

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 \pm 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 \pm SD $=-0.44\pm 4.44$ 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 \pm SD $=-0.71\pm 3.55$ 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. (*Hypertension*. 2019;74:117-129. DOI: 10.1161/HYPERTENSIONAHA.119.12853.) • [Online Data Supplement](#)

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.

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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/m²; 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 method³ 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 statement² 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 Analyse¹³ (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 ET¹⁴ (DiaTecne, San Donato Milanese, Italy) and SphygmoCor 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 pOpmètre 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 ($1000/\text{PWV}$, 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

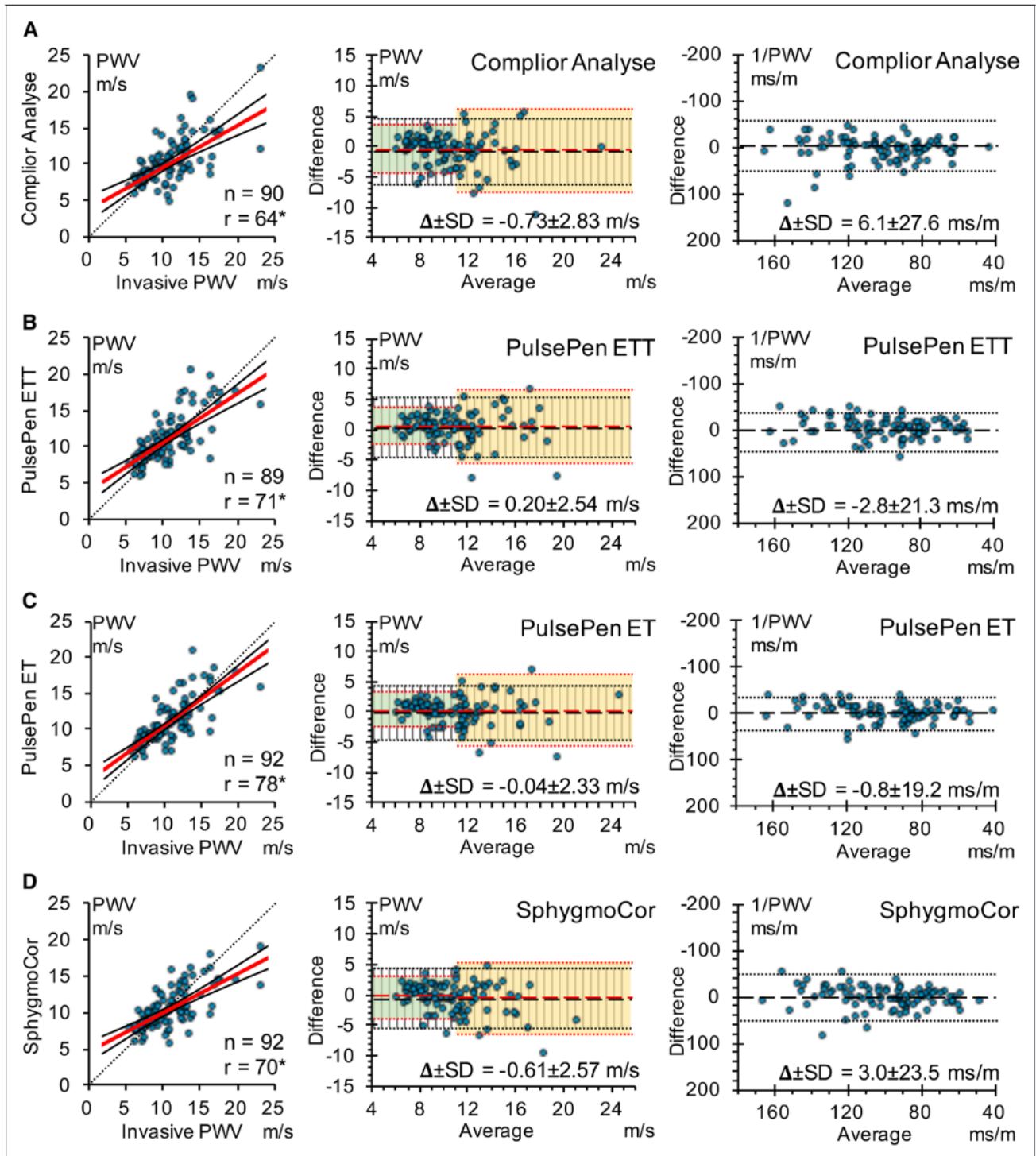


Figure 1. Relationship between pulse wave velocity values acquired by invasive and noninvasive methods (I). Carotid-femoral pulse wave velocity (PWV) was measured using 80% of the direct carotid-femoral tape measure distance. **A**, Complior Analyse; **B**) PulsePen ETT; **C**) PulsePen ET; and **D**) 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

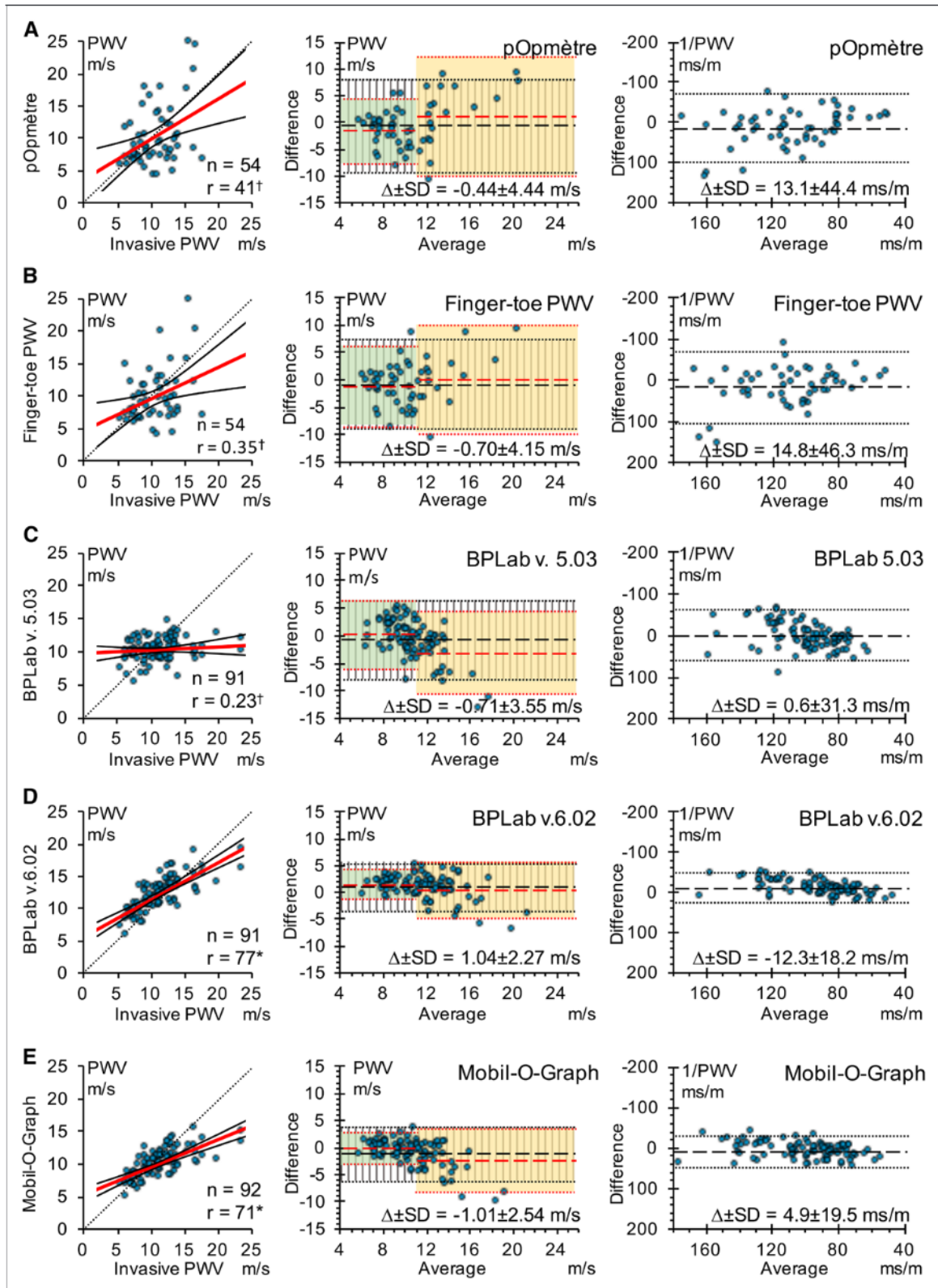


Figure 2. Relationship between pulse wave velocity values acquired by invasive and noninvasive methods (II). **A**, pOpmètre; **B**) finger-toe pulse wave velocity (PWV), evaluated analyzing the waves recorded by pOpmètre with the same software used for invasive PWV assessment (foot-to-foot method using 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 ($\text{age}^2/1000 + 0.034 \times \text{systolic BP}$) 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

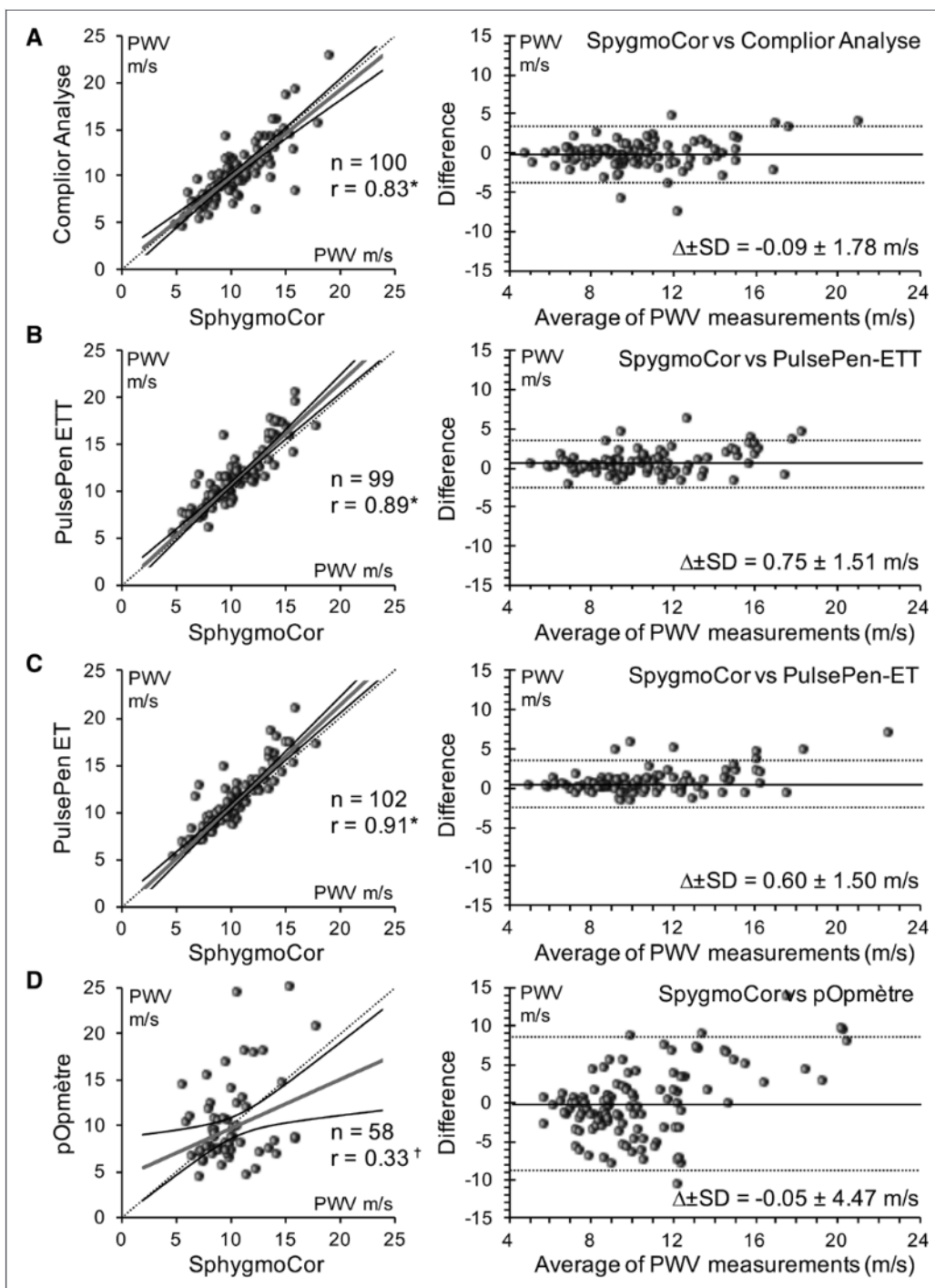


Figure 3. Relationship between pulse wave velocity values acquired by SphygmoCor and the other noninvasive methods. On the left, the scatter plots show linear correlation between pulse wave velocity (PWV) values measured by the SphygmoCor vs PWV measured by the other noninvasive devices. A linear regression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

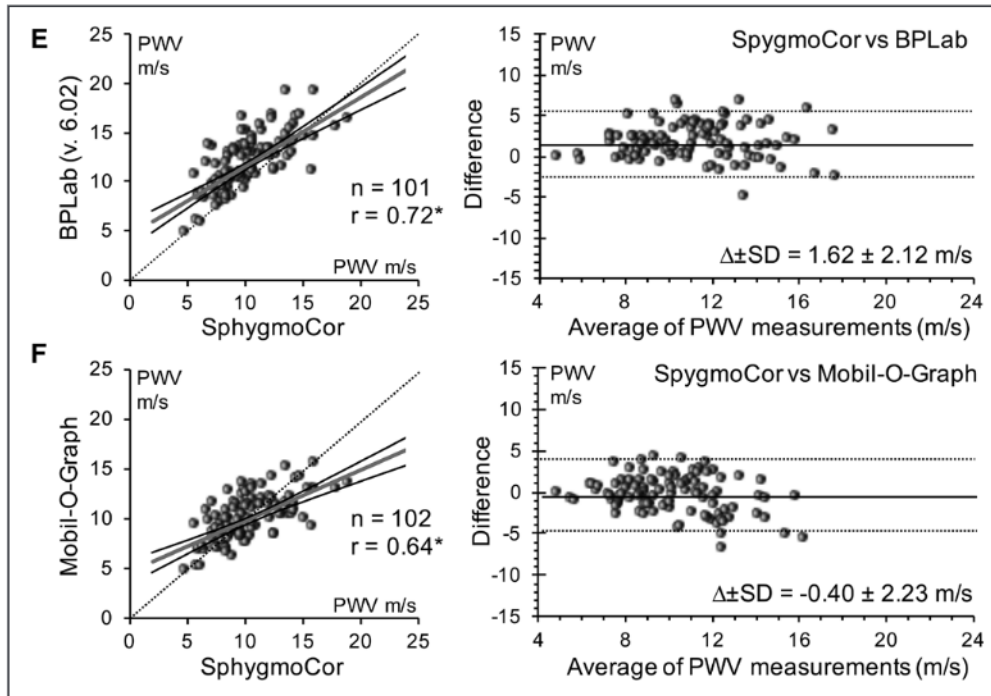


Figure 3 Continued. On the right, Bland-Altman analysis shows differences observed between SphygmoCor and other noninvasive measurements of PWV according to the average values. The mean values of differences (solid lines) ± 1.96 SD (dotted lines) are shown.

