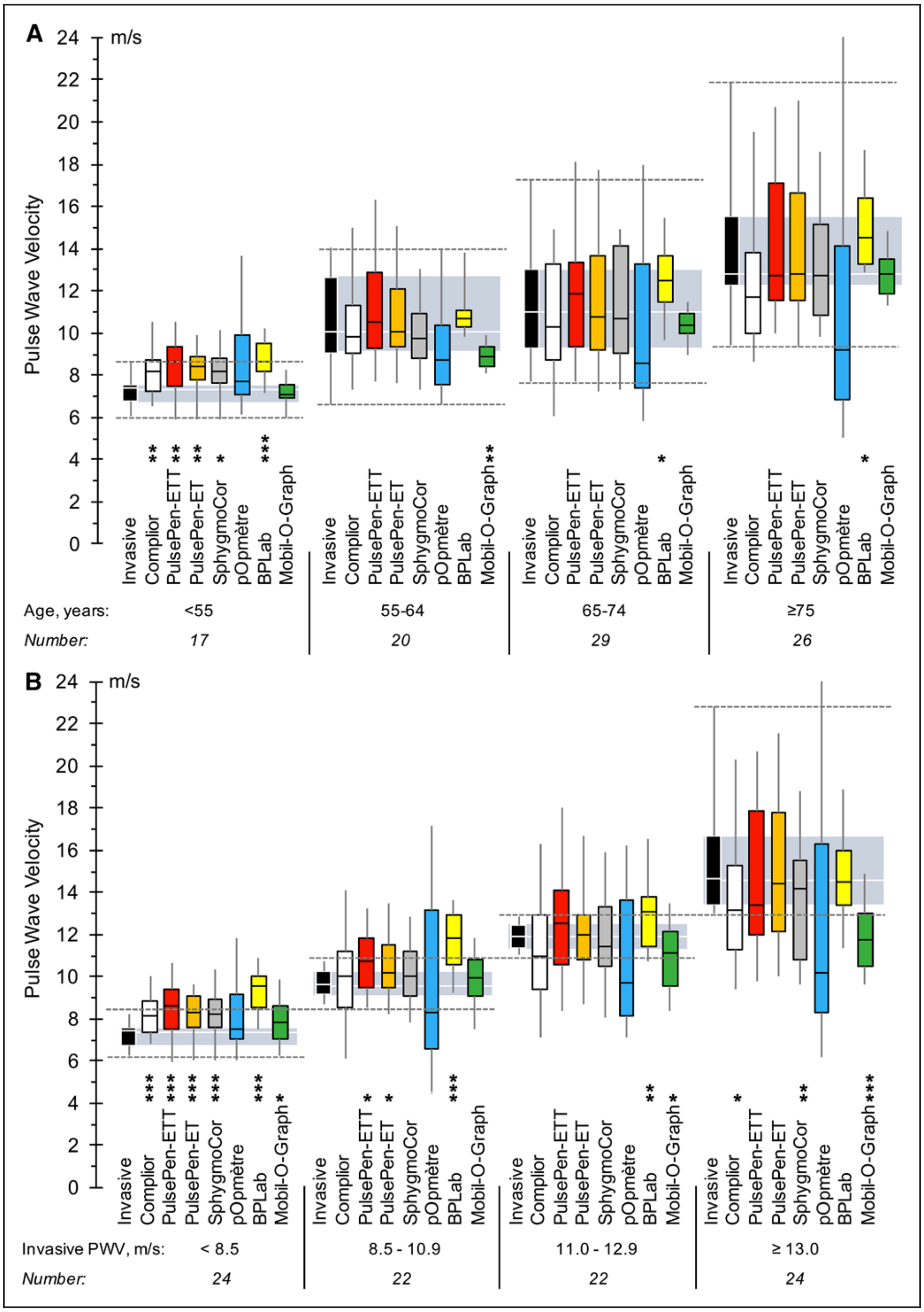

Figure 4. Pulse wave velocity (PWV) measured by invasive and noninvasive methods when stratifying the population by age (**Upper**) and pulse wave velocity quartiles (**Lower**). Data are expressed as median (horizontal line), within rectangles showing the interval between the first and third quartile; vertical lines show the distribution of values (from the minimum to the maximum value). PWV defines pulse wave velocity. For each class of age (**A**) and class of PWV values (**B**), mean value of invasive PWV is shown as a horizontal white line; the interval between the first and third quartiles of invasive PWV is shown as gray background area; the minimum and the maximum value of invasive PWV are shown as horizontal dashed lines. *$P<0.05$; **$P<0.01$; and ***$P<0.001$ vs PWV measured by invasive standard method.

an underestimation which was significant only for Complior and SphygmoCor. Moreover, the stronger relationship with age of invasive aortic PWV as compared with that of noninvasive cf-PWV could be justified by the higher arterial muscular component in the arterial path considered by cf-PWV which is not modified by age.

Increasing aortic length with age is another potential factor that could play some role in the discrepancy between invasive and noninvasive measures. However, Sugawara et al[10] showed that if the ascending aortic length is positively and strongly associated with age, on the contrary, lengths of the descending aorta, carotid, and iliac arteries are not related to age. Moreover,

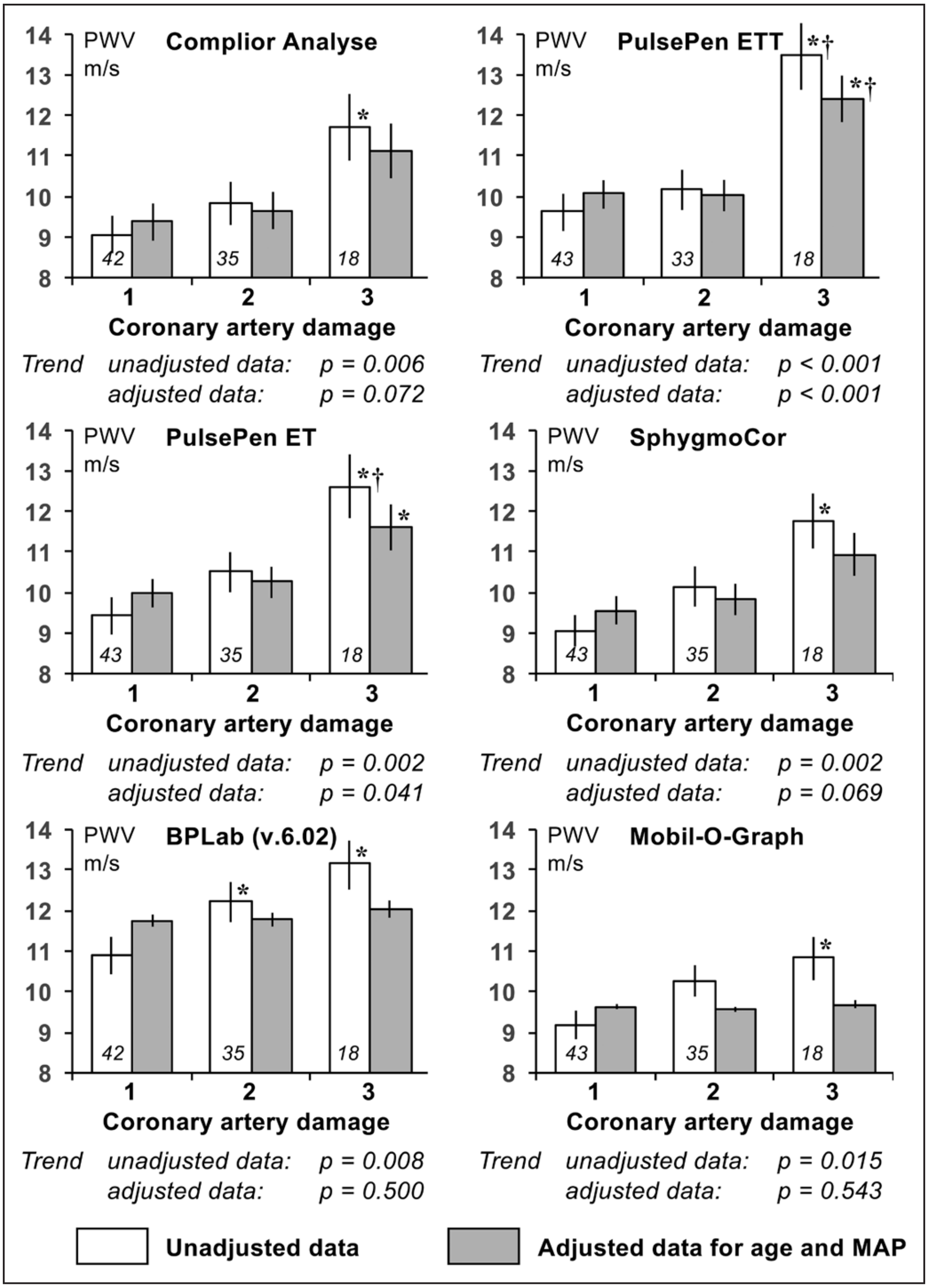

Figure 5. Pulse wave velocity values provided by noninvasive methods at different degree of coronary artery damage. The severity of coronary damage was staged considering the Syntax score and the number of coronary branches involved, from 1: normal coronary arteries or mild damage, to 3: severe coronary damage (more details in the text). White columns show unadjusted data; gray columns show data adjusted for age and mean arterial pressure. Data are expressed as estimated marginal means±SE. MAP, mean arterial pressure; and PWV, pulse wave velocity. *$P<0.05$ vs stage 1 and †$P<0.05$ vs stage 2.