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 ($\text{age}^2/1000 + 0.06 \times \text{systolic BP} + 6.43 \times \text{spDist/rwTT} - 3.78$) 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 pOp-mètre) 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,

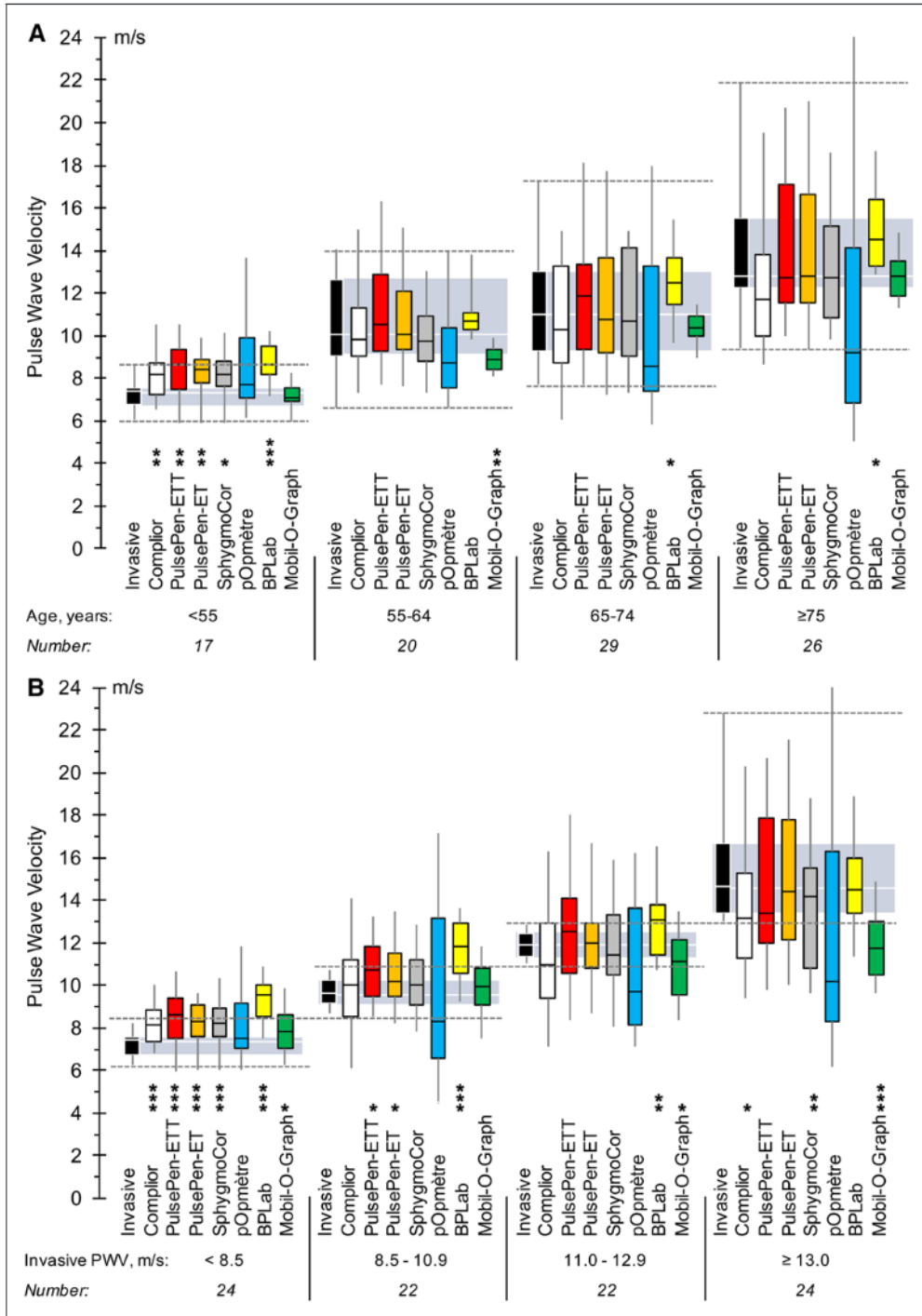


Figure 4. Pulse wave velocity (PWV) measured by invasive and noninvasive methods when stratifying the population by age (**Upper**) and pulse wave velocity quartiles (**Lower**). Data are expressed as median (horizontal line), within rectangles showing the interval between the first and third quartile; 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 al¹⁰ 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,

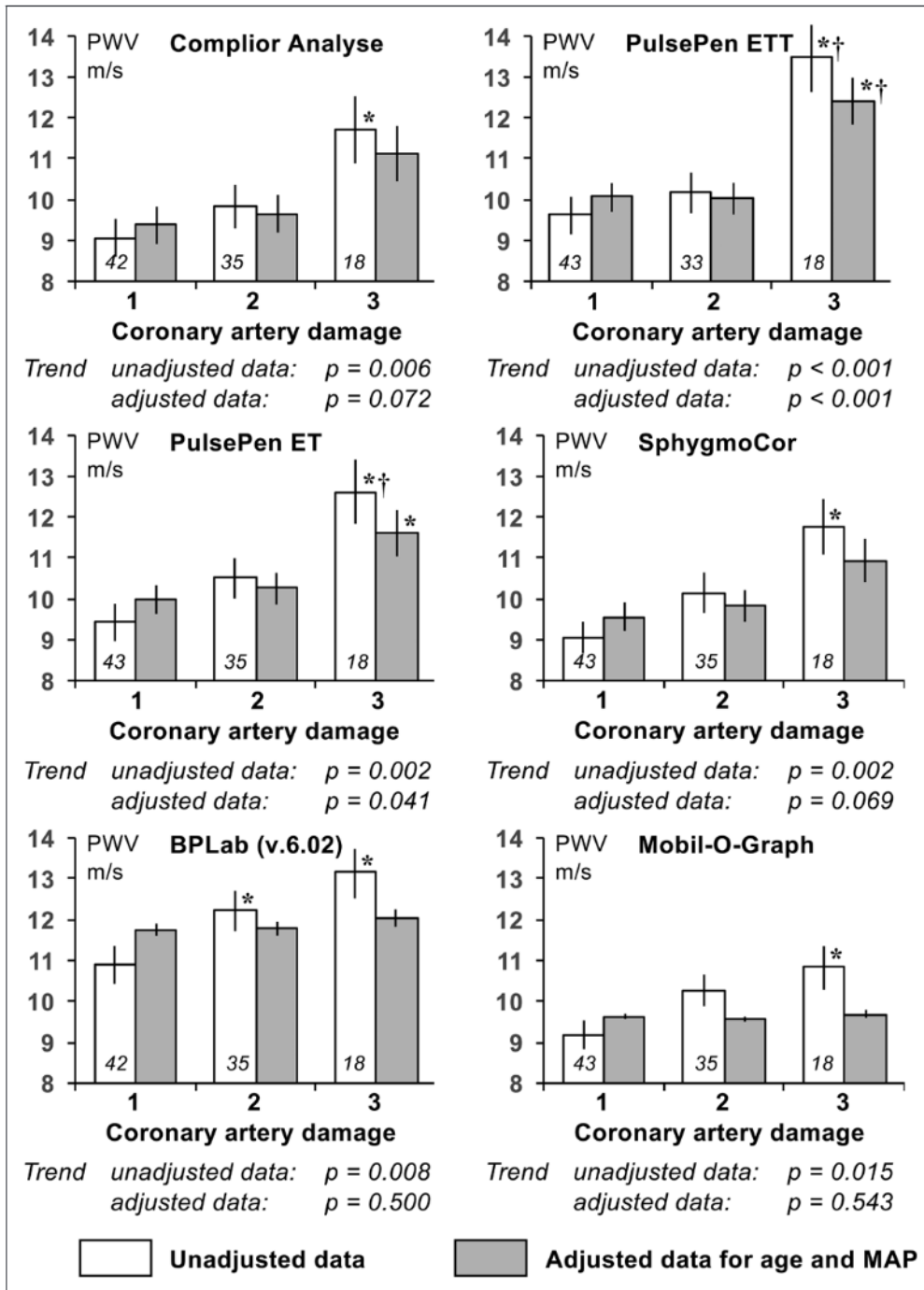


Figure 5. Pulse wave velocity values provided by noninvasive methods at different degree of coronary artery damage. The severity of coronary damage was staged considering the Syntax score and the number of coronary branches involved, from 1: normal coronary arteries or mild damage, to 3: severe coronary 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 al¹² 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 pOpmetre	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; r², 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 al²⁴ 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 \pm 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 algorithm¹⁶, 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 mmHg), a decrease in diastolic BP (3.9 mmHg), 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 Axelifa 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?

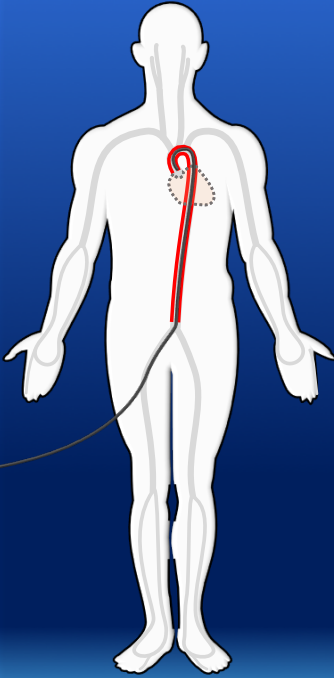
- Propagative methods including a large pathway of muscular arteries in the aortic pulse wave velocity assessment (pOpmètre) showed only a weak correlation with invasive estimates of aortic stiffness.

- 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.

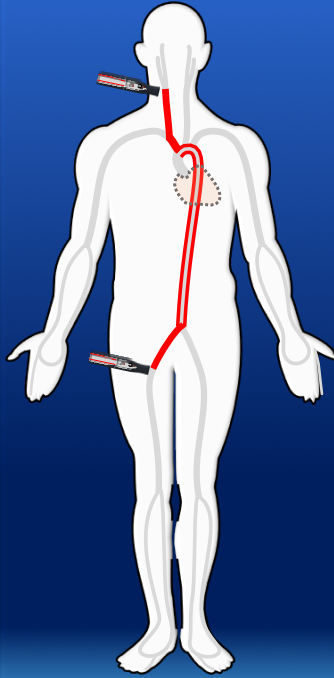
Summary

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.

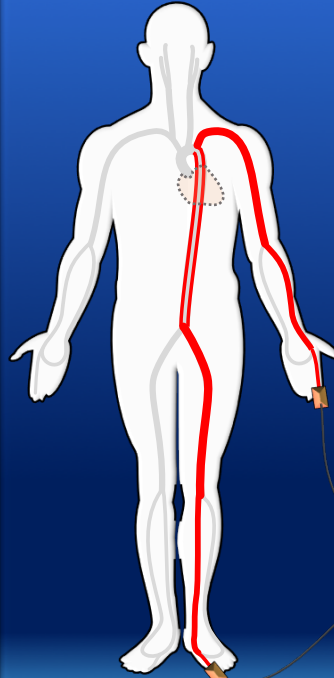
Aortic Pulse Wave Velocity



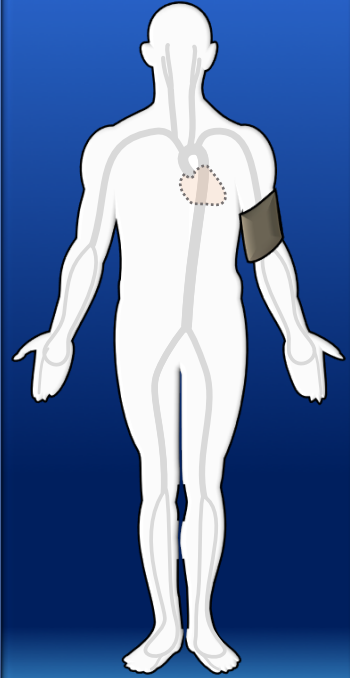
Reference Method
**Invasive Aortic
Pulse Wave
Velocity**



Carotid-Femoral PWV
- Complior Analyse
- PulsePen ET
- PulsePen ETT
- SphygmoCor



Finger-Toe PWV
- pOpmètre



Cuff-based Methods
- BPLab v.5.03
- BPLab v.6.02
- Mobil-O-Graph



Good agreement with
invasive aortic PWV

Weak correlation with
invasive aortic PWV

PWV entirely
dependent on age and
blood pressure values
Negative proportional bias
at Bland-Altman plot



RECOMMENDED
in clinical trials and
in daily clinical practice

Supplemental Data

Non-Invasive Estimation of Aortic Stiffness Through Different Approaches: Comparison with Intra-Aortic Recordings

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Supplemental Methods

Sample size

Considering a standard deviation of the difference between PWV measurements with two devices of 0.8 m/s, a sample size of 90 patients would provide a confidence interval of 0.08 m/s for the difference between devices. Based on this calculation, we included 102 patients in our study, considering a 10% drop-out rate.

Operators

Seven skilled operators, with proven experience in the evaluation of arterial stiffness parameters and in the use of applanation tonometers, performed all the measurements. Two weeks training, prior to the study, was provided to all operators and their expertise was ascertained with all devices. Data concerning intra-operator and inter-operator reproducibility were published in a previous paper from our group¹ (further details are shown in Table S1).

Four operators took care of one patient at a time: two operators handled the cuff-based devices (BPLab and Mobil-O-Graph) and photodiodes (pOpmètre) on the left side of the patient, while the other two dealt with the devices measuring cf-PWV on the patient's right side (Complior, PulsePen and SphygmoCor). Except for the pOpmètre, 2 sets of measurements were sequentially performed, for an average total duration of about 15 minutes each. With the aim of limiting the patient's discomfort, a maximum test time of 30 minutes was established. Whenever a technical difficulty in obtaining two high quality recordings for each device would have prevented to comply with these pre-set time limits, only one measurement was performed (which happened 8 times with Complior, 5 times with PulsePen-ETT, 4 times with PulsePen-ET, 5 times with SphygmoCor, 12 times with pOpmètre, 9 times with BPLab, 3 times with Mobil-O-Graph).

Assessment of mean arterial pressure

Mean arterial pressure (MAP) for each measurement was then calculated by applying the form factor, with the formula²: $MAP = \text{diastolic BP} + \text{pulse pressure} \times \text{form factor}$.

Form factor was calculated on the pulse pressure waveform measured at the brachial level by PulsePen tonometer. It is the ratio between the mean value of the brachial pulse pressure, defined by the integral of the brachial pulse waveform, and the amplitude of whole brachial pulse pressure wave.

After the non-invasive assessment, the patient underwent invasive aortic PWV measurements.

Evans's Empirical Classifications of Interpreting Correlation Strength by Using 'r'³.

r	Correlation
< 0.20	very weak
0.20 – 0.39	weak
0.40 – 0.59	moderate
0.60 – 0.79	strong
≥ 0.80	very strong

Quality control systems for non-invasive devices

Complior Analyse automatically performs quality checks and acquires only 10 appropriate, even non-consecutive, complexes. Furthermore, in this study an independent operator reviewed the measurements and discarded poor quality curves.

Both the *PulsePen devices* (ETT and ET models) use a ‘quality index’ allowing for real-time recording of the last validated 10 complexes and for quality checks by the operator. The software shows to the operator when a good quality signal has been acquired and the curves overlap for more than 80%. Any ectopic beat and aberrant complex were omitted from the calculation in off-line review mode and only data with a quality index >85% were included in the analysis.

To ensure the quality of *SphygmoCor* data, its software calculates an “operator index” based on the variability of electrocardiographic trace and pressure curves. In this study, only data with an index >85 were considered.

The built-in quality controls in *BPLab* automatically start a new measurement if any error or misreading occur, and the Vasotens clinical report screen allows for a visual assessment of the curves. As stated by the manufacturer, only pairs of PWV measurements with inter-individual variability <10% for both PWV and PW transit time (PWTT) values were regarded as reliable. Thus, the measurement session lasted until at least 4 measures for each patient, meeting the declared criteria, were acquired, given that the study protocol required a minimum of two measures per device.

The software of *pOpmètre* displays the variation coefficient (CV%) of recorded measurements, accepting as valid only the measurements with a CV below 10% for both finger-toe PWV and finger-toe TT. The travelled distance is estimated using subject’s height. A further validation of the curves recorded in our study was blindly performed by the manufacturer. Moreover, the pulse waves recorded by the pOpmètre were analyzed one by one and only the exams characterized by curves with a good morphology were inserted into the database. In several examinations, it was not possible to record the entire pressure wave: the foot and / or the apex of the pressure waves were cut off. Since the calculation of the transit time between finger and toe is defined by the maximum of the second derivative, the software of the pOpmètre provided measurements of the PWV even in the presence of truncated pulse waveforms. Despite these waves were considered of good quality for the pOpmètre, however, in order to have data as reliable as possible on this method, we excluded from the analysis all the curves characterized by morphological alterations. The number of curves considered in the calculation of the finger-toe PWV and the amplitude of the signal were also considered in the validation of the measurements.

Procedures in recording pOpmètre signals

The pOpmètre recordings were performed using a dedicated battery-powered laptop and disabling all wireless systems. A minimum distance of 1.5 meters from any other device or energy source was adhered to and the sensor cables were fully unwound to avoid electromagnetic interference. A particular attention was drawn on positioning of the photodiodes so that the pulp was in contact with the photodiode, not leaving an empty space between the sensor and the finger/toe. Sensors were placed just below the distal interphalangeal joint after patients had repeatedly contracted hand and feet for 10 seconds to promote blood supply. In patients with peripheral vasoconstriction or low skin temperature we used a hot water bottle to induce vasodilation. Artificial light was turned off. A canvas was placed around the probe, in order to reduce the interference of light. The patient was asked not to move the upper and lower limbs during the recording. Considering patient discomfort, in the absence of an appropriate signal, the acquisition by pOpmètre was extended until the patient was called for angiography. Two or more measurements were performed.

Pulse waves were acquired using the pOplight[®] software, version 2.1.0, whereas finger-toe PWV was estimated with the more recent software version 2.2.1. In order to verify the possible bias in measurements related to the algorithm implemented in this device⁴, finger-toe TT 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).

Drop-out in pOpmètre measurements.

An important limitation of this study concerns the low number of reliable measurements obtained with the pOpmètre. Although all the instructions prescribed by the manufacturer were meticulously followed, in 44 patients it was not possible to obtain a reliable value of finger-toe PWV.

- Abnormal pulse waves or low amplitude curves were recorded in 37 patients. The main causes in the failure to record good quality pulse waves were the following. First, the widespread vasculopathy and ischemic reduction in peripheral circulation characterizing the majority of patients enrolled in this study. Second, in this study, the first series of the pOpmètre device was provided by Axelife, which was characterized by defects in the signal acquisition system. More recent models of pOpmètre are actually more sensitive and accurate in the acquisition of the peripheral pulse.
- It was not possible to obtain any recording of pulse wave in 5 patients.
- Finally, 2 patients were called for angiography before performing the exam, and it was not possible to perform the exam.

Supplemental References

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Table S1. Inter-Operator Repeatability.

The measurements of carotid-femoral PWV (cf-PWV, operator-dependent systems) were performed by 2 operators: a fixed expert operator (M.R.) associated with a second expert operator. Three other experienced operators took turns in the acquisition of pressure waves.

The coefficient of variation (CV) for the cf-PWV measured by each operator was calculated as strongly recommended by Bland⁵. The within-subject CV was calculated as the square root of the mean within-subject variance (σ_w^2) / subject mean squared (μ_s^2), as follow:

$$\sqrt{E \left[\frac{\sigma_w^2}{\mu_s^2} \right]}, \quad \text{where } E[x] \text{ is the expected value of random variable } x.$$

Operator:	Coefficient of Variation (%)			
	I	II	III	Pooled
Measurements / Total	61.8%	15.7%	22.5%	100%
Complior	8.1	8.9	7.7	8.2
PulsePen-ETT	8.0	7.1	8.6	8.0
PulsePen-ET	5.5	7.1	5.7	5.8
SphygmoCor	9.2	9.9	9.8	9.5

Table S2. Overview of Technical Specifications and General Features of Non-Invasive Devices

Device	Complior Analyse	PulsePen ETT	PulsePen ET	SphygmoCor Px/Vx	pOpmètre	BPLab	Mobil-O-Graph
Manufacturer	Alam Medical (France)	DiaTecne (Italy)	DiaTecne (Italy)	AtCor Medical (Australia)	Axelife (France)	Petr Telegin (Russia)	I.E.M. (Germany)
Aortic PWV assessment	Carotid-femoral PWV	Carotid-femoral PWV	Carotid-femoral PWV	Carotid-femoral PWV	Finger-toe PWV	Cuff-based method	Cuff-based method
Probes	2 piezoelectric sensors	2 tonometers	1 tonometer + ECG	1 tonometer + ECG	2 photodiode sensors	Upper arm cuff Oscillometric system	Upper arm cuff Oscillometric system
Recording time	10 cardiac cycles	10 cardiac cycles	10 cardiac cycles	10 s	10 cardiac cycles	4-8 cardiac cycles	10 s
Method	Simultaneous pulse wave recording at carotid and femoral artery	Simultaneous pulse wave recording at carotid and femoral artery	Sequential ECG-gated pulse wave recording at carotid and femoral artery	Sequential ECG-gated pulse wave recording at carotid and femoral artery	Simultaneous pulse wave recording at finger and toe	5.03 SW version: analysis of reflected wave transit time 6.02 SW version: algorithm primarily based on age and systolic blood pressure.	Algorithm primarily based on age and systolic blood pressure
Transit time assessment	Foot-to-foot method: intersecting tangent algorithm	Foot-to-foot method: intersecting interpolating algorithm	Foot-to-foot method: intersecting interpolating algorithm	Foot-to-foot method: intersecting tangent algorithm	Maximum of the second derivative algorithm	–	–
Sampling rate	1 kHz	1 kHz	1 kHz	128 Hz	1 kHz	100 Hz	100 Hz
Central BP assessment	Direct method from carotid artery	Direct method from carotid artery	Direct method from carotid artery	Transfer function from radial artery	From digital volume pulse by photodiode sensor on the finger	Brachial oscillometric blood pressure cuff-based method	Brachial oscillometric blood pressure cuff-based method
24H monitoring	No	LP software allows up to 24h track recording	LP software allows up to 24h track recording	No	No	Ambulatory blood pressure monitoring (ABPM)	Ambulatory blood pressure monitoring (ABPM)
Weight, g	450	121	88	2800	375	226	240
Other characteristics		Pocket-size wireless system	Pocket-size wireless system			Handheld system	Handheld system

Supplemental Results

Table S3. Anthropometric and Clinical Characteristics of the Enrolled Patients.

Characteristic	Class of Age, years				Pooled
	<55	55-64	65-74	≥75	
Number of patients	22	22	30	28	102
Age, years	46.9 ± 9.5	60.4 ± 2.8	69.2 ± 2.9	79.0 ±	65.2 ± 12.7
Sex, men/women	17 / 5	17 / 5	21 / 9	17 / 11	72 / 30
Height, cm	173 ± 8	171 ± 9	167 ± 8	166 ± 7	169 ± 8
Weight, kg	79 ± 19	78 ± 12	71 ± 14	74 ± 14	75 ± 15
BSA, m ²	1.91 ± 0.23	1.90 ± 0.18	1.79 ± 0.20	1.81 ±	1.85 ± 0.20
BMI, kg/m ²	26.4 ± 6.2	26.7 ± 2.9	25.4 ± 3.3	26.9 ±	26.3 ± 4.3
<i>History</i>					
Smoking, n (%)	6 (27.3)	8 (36.4)	6 (20.0)	3 (10.7)	23 (22.5)
Diabetes, n (%)	1 (4.5)	7 (31.8)	9 (30.0)	9 (32.1)	26 (25.5)
Hypertension, n (%)	9 (40.9)	13 (59.1)	20 (66.7)	25 (89.3)	67 (65.7)
Dyslipidaemia, n (%)	10 (45.5)	8 (36.4)	20 (66.7)	19 (67.9)	57 (55.9)
Thyroid disease, n (%)	2 (9.1)	2 (9.1)	3 (10.0)	3 (10.7)	10 (9.8)
Peripheral artery disease, n (%)	0	4 (18.2)	5 (16.7)	4 (14.3)	13 (12.7)
Cerebrovascular disease, n (%) (%)	0	1 (4.5)	3 (10.0)	3 (10.7)	7 (6.9)
Carotid artery stenosis, n (%) (%)	1 (4.5)	1 (4.5)	3 (10.0)	8 (28.6)	13 (12.7)
Heart valve disease, n (%)	4 (18.2)	1 (4.5)	6 (20.0)	7 (25.0)	18 (17.6)
Arrhythmia, n (%)	1 (4.5)	1 (4.5)	3 (10.0)	3 (10.7)	8 (7.8)
Pacemaker, n (%)	1 (4.5)	0	0	2 (7.1)	3 (2.9)
ICD, n (%)	1 (4.5)	1 (4.5)	0	0	2 (2.0)
Syntax score 1-22, n (%)	4 (18.2)	8 (36.4)	7 (23.3)	13 (46.4)	32 (31.4)
Syntax score 23-32, n (%)	2 (9.1)	0	3 (10.0)	4 (14.3)	9 (8.8)
Syntax score >32, n (%)	0	3 (13.6)	5 (16.7)	1 (3.6)	9 (8.8)
Coronary artery bypass graft, n	1 (4.5)	1 (4.5)	2 (6.7)	2 (7.1)	6 (5.9)
Stenting, n (%)	3 (13.6)	4 (18.2)	5 (16.7)	5 (17.9)	17 (16.7)
<i>Treatment:</i>					
Diuretics, n (%)	4 (18.2)	7 (31.8)	4 (13.3)	12 (42.9)	27 (26.5)
α-lytics, n (%)	1 (4.5)	3 (13.6)	6 (20.0)	5 (17.9)	15 (14.7)
β-blockers, n (%)	13 (59.1)	14 (63.6)	19 (63.3)	15 (53.6)	61 (59.8)
Ca-antagonists, n (%)	1 (4.5)	6 (27.3)	12 (40.0)	10 (35.7)	29 (28.4)
ACEi, n (%)	7 (31.8)	12 (54.5)	18 (60.0)	11 (39.3)	48 (47.1)
ARBs, n (%)	3 (13.6)	4 (18.2)	5 (16.7)	10 (35.7)	22 (21.6)
Lipid lowering, n (%)	11 (50.0)	13 (59.1)	19 (63.3)	17 (60.7)	60 (58.8)

ACEi, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; BMI, body mass index; BSA, body surface area; ICD, implantable cardioverter defibrillator; RAAS, renin-angiotensin-aldosterone system; Syntax Score, angiographic grading tool to determine the complexity of coronary artery disease⁶. Data are expressed as mean ± standard deviation or percentage.