Van Bortel et al[12] found that a correction of PWV for age in patients older than 50 is not advisable. Taking into account the results of these studies, we therefore considered it inappropriate to modify the distance measurement according to age.

The differences between invasive aortic PWV and noninvasive cf-PWV increased with increasing PWV values: higher differences in PWV values were found in patients with greater arterial stiffness. The calculation of the PWV as inverse of the transit time (which makes PWV proportional to the square root of the inverse of the distensibility, as formalized in the Bramwell-Hill equation) emphasizes the importance of PWV measurement as an index of distensibility. Such a calculation, however, generates a higher variance for high PWV values. Thus, for higher values of PWV small differences in the pulse wave transit time translate into large differences in PWV value. Our results agree with previous comparative study

Table. Results of Multiple Regression Analysis with Pulse Wave Velocity (PWV) Measured by Each Method as Dependent Variable

Dependent Variable	r^2 Model	Independent Variables	β Value	SE	*P* Value	r^2 Contribution
PWV by invasive method	0.535	Intercept	–10.041	2.324	<0.0001	
		Age	0.154	0.026	<0.0001	0.372
		Systolic BP	0.050	0.010	<0.0001	0.131
		Heart rate	0.052	0.021	0.0159	0.032
PWV by Complior Analyse	0.454	Intercept	–7.508	2.102	0.0006	
		Age	0.059	0.020	0.0039	0.163
		Systolic BP	0.062	0.012	<0.0001	0.202
		Heart rate	0.084	0.022	0.0002	0.088
PWV by PulsePen ETT	0.564	Intercept	–10.250	2.144	<0.0001	
		Age	0.081	0.020	<0.0001	0.261
		Systolic BP	0.075	0.011	0.0001	0.240
		Heart rate	0.088	0.023	<0.0001	0.063
PWV by PulsePen ET	0.549	Intercept	–10.890	2.134	<0.0001	
		Age	0.088	0.022	<0.0001	0.268
		Systolic BP	0.068	0.012	<0.0001	0.195
		Heart rate	0.102	0.023	<0.0001	0.087
PWV by SphygmoCor	0.519	Intercept	–6.152	1.810	0.0010	
		Age	0.091	0.018	<0.0001	0.337
		Systolic BP	0.052	0.010	<0.0001	0.153
		Heart rate	0.050	0.021	0.0175	0.029
PWV by pOpmètre	0.115	Intercept	5.758	3.582	0.111	
		Age	0.102	0.040	0.012	0.100
		Systolic BP	0.015	0.021	0.498	0.000
		Heart rate	–0.058	0.047	0.218	0.015
PWV by BPLab (v.6.02)	0.978	Intercept	–6.276	0.369	<0.0001	
		Age	0.129	0.004	<0.0001	0.718
		Systolic BP	0.063	0.002	<0.0001	0.257
		Heart rate	0.014	0.004	0.0011	0.003
PWV by Mobil-O-Graph	0.967	Intercept	–4.355	0.369	<0.0001	
		Age	0.136	0.004	<0.0001	0.855
		Systolic BP	0.037	0.002	<0.0001	0.112
		Heart rate	0.004	0.004	0.3657	0.000
PWV by BPLab (v.6.02)	0.973	Intercept	–1.762	0.205	<0.0001	
		Age-squared	0.001	0.000	<0.0001	0.700
		Systolic BP	0.064	0.001	<0.0001	0.272
PWV by BPLab (v.6.02)	0.999	Intercept	–3.761	0.370	<0.0001	
		Age-squared	0.001	0.000	<0.0001	0.700
		Systolic BP	0.064	0.001	<0.0001	0.272
		spDist/rwTT	6.432	0.072	<0.0001	0.027
PWV by Mobil-O-Graph	0.990	Intercept	–0.158	0.141	0.2647	
		Age-squared	0.001	0.000	<0.0001	0.891
		Systolic BP	0.035	0.001	<0.0001	0.100
PWV by Mobil-O-Graph		Age-squared	0.001	0.000	<0.0001	0.980
		Systolic BP	0.033	0.001	<0.0001	0.019

In the lower table age was replaced by age-squared and intercept (not significant) excluded in the last model. β indicates regression coefficients; BP, blood pressure; PWV, pulse wave velocity; r^2, coefficient of determination; and spDist/rwTT, distance between the suprasternal notch and the pubic symphysis and the delay of the reflected wave.

of a noninvasive device with the invasive method,[16] which showed significantly lower values of cf-PWV measured by SphygmoCor compared with aortic PWV measured invasively in patients over 70 years old and an overall mean difference of 0.5±1.9 m/s between the 2 methods.