Table S4. Correlation and Mean Differences in Pulse Wave Velocity Values Between Devices.

Device I									
Complior									
N	90								
r	0.64								
p	<0.0001								
$\Delta \pm SD$	-0.73 \pm 2.83								
PulsePen ETT									
N	89	97							
r	0.71	0.83							
p	<0.0001	<0.0001							
$\Delta \pm SD$	0.20 \pm 2.54	-0.86 \pm 1.80							
PulsePen ET									
N	92	100	99						
r	0.78	0.86	0.95						
p	<0.0001	<0.0001	<0.0001						
$\Delta \pm SD$	-0.04 \pm 2.33	-0.68 \pm 1.78	0.21 \pm 0.99						
SphygmoCor									
N	92	100	99	102					
r	0.70	0.83	0.89	0.91					
p	<0.0001	<0.0001	<0.0001	<0.0001					
$\Delta \pm SD$	-0.61 \pm 2.57	-0.09 \pm 1.78	0.75 \pm 1.51	0.60 \pm 1.50					
pOpmètre									
N	54	58	57	58	58				
r	0.41	0.29	0.26	0.28	0.33				
p	0.0021	0.0272	0.0508	0.0333	0.0114				
$\Delta \pm SD$	-0.44 \pm 4.44	-0.08 \pm 4.59	0.85 \pm 4.84	0.46 \pm 4.67	0.05 \pm 4.47				
BPLab (Vasotens 5.03)									
N	91	99	98	101	101	57			
r	0.23	0.29	0.32	0.32	0.30	0.14			
p	0.0283	0.0036	0.0013	0.0011	0.0023	0.2990			
$\Delta \pm SD$	-0.71 \pm 3.55	0.04 \pm 3.42	0.74 \pm 3.57	0.68 \pm 3.73	0.09 \pm 3.14	0.31 \pm 4.37			
BPLab (Vasotens 6.02)									
N	91	99	98	101	101	57	101		
r	0.77	0.54	0.69	0.68	0.72	0.21	0.36		
p	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.1169	0.0002		
$\Delta \pm SD$	1.04 \pm 2.27	-1.72 \pm 2.85	-0.84 \pm 2.42	-1.03 \pm 2.57	-1.62 \pm 2.12	-2.00 \pm 4.49	1.61 \pm 2.74		
Mobil-O-Graph									
N	92	100	99	102	102	58	101	101	
r	0.71	0.46	0.62	0.61	0.64	0.21	0.17	0.94	
p	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.1136	0.0892	<0.0001	
$\Delta \pm SD$	-1.01 \pm 2.54	0.28 \pm 2.94	1.17 \pm 2.59	1.00 \pm 2.77	0.40 \pm 2.23	0.08 \pm 4.69	-0.29 \pm 2.84	2.00 \pm 1.00	
Device II									
\rightarrow	Invasive	Complior	PulsePen ETT	PulsePen ET	SphygmoCor	pOpmètre	BPLab 5.03	BPLab 6.02	

Δ , mean differences, indicates pulse wave velocity (PWV, m/s) measured by Device I (first column) minus PWV measured by Device II (last row); N, number of patients; p, probability value; r, Pearson correlation coefficient; SD, Standard deviation.

Table S5. Correlation and Mean Differences Between the Values of the Inverse of Pulse Wave Velocity (1/PWV) Between Devices.

Device I								
Complior								
N	90							
r	0.57							
p	<0.0001							
Δ±SD	6.1±27.6							
PulsePen ETT								
N	89	97						
r	0.72	0.80						
p	<0.0001	<0.0001						
Δ±SD	-2.8±21.3	8.3±18.7						
PulsePen ET								
N	92	100	99					
r	0.78	0.80	0.95					
p	<0.0001	<0.0001	<0.0001					
Δ±SD	-0.8±19.2	6.6±18.9	-1.9±9.3					
SphygmoCor								
N	92	100	99	102				
r	0.66	0.83	0.89	0.92				
p	<0.0001	<0.0001	<0.0001	<0.0001				
Δ±SD	3.0±23.5	2.3±17.6	-6.0±13.6	-4.3±11.9				
pOpmètre								
N	54	58	57	58	58			
r	0.29	0.22	0.17	0.10	0.18			
p	0.0334	0.0970	0.2061	0.4551	0.1764			
Δ±SD	13.1±44.4	-8.6±45.0	-18.0±44.3	-14.2±46.2	-10.5±44.9			
BPLab (Vasotens 5.03)								
N	91	99	98	101	101	57		
r	0.25	0.36	0.38	0.39	0.37	0.05		
p	0.0168	0.0003	0.0001	<0.0001	0.0001	0.7119		
Δ±SD	0.6±31.3	6.8±30.9	-0.2±28.1	0.7±28.3	5.0±29.2	12.4±43.9		
BPLab (Vasotens 6.02)								
N	91	99	98	101	101	57	101	
r	0.80	0.60	0.74	0.77	0.76	0.09	0.44	
p	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.5055	<0.0001	
Δ±SD	-12.3±18.2	17.3±25.7	9.0±19.5	10.8±18.6	15.1±19.1	27.2±44.1	11.0±24.3	
Mobil-O-Graph								
N	92	100	99	102	102	58	101	101
r	0.76	0.51	0.68	0.71	0.70	0.10	0.26	0.96
p	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.4551	0.0086	<0.0001
Δ±SD	4.9±19.5	-0.1±29.2	-8.7±22.2	-6.7±21.5	-2.4±21.8	9.7±46.6	7.3±30.9	-17.4±8.2
Device II								
→	Invasive	Complior	PulsePen ETT	PulsePen ET	SphygmoCor	pOpmètre	BPLab 5.03	BPLab 6.02

Δ, mean differences, indicates the inverse of pulse wave velocity value (1/PWV, ms/m) measured by Device I (first column) minus 1/PWV measured by Device II (last row); N, number of patients; p, probability value; r, Pearson correlation coefficient; SD, Standard deviation.

Table S6. Heart Rate and Blood Pressure Values Changes During Non-Invasive and Invasive Procedures

Parameters	Non-invasive			Invasive	t-test invasive vs non-invasive average values	
	Set 1	Set 2	Average		Mean difference	p
SBP, mmHg	142 ± 23	142 ± 23	142 ± 22	148 ± 31	5.86	0.008
DBP, mmHg	77 ± 10	76 ± 10	77 ± 9	73 ± 13	-3.92	<0.001
PP, mmHg	65 ± 20	66 ± 21	65 ± 20	75 ± 25	9.77	<0.001
MAP, mmHg	102 ± 13	102 ± 13	102 ± 13	102 ± 19	0.02	0.988
HR, bpm	63 ± 10	63 ± 11	63 ± 10	67 ± 12	4.22	<0.001

Set 1 and Set 2 indicate the first and the second session in which non-invasive tests were performed.

DBP, diastolic blood pressure; HR, heart rate; MAP, mean arterial pressure; PP, pulse pressure; SBP, systolic blood pressure;

Table S7. Multivariate analysis exploring the influence of change in heart rate, systolic and diastolic blood pressure (BP), on the differences in pulse wave velocity during non-invasive and invasive measurements:

Device	Multivariate analysis			
	Parameters	r^2 (model)	β	p
Complior Analyse		0.147		
	Systolic BP		0.282	0.079
	Diastolic BP		0.115	0.479
	Heart rate		-0.144	0.157
PulsePen ETT		0.112		
	Systolic BP		0.275	0.093
	Diastolic BP		0.015	0.926
	Heart rate		0.138	0.182
PulsePen ET		0.254		
	Systolic BP		0.174	0.244
	Diastolic BP		0.361	0.019
	Heart rate		-0.035	0.707
SphygmoCor		0.078		
	Systolic BP		0.296	0.051
	Diastolic BP		0.220	0.152
	Heart rate		0.030	0.749
pOpmètre		0.092		
	Systolic BP		0.443	0.008
	Diastolic BP		-0.283	0.093
	Heart rate		0.121	0.248
BPLab		0.368		
	Systolic BP		0.272	0.117
	Diastolic BP		0.230	0.196
	Heart rate		0.186	0.067
Mobil-O-Graph		0.097		
	Systolic BP		0.305	0.048
	Diastolic BP		0.010	0.950
	Heart rate		-0.006	0.953

Table S8. The Average Running Time of an Exam for Each Device.

Devices	Time (mean \pm SD)
Complior	2m 27s \pm 1m 22s
PulsePen TT	1m 49s \pm 0m 44s
PulsePen ET	2m 56s \pm 1m 10s
SphygmoCor	2m 49s \pm 1m 16s
pOpmètre	13m 54s \pm 10m 54s
BPLab	4m 46s \pm 4m 28s
Mobil-O-Graph	2m 25s \pm 2m 14s

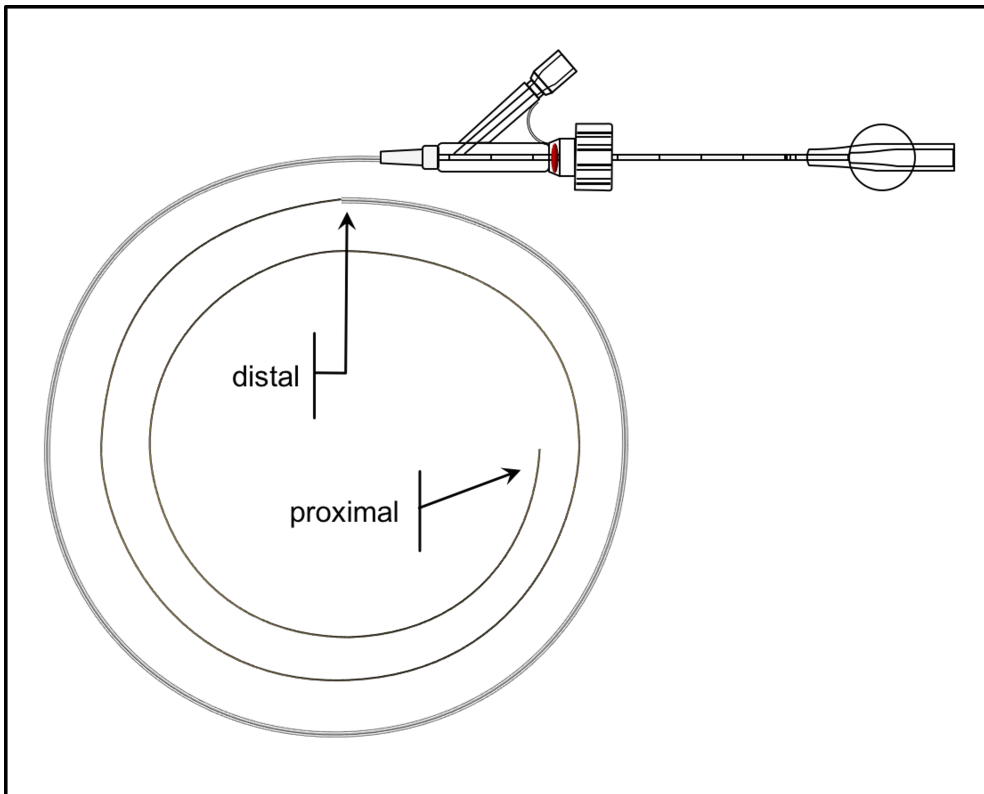


Figure S1. FS-Stiffcath (Flag Vascular, Monza, Italy).

The catheter is made of thermoplastic polymers mixed with a radiopaque additive. It consists of two tubular elements, with a lumen each and coaxially aligned to slide over one another, in order to provide the simultaneous recording of proximal and distal pressure waves. A graduated scale allows direct reading of the distance between the two openings.