A further inclusion of a large pathway of muscular arteries in the assessment of aortic PWV, as with finger-toe PWV estimates by pOpmètre, significantly reduced the correlation of this parameter with both invasive aortic PWV and noninvasive cf-PWV and weakened its relationship with age. Indeed, the pOpmètre device includes all the upper and lower limbs arteries, in which pulse waves travel in opposite direction, in the frame of a PWV measurement. The weak correlation between the PWV values provided by pOpmètre and those obtained through the invasive aortic recordings seems thus to be mainly due to the intrinsic limitations of the method itself (finger-toe propagative method including extensive pathways of muscular arteries), rather than to defects of the device or of its software. A weak correlation persists also when aortic invasive and finger-toe signals were evaluated in the same way, using for both the foot-to-foot wave method and intersect tangent algorithm. The meaning of finger-toe PWV thus does not appear to be yet well defined, and the interpretation of this measurement is still under debate, as it might provide information on other pathophysiological mechanisms that need to be clarified in future studies.

Cuff-Based and Algorithm-Based Systems

The first version of BPLab (Vasotens 5.03 software version) provided aortic PWV by a proprietary algorithm which analyzed the oscillometric pressure wave recorded on the upper arm and calculated the reflected wave transit time, that is, the delay between direct and reflected wave. In our study, aortic PWV measured by this Vasotens 5.03 software version did not show significant differences from the invasive method at paired *t* test evaluation. However, only a weak correlation with both invasive aortic PWV and noninvasive cf-PWV values and a weak relationship with age were found, indicating a clear tendency of this method to become inaccurate for both higher and lower PWV values, producing an underestimation of PWV values in the elderly, and an overestimation in young patients.

Even if the use of timing of reflected waves should seem an interesting and promising method in estimation of aortic PWV,[23] Westerhof et al[24] and Mitchell et al[25,26] seriously questioned this principle, showing that return time of the reflected wave is not closely related to aortic PWV. Indeed, these studies have highlighted the reasons why PWV measured by BPLab implemented with 5.03 Vasotens version does not agree with true invasive aortic PWV. Based on the results of our study, this version of BPLab cannot be considered a reliable system to evaluate aortic PWV in subjects across a wide age range, indicating the need for an improvement in the algorithm used by this device.

Conversely, BPLab with the new Vasotens 6.02 software version and Mobil-O-Graph used similar approaches to the estimation of aortic PWV and provided similar results. These 2 devices showed a good correlation with invasive aortic PWV and with noninvasive cf-PWV measured by PulsePen and SphygmoCor revealing, however, a negative proportional bias at Bland-Altman plot. Thus, theoretically, BPLab and Mobil-O-Graph should be considered the best methods to estimate PWV, performing easy and operator-independent measurements and providing reliable aortic PWV values. However, the algorithm used by both these devices yielded estimates of PWV which are mainly calculated from age and systolic BP. On the one hand, considering these 2 factors together obviously increases the prognostic predictive power of the PWV estimated by BPLab and Mobil-O-Graph. On the contrary, this approach does not provide additional prognostic information beyond that already supplied by these classical risk factors given that, through this algorithm, estimates of PWV are mostly derived from age and BP. At present, an increase in aortic PWV is considered as an independent predictor of coronary heart disease and stroke, over and above other traditional major risk factors. This main point of strength of PWV measurement might thus be lost when using BPLab or Mobil-O-Graph to assess arterial stiffness because the estimates of PWV they provide do not faithfully reflect other factors beyond age and BP levels.

This important limitation of these systems has been highlighted also in our study. Indeed, analysis of the relationship between PWV values and degree of coronary artery damage showed a significant increase in estimated PWV provided by all the evaluated devices in patients with severe coronary impairment. However, after adjustment of PWV values for age, the PWV values provided both by BPLab and Mobil-O-Graph were equivalent in subjects with coronary arteries free of damage and in those with seriously damaged coronary vessels.