Both lumens were connected to an external TruWave pressure transducer (Edwards Lifescience, Irvine, CA, USA; impedance of 300 ohms \pm 5%, pressure sensitivity of 5 μ V/mmHg/V \pm 10%) via a 100-cm long fluid-filled line. This system was characterized by 977 Hz sampling rate. The frequency response of the 8 French catheter system was evaluated in the standard manner by the 'pop test'⁷. The underdamped natural frequency was 45 Hz, with a damping coefficient of 0.46. The system was calibrated against a mercury sphygmomanometer, zeroed and checked for air bubbles before each new examination. Invasive PWV recordings were reviewed during the on-going catheterization by the Mac-Lab IT Hemodynamic Recording System software (GE Healthcare, Chicago, United States) and analyzed off-line by a custom-designed software (SPEGL, Milan, Italy).

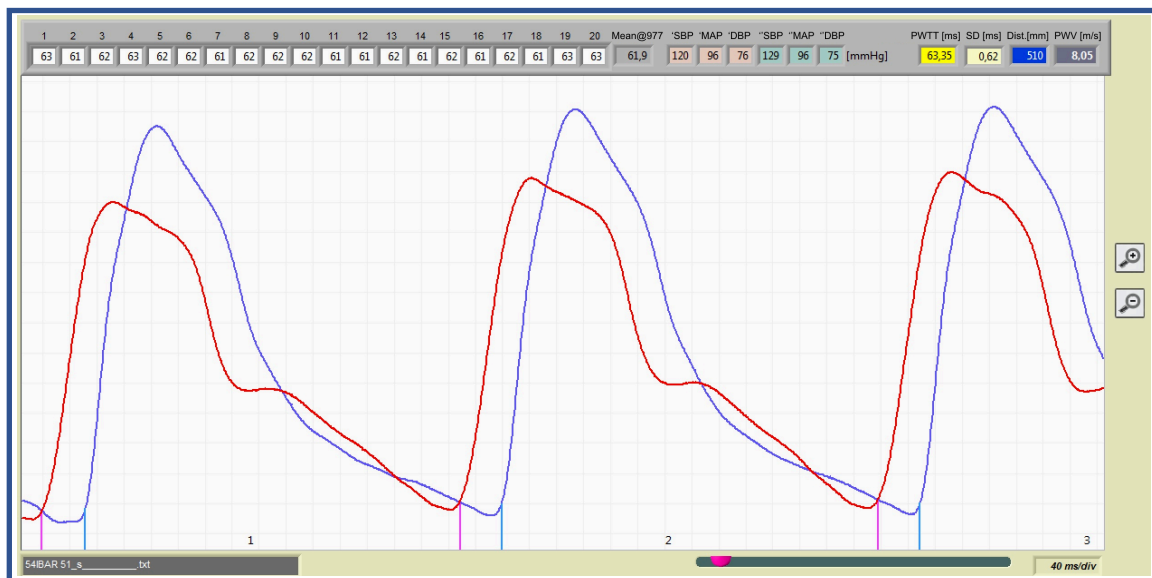
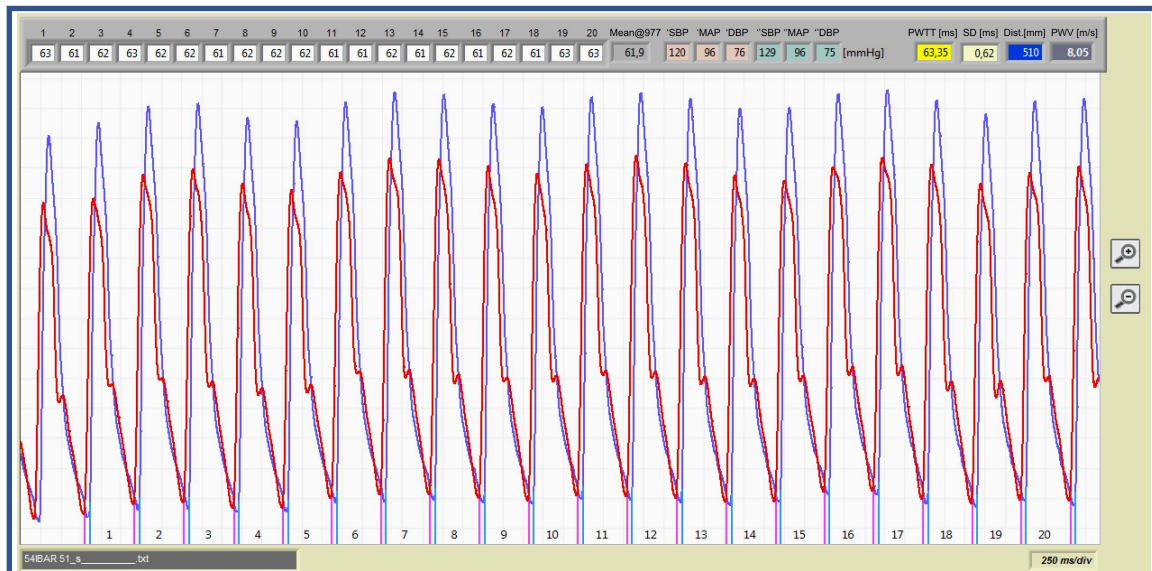


Figure S2. Aortic Invasive Pulse Wave Velocity Analysis (Example).

Pulse wave velocity was calculated by a custom-designed software, using foot-to-foot method and intercept tangent algorithm. Pulse waves were acquired with a 977 Hz sampling rate.

Dist., distance between proximal and distal pressure wave recorder; PWTT, pulse wave transit time; PWV, pulse wave velocity; SD, standard deviation.

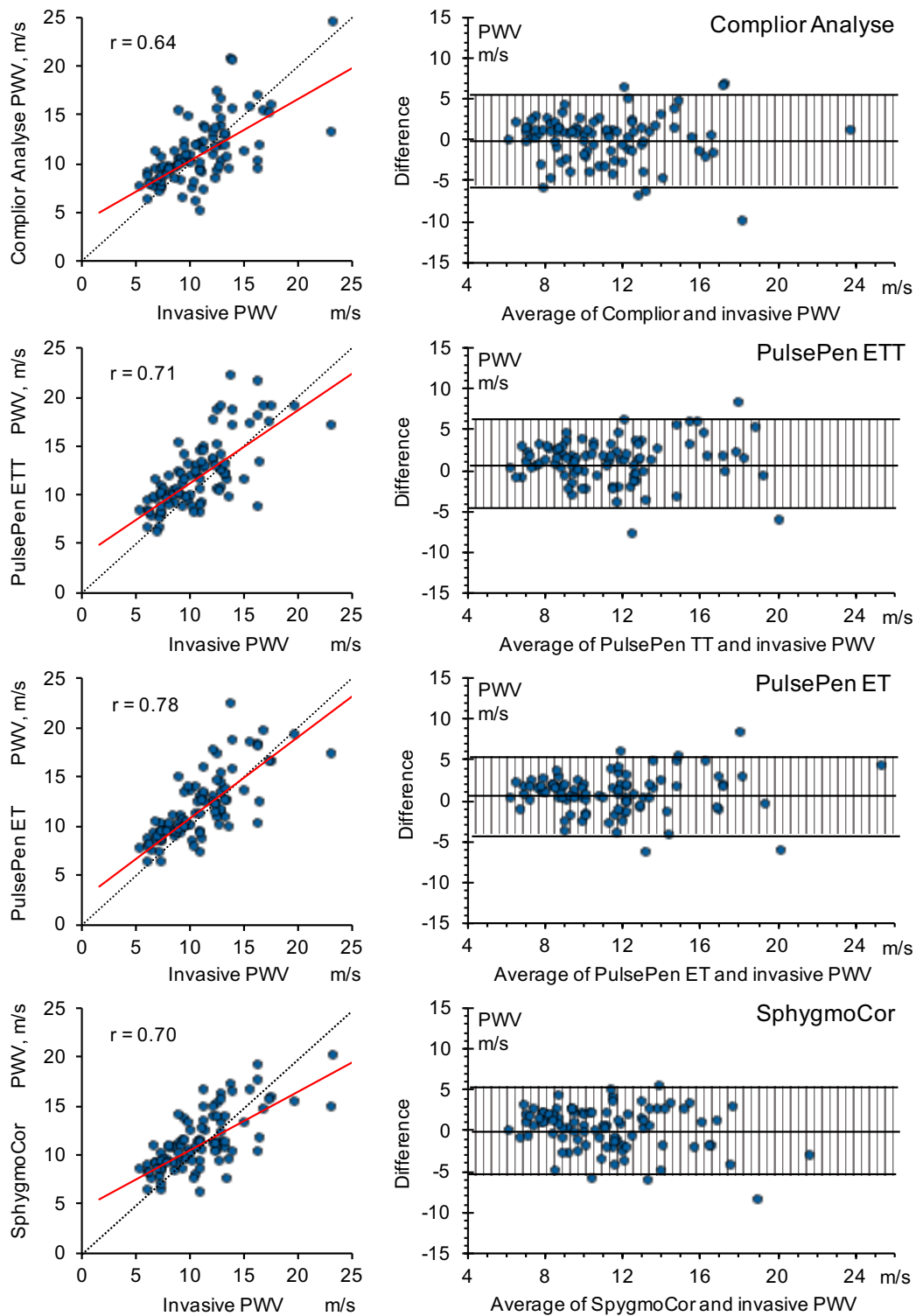


Figure S3. Relationship between carotid-femoral pulse wave velocity using subtracted distance-based method and invasive reference aortic PWV.

On the left, the scatter plots show linear correlation between pulse wave velocity (PWV) values measured by the invasive reference method versus carotid-femoral PWV. A linear regression line (solid line) and the $y = x$ line (dotted line) are also shown in each panel. On the right, Bland-Altman analysis shows differences observed between invasive and non-invasive measurements of PWV according to the average values. The area characterized by vertical lines and delimited by solid lines shows the mean values of differences ± 1.96 standard deviation of pooled data.

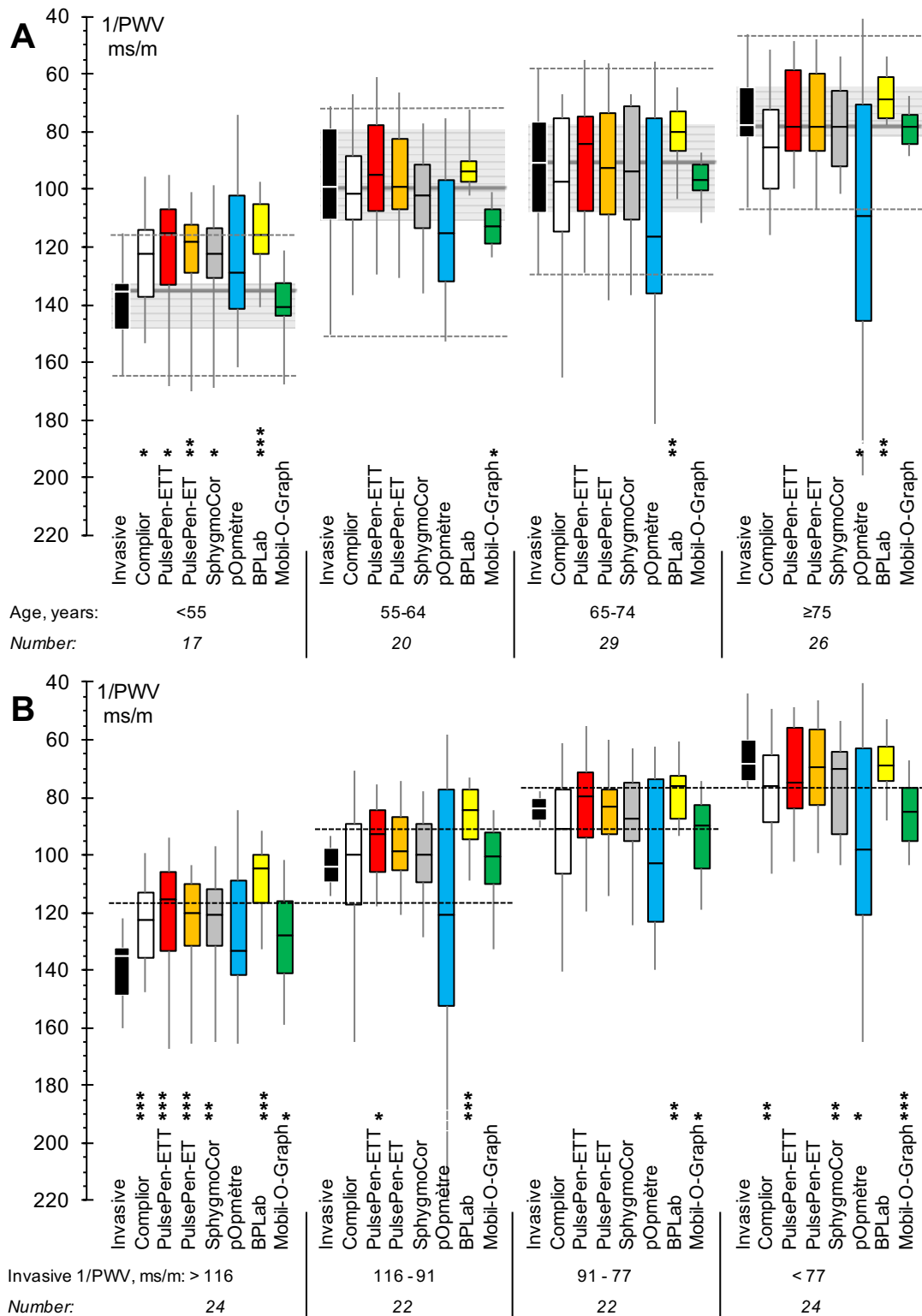


Figure S4. Inverse of pulse wave velocity values (1/PWV, ms/m) measured by invasive and non-invasive methods when stratifying the population by age (upper panel) and pulse wave velocity quartiles (lower panel).

Data are expressed as median (horizontal line), within rectangles showing the interval between the first and third quartiles; vertical lines show the distribution of values (from the minimum to the maximum value). *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$ versus 1/PWV measured by invasive standard method.

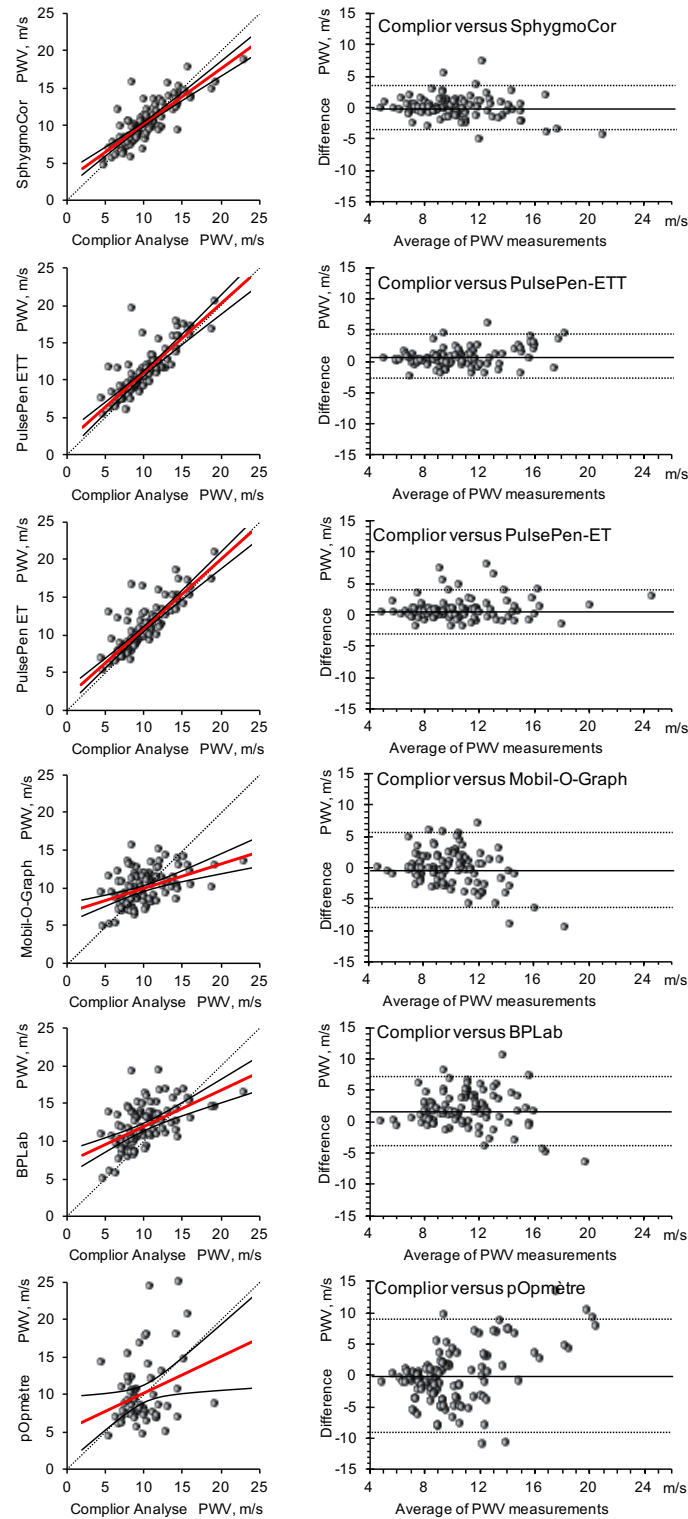


Figure S5. Relationship between pulse wave velocity values acquired by Complior Analyse and the other non-invasive methods.

On the left, the scatter plots show linear correlation between pulse wave velocity (PWV) values measured by the Complior Analyse versus PWV measured by the other non-invasive devices. A linear regression line (solid line) and the $y = x$ line (dotted line) are also shown in each panel. On the right, Bland-Altman analysis shows differences observed between Complior Analyse and other non-invasive measurements of PWV according to the average values. The mean values of differences (solid lines) ± 1.96 standard deviation (dotted lines) are shown.

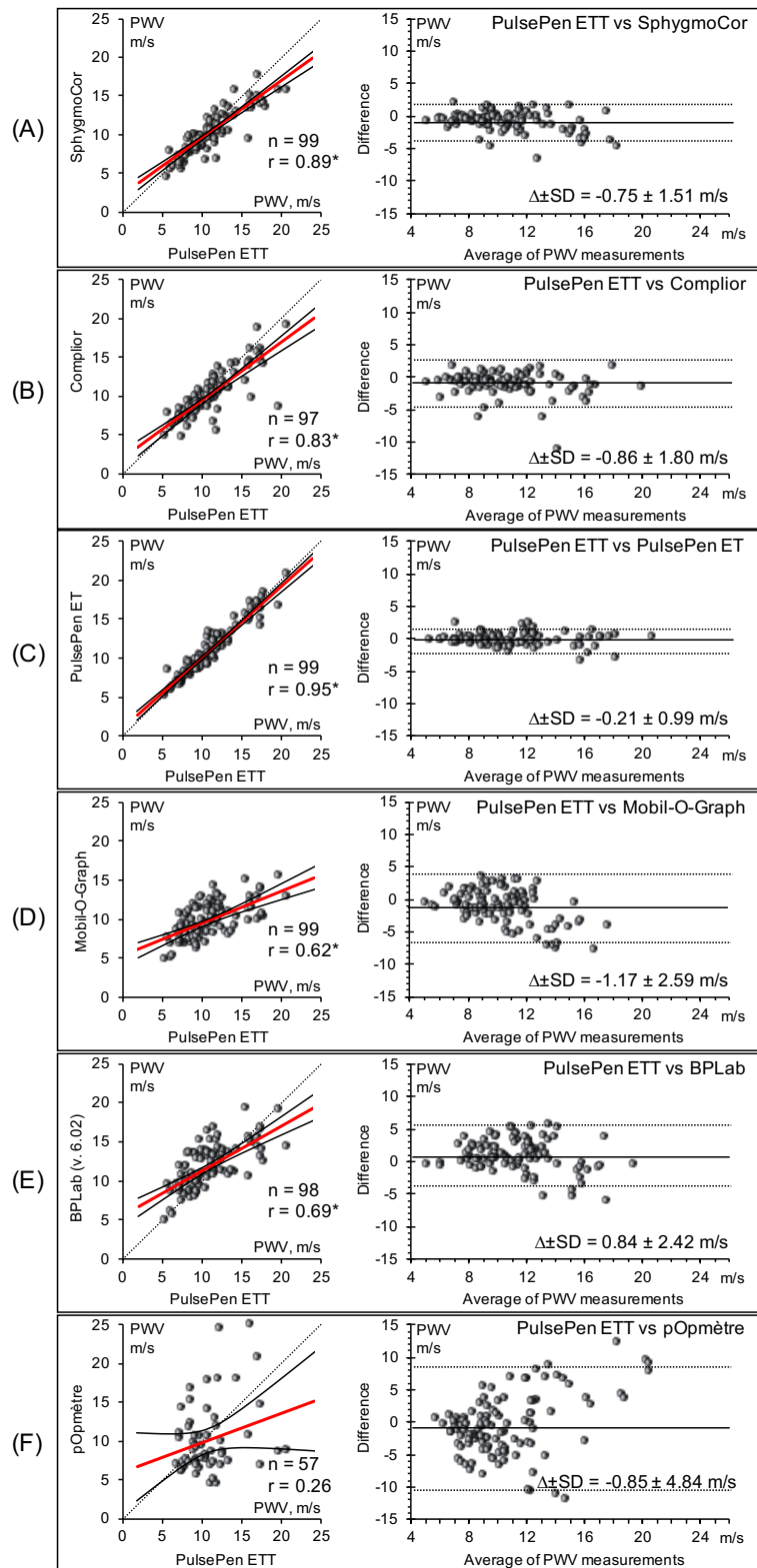


Figure S6. Relationship between pulse wave velocity values acquired by PulsePen-ETT and the other non-invasive methods.

On the left, the scatter plots show linear correlation between pulse wave velocity (PWV) values measured by the PulsePen-ETT versus PWV measured by the other non-invasive devices. A linear regression line (solid line) and the $y = x$ line (dotted line) are also shown in each panel. On the right, Bland-Altman analysis shows differences observed between PulsePen-ETT and other non-invasive measurements of PWV according to the average values. The mean values of differences (solid lines) ± 1.96 standard deviation (dotted lines) are shown.

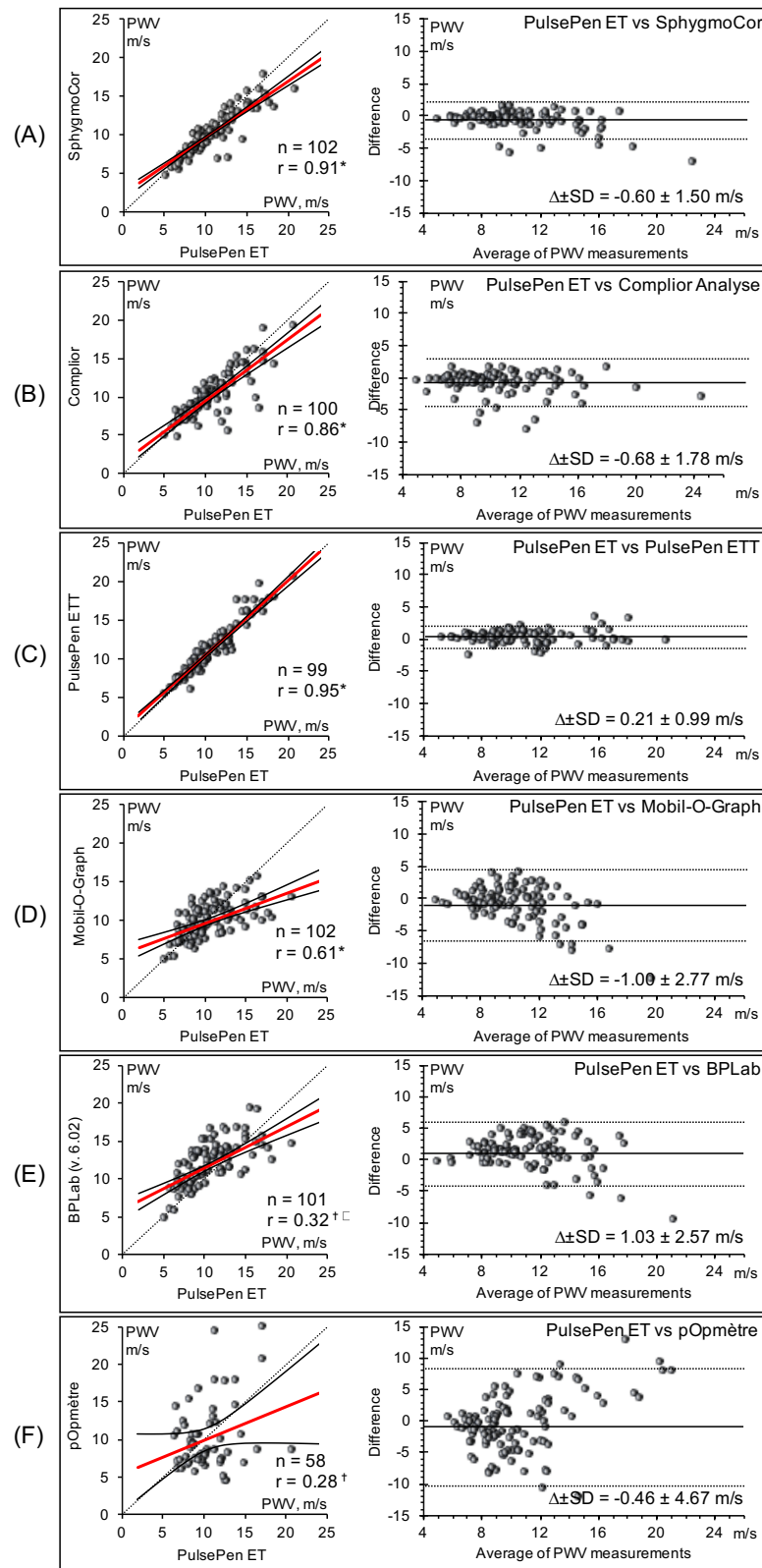


Figure S7. Relationship between pulse wave velocity values acquired by PulsePen-ET and the other non-invasive methods.

On the left, the scatter plots show linear correlation between pulse wave velocity (PWV) values measured by the PulsePen-ET versus PWV measured by the other non-invasive devices. A linear regression line (solid line) and the $y = x$ line (dotted line) are also shown in each panel. On the right, Bland-Altman analysis shows differences observed between PulsePen-ET and other non-invasive measurements of PWV according to the average values. The mean values of differences (solid lines) ± 1.96 standard deviation (dotted lines) are shown.