Moreover, the results of a recent study of ours involving a population with Marfan syndrome questioned the ability of these algorithm-based systems to provide an accurate evaluation of early vascular aging.[27] Aortic PWV estimated by Mobil-O-Graph and cf-PWV were evaluated in a cohort of mostly young patients, characterized by low BP values and precocious arterial stiffening, due to altered synthesis of fibrillin-1 protein. Aortic PWV estimated by Mobil-O-Graph was closely related to age-squared and systolic BP values of Marfan patients, resulting significantly ($P<0.0001$) lower than cf-PWV provided by arterial tonometry (mean±SD, 6.1±1.3 m/s versus 8.8±3.1 m/s).

More correctly, BPLab and Mobil-O-Graph should be considered as algorithm-based systems, rather than oscillometric cuff-based systems. Indeed, these devices do not provide measurements, nor estimations of aortic PWV, but rather provide the calculation of the expected PWV values for a given age and a given brachial systolic BP.

Although the developers of the Mobil-O-Graph claim that, in addition to age and systolic BP, several other parameters from pulse wave analysis and wave separation analysis are combined in the ARCSolver algorithm[16], the role of these factors appears negligible in the computation of PWV. Likewise, even if the ratio between the sternum-pubic distance and the timing of wave reflections is implemented in the BPLab algorithm; however, these variables account for <3% of the variance in the estimated PWV.

Because of its intrinsic features, a BP-based algorithm for evaluation of PWV could also engender misleading results when exploring changes in PWV in conditions characterized by changes in BP, such as in response to pharmacological treatment, after exposure to environmental factors, food consumption, or during physical activity. In these cases, PWV values obtained through this algorithm might mostly reflect changes in BP levels rather than changes in arterial distensibility. Algorithm-based systems, such as BPLab and Mobil-O-Graph, do not appear therefore to be adequate methods in clinical trials, in epidemiological studies or in studies on subjects at high cardiovascular risk, all conditions in which other factors beyond age and changes in BP levels might play a role.

Study Limitations

Invasive and noninvasive measurements were not recorded simultaneously, but with a time delay of 20 to 50 minutes. This is the main limitation of this study. An increase in heart rate (mean difference: 4.2 bpm) and systolic BP (5.9 mm Hg), a decrease in diastolic BP (3.9 mm Hg), without any change in mean arterial pressure values were observed during the invasive compared with the noninvasive procedures. These slight variations in heart rate and BP can only partly justify the differences found between PWV values measured with invasive and noninvasive methods, but they should be considered when interpreting the results of this study.

Perspectives

Among the evaluated methods, only cf-PWV (Complior, PulsePen ET, PulsePen ETT, and SphygmoCor) demonstrated sufficient reliability to estimate aortic stiffness, as a sign of early vascular aging. In daily clinical practice and in scientific research, other systems should thus be used with caution and with a proper understanding of their inherent limitations.

The PWV values estimated by BPLab and Mobil-O-Graph algorithms also show a good correlation with invasive PWV, although their estimation of PWV mainly from age and BP values appear to be unsuitable for the evaluation of subclinical organ damage in the individual patient or for the quantification of temporal changes in arterial structure and function independent of age and BP.

The development of easy-to-use and operator-independent noninvasive systems for the evaluation of PWV is suitable, to allow the evaluation of the degree of arteriosclerosis in daily clinical practice.

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Disclosures

P. Salvi has served as a consultant for DiaTecne srl. F. Scalise is founder and stockholder of Flag Vascular srl. S.C. Millasseau has served as a consultant for Alam Medical SAS, AtCor Medical Pty Ltd, OOO Petr Telegin. Flag Vascular srl, OOO Petr Telegin, Alam Medical SAS, I.E.M. GmbH, and Axelife collaborated on the study by providing the devices and technical assistance limited to the duration of the study. The other authors report no conflicts.

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Novelty and Significance

What Is New?

- For the first time, several noninvasive methods to estimate aortic stiffness were compared with a true" aortic pulse wave velocity, invasively assessed.

What Is Relevant?

- Propagative methods including a large pathway of muscular arteries in the aortic pulse wave velocity assessment (pOpmètre) showed only a weak correlation with invasive estimates of aortic stiffness.
- Algorithm-based systems (BPLab and Mobil-O-Graph) are closely linked to changes in age and blood pressure. Thus these devices appear unable to detect a condition of early vascular aging.

Summary

Methods estimating carotid-femoral pulse wave velocity (Complior Analyse, PulsePen ET, PelsePen ETT, and SphygmoCor) should be considered the best noninvasive approach to reliably assess aortic stiffness, independently from other determinants.