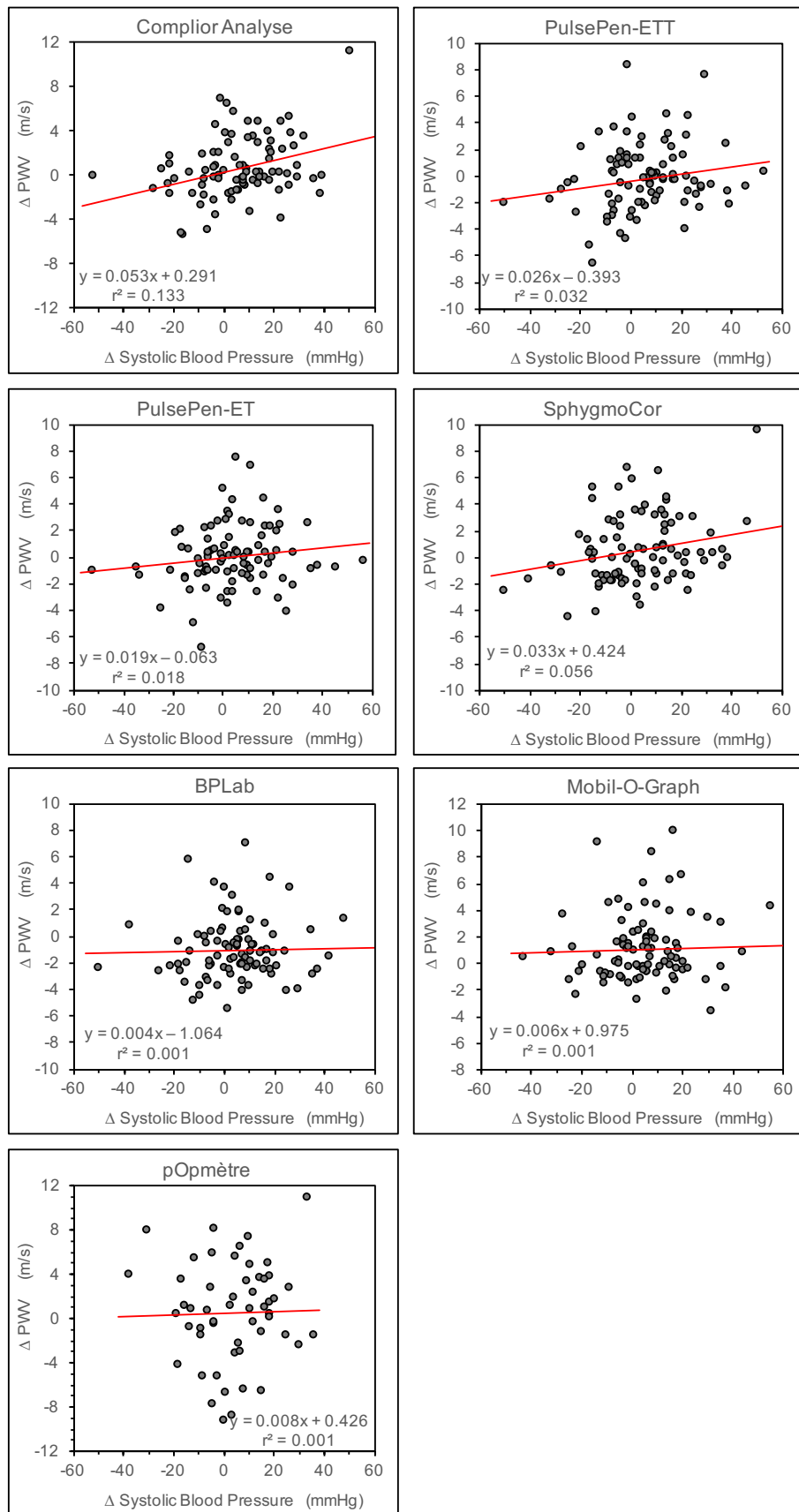


Figure S8. Relationship between changes in systolic blood pressure and differences in pulse wave velocity (PWV) during non-invasive and invasive measurements.

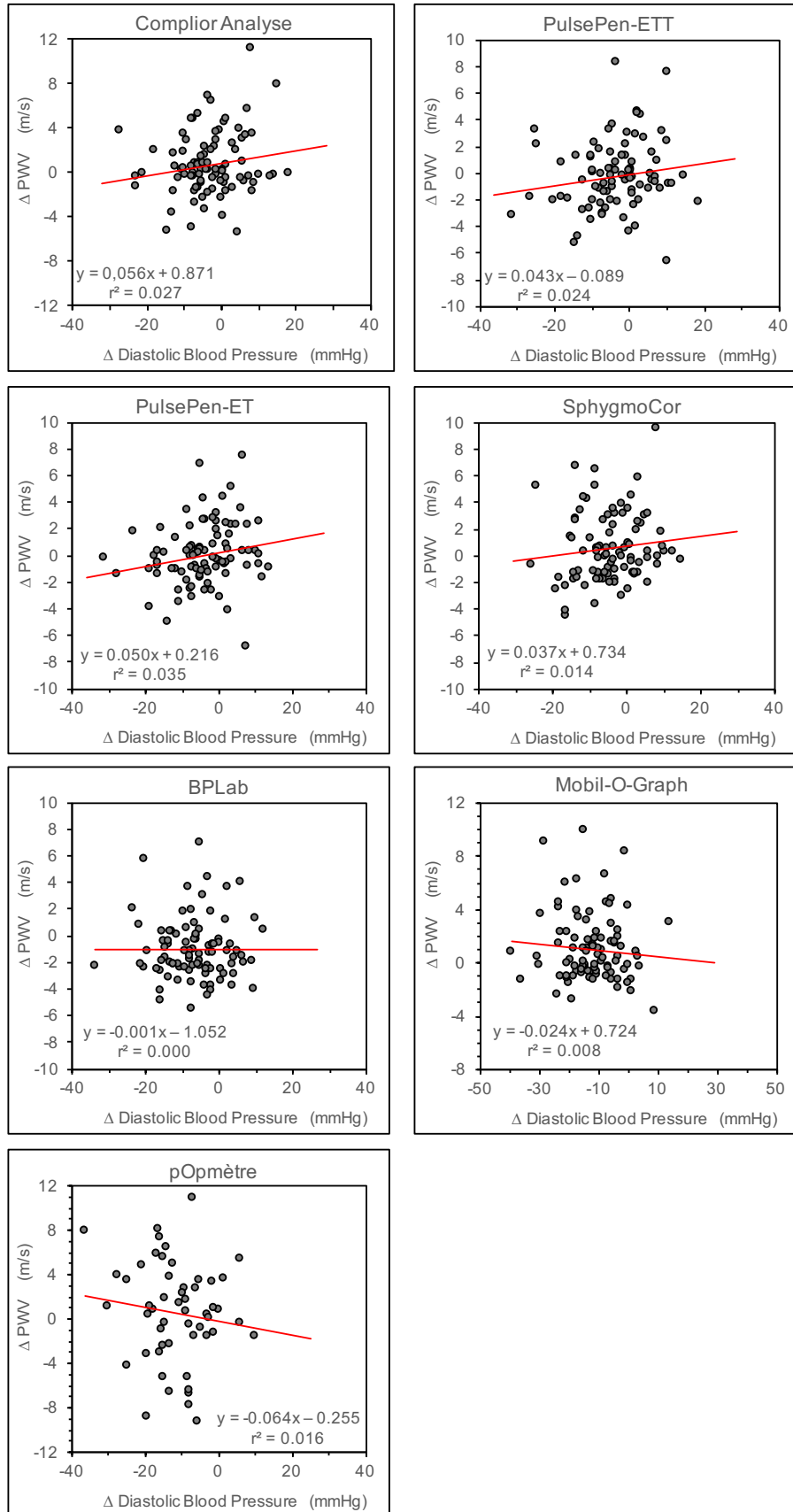


Figure S9. Relationship between changes in diastolic blood pressure and differences in pulse wave velocity (PWV) during non-invasive and invasive measurements.

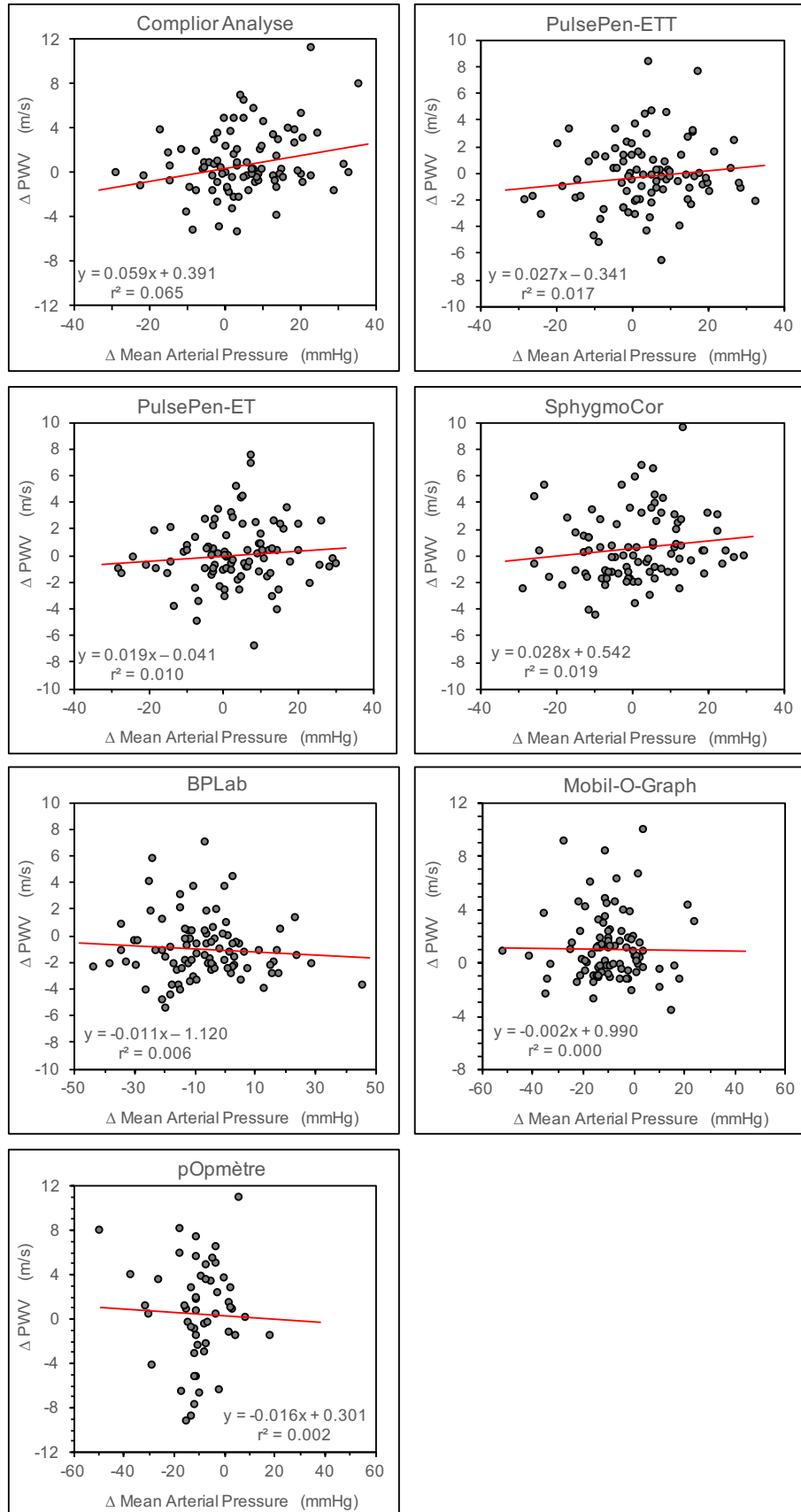


Figure S10. Relationship between changes in mean arterial pressure and differences in pulse wave velocity (PWV) during non-invasive and invasive measurements.

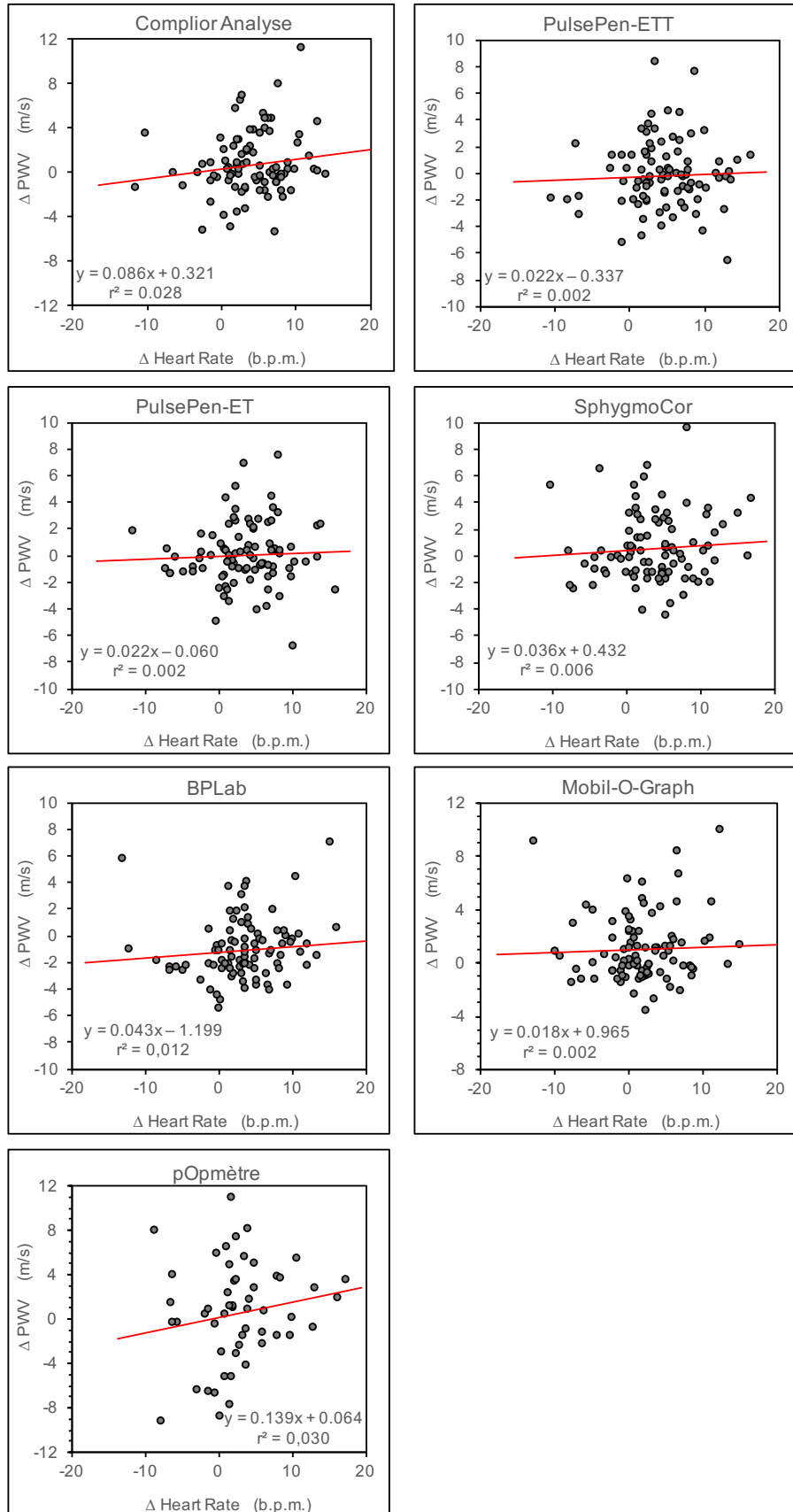


Figure S11. Relationship between changes in heart rate and differences in pulse wave velocity (PWV) during non-invasive and invasive measurements.

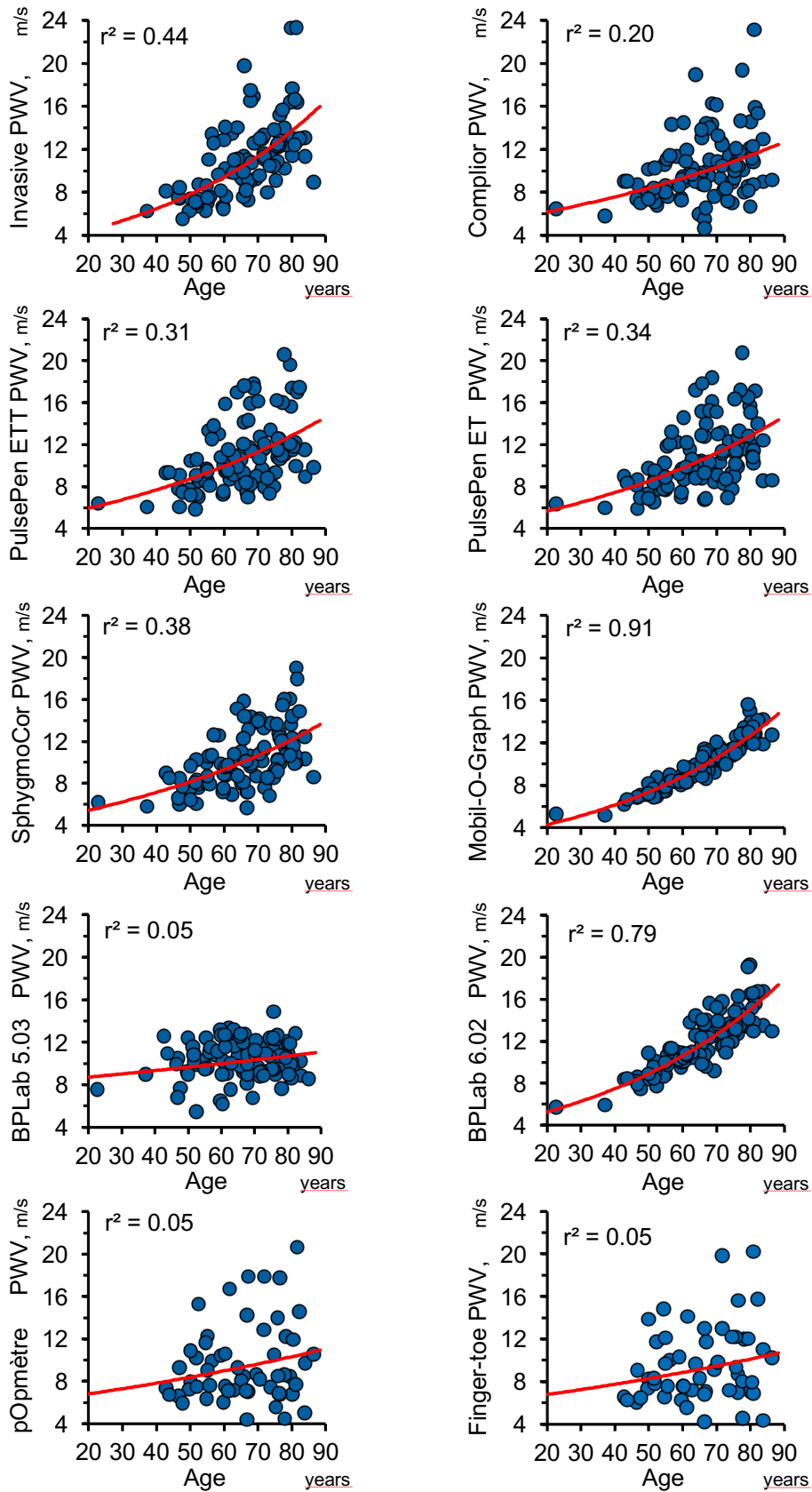


Figure S12. Exponential regression analysis between age and aortic pulse wave velocity (PWV) measured by invasive and non-invasive methods.

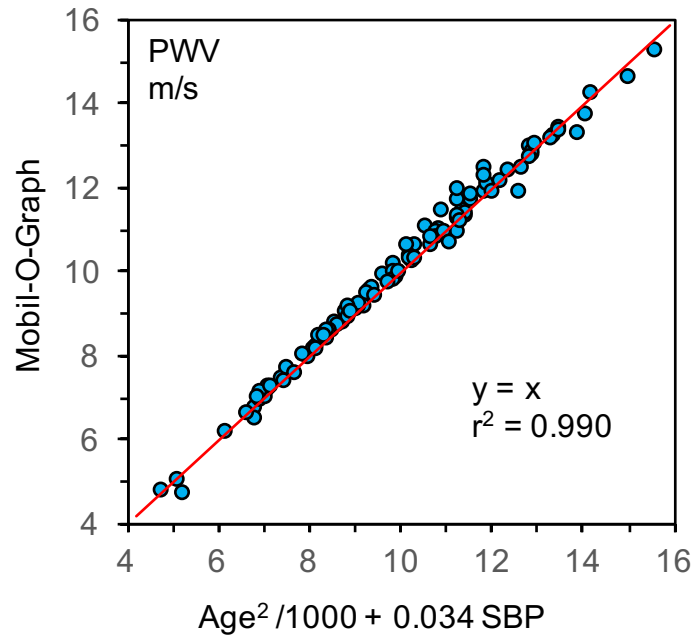
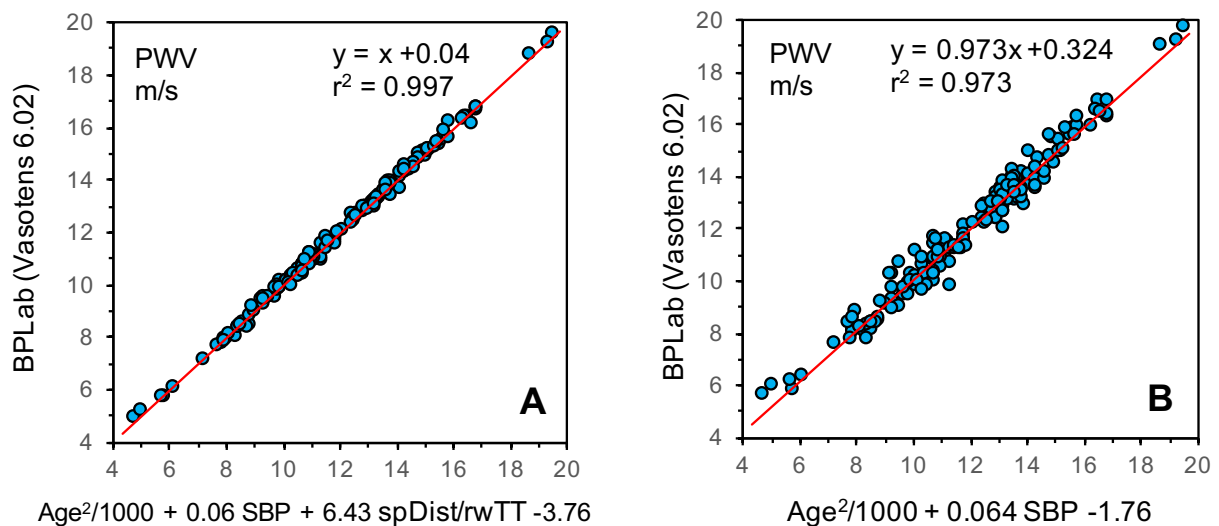


Figure S13. Factors affecting pulse wave velocity (PWV) estimated by Mobil-O-Graph. Pulse wave velocity by Mobil-O-Graph is very strongly dependent ($r^2 = 0.99$) on squared-age (age^2) and brachial systolic blood pressure (SBP).

Figure S14. Factors affecting pulse wave velocity (PWV) estimated by BPLab.

Panel



Panel A: pulse wave velocity (PWV) by BPLab depends ($r^2 > 0.99$) on squared-age (age^2), brachial systolic blood pressure (SBP) and the relationship of the distance between the suprasternal-notch and the pubic symphysis and the delay of the reflected wave (spDist/rwTT). This last parameter plays only a secondary role in the definition of PWV, as demonstrated in Panel B, where only squared-age and brachial systolic blood pressure are considered.

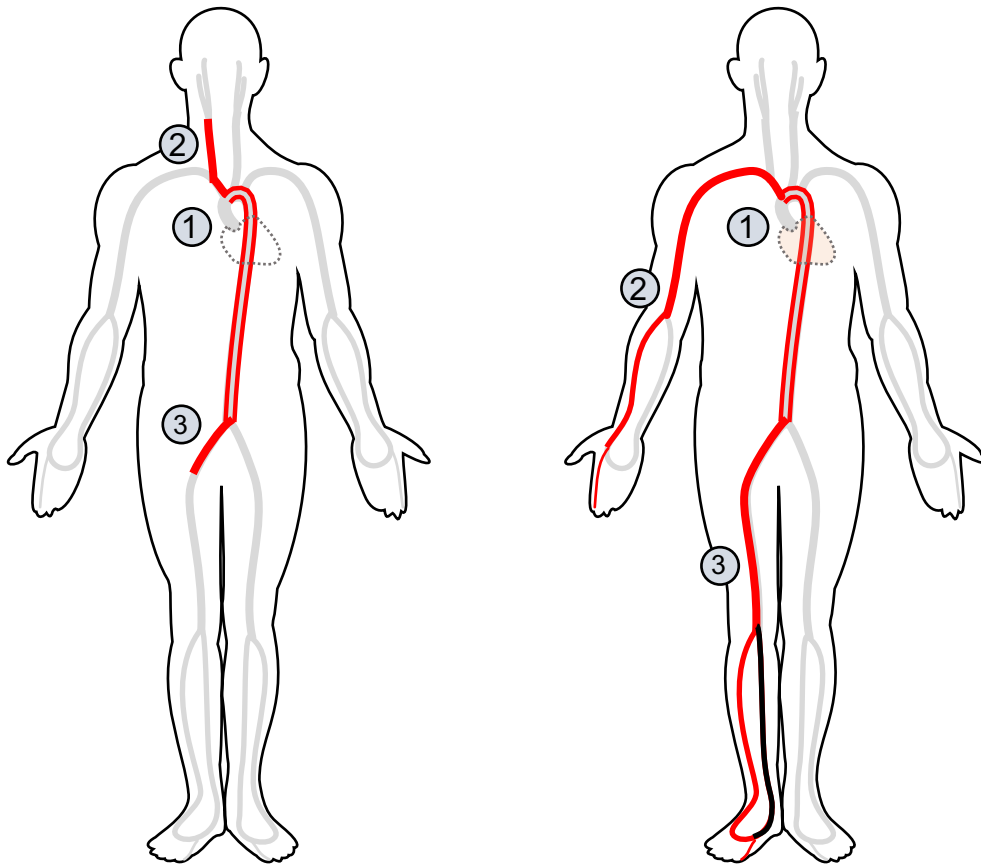


Figure S15. Pressure wave pathway in carotid-femoral (left panel) and finger-toe (right panel) pulse wave velocity assessment.

These methods do not exactly assess aortic distensibility.

In carotid-femoral pulse wave velocity (cf-PWV, by Complior, PulsePen and SphygmoCor):

- (1) the ascending aorta is excluded by cf-PWV measurement;
- (2) the brachiocephalic trunk and the common carotid artery are included in the cf-PWV measurement, even if in this arterial district pulse wave travels in opposite direction and at different speed;
- (3) the iliac arteries and the initial part of femoral arteries are included in the evaluation of cf-PWV.

In finger-toe pulse wave velocity (by pOpmètre):

- (1) the ascending aorta is excluded by finger-toe PWV measurement;
- (2) all the upper limb muscular arteries are included in the finger-toe PWV measurement, even if in this arterial district pulse wave travels in opposite direction and at different speed;
- (3) all the lower limb muscular arteries are included in the evaluation of finger-toe PWV.