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Feasibility of Calculating Aortic Pulse Wave Velocity from Oscillometric Upper Arm Pulse Waves Using the Antares Algorithm

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Abstract

Background: Antares is an algorithm for oscillometric blood pressure (BP) monitors to determine aortic pulse wave velocity (PWV) solely using oscillometric pulse waves without dependence of any other input. The aim of this study is to test Antares PWV for feasibility and whether the known age and blood pressure dependence of PWV can be shown with Antares PWV.

Methods: In total, 259 patients were investigated for PWV as sub-study of the invasive validation of Antares algorithm, of which 219 entered analyses. Non-invasive PWV determination by Antares algorithm, integrated into an oscillometric BP monitor (custo screen 400) was compared to five different ePWV equations based on age, BP, or both. Additionally, in a subset of 27 patients, comparison of ARCSolver PWV algorithm (Mobil-O-Graph) with Antares PWV and ePWV was conducted.

Results: Mean differences \pm SD between Antares PWV and (A) ePWV (based on age and systolic BP) was -0.05 ± 1.06 m/s (Spearman's rank correlation coefficient, $r_s = 0.805$); (B) ePWV (based on age) was -1.75 ± 1.17 m/s ($r_s = 0.829$); (C) ePWV (based on mean BP) was -1.35 ± 1.24 m/s ($r_s = 0.763$), and (D) ePWV (based on age and mean BP) was -1.64 ± 1.22 m/s ($r_s = 0.810$) and -1.69 ± 1.18 m/s ($r_s = 0.802$). Comparison of Antares PWV with ARCSolver PWV revealed a mean difference of -0.65 ± 1.31 m/s ($r_s = 0.854$).

Conclusion: The Antares algorithm confirmed its feasibility to use an oscillometric BP monitor as a single-point measurement device to calculate aortic PWV with acceptable comparability and high correlation to both estimated PWV and ARCSolver PWV. Antares achieves these results solely based on analysis of waveform features without requiring any secondary input, like BP or age.

Keywords: Pulse wave velocity, Pulse wave analysis, Antares PWV, Custo screen 400, ARCSolver, Mobil-O-Graph, Estimated PWV

1 Introduction

Due to increasing evidence that aortic pulse wave velocity (PWV) is a better predictor of cardiovascular events and total mortality than brachial blood pressure, the

need for operator-friendly accurate diagnostic PWV devices is growing [1]. The determination of PWV, which is inversely related to arterial wall distensibility, offers an easy to understand and potentially useful approach for cardiovascular risk stratification [2].

Two types of non-invasive devices to estimate aortic PWV exist. (A) Two-point measurement devices: determination of the difference in travel time of pulse waves

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between two different sensor/probe positions, e.g., SphygmoCor (AtCor, Medical, West Ride, Australia), Complior Analyse (Alam Medical, Vincennes, France), or PulsePen (DiaTecne, San Donato Milanese, Italy). (B) Single-point measurement devices: determination of the time difference between the forward and backward wave considering the wave reflection model on one position, based on pulse wave analysis (PWA) algorithms, e.g., Mobil-O-Graph (IEM, Stolberg, Germany), Vasotens (BPLab, Petr Telegin, Nizhny Novgorod, Russia), and Arteriograph (Tensiomed, Budapest, Hungary). The Mobil-O-graph has an integrated software (ARCSolver, Austrian Institute of Technology, Vienna, Austria) that provides estimations of both central blood pressure and PWV. Several invasive validations of this algorithm have been published [3, 4]. Nevertheless, there are data from an invasive study comparing seven different devices providing PWV in which ARCSolver and Vasotens/BPLab v.6.02 algorithms showed a good correlation ($r > 0.70$) with invasive aortic PWV [5]. Both algorithms provide estimates of PWV seemingly calculated from age and systolic blood pressure (SBP), which were the entirely dependent factors according to a multivariate analysis ($r^2 = 0.99$) [5].

Despite the knowledge of the predictive value of PWV, it is rarely used in clinical practice, which is partly due to shortcomings in the applicability of current two-point measurement devices and partly due to the questioned ability of accurate PWV detection using algorithm-based systems [5, 6].

Based on the fact that arterial aging, measured as PWV, has strong correlations to age and BP [7], several equations for estimation of aortic PWV based solely on age and BP were published. We have chosen five different equations: (1) based on age alone (“Boutouyrie1” [7]), (2) based on mean BP (“Boutouyrie2” [7]), (3) based on age and SBP, the “Salvi” equation [5], and (4) and (5) based on age and mean BP, “Greve1” and “Greve2” equations to be compared to the novel Antares PWV algorithm. The equations “Boutouyrie1” and “Boutouyrie2” were developed in the project “The Reference Values for Arterial Stiffness’ Collaboration” based on data from 16,867 healthy subjects in which PWV was mainly measured with the two-point measurement device SphygmoCor or the Complior device.

Antares (Redwave Medical GmbH, Jena, Germany) is an algorithm to estimate indices of arterial stiffness, like central BP and aortic PWV, which can be integrated into automated blood pressure monitors using the oscillometric method for blood pressure measurement on the upper arm. The special feature of the Antares algorithm is to enable oscillometric BP monitors to act as single-point measurement devices, using only oscillometric

Table 1 Patient characteristics ($n = 219$)

	Data
Gender (female/male)	62/157
Age (years)	64 ± 13 (26–87)
Heart rate (1/min)	76 ± 15 (48–120)
Height (cm)	173 ± 9 (149–195)
Weight (kg)	86 ± 17 (50–129)
BMI (kg/m^2)	29 ± 5 (18–42)

Data are presented as mean \pm standard deviation (min–max)

Table 2 Overview of the age-specific distribution as well as the pulse wave velocities clustered by velocity

	Number	Percentage
Number of patients	219	100.0
Age ≤ 30 years	3	1.4
Age > 30 years ≤ 60 years	78	35.6
Age > 60 years	138	63.0
PWV ≤ 6 m/s	13	5.9
PWV > 6 m/s ≤ 8 m/s	52	23.7
PWV > 8 m/s ≤ 10 m/s	91	41.6
PWV > 10 m/s ≤ 12 m/s	57	26.0
PWV > 12 m/s	6	2.7

pulse waves and no other secondary input data (e.g., age, BP) to provide aortic PWV values.

The aim of this study is to test Antares PWV for feasibility and whether the known age and blood pressure dependence of PWV can be shown with Antares PWV.

2 Materials and Methods

In total, 259 patients undergoing oscillometric determinations of the Antares PWV were included in this study. Nineteen patients were excluded due to large difference between invasive mean arterial pressure (MAP) and oscillometric MAP (more than ± 12 mmHg), eight patients because of severe arrhythmia during the measurements. We also excluded six patients with high or low blood pressure (defined as systolic BP < 90 mmHg or > 210 mmHg, and diastolic BP < 45 mmHg or > 110 mmHg). Another seven patients were excluded due to poor signal quality that could not be analyzed. This resulted in a final sample of 219 patients available for this analysis. All patients who entered this analysis were Caucasians, and 182 of them were within a heart rate range of 60–100/min (83.1%). Table 1 shows the patient characteristics. Table 2 provides an overview of the age-specific distribution as well as the pulse wave velocities clustered by velocity.

Study centers: The measurements were carried out in three German study centers: Bad Oeynhausen, Greifswald, and Bad Berka (for details please see affiliations of the authors). Most patients were included in Bad Berka (102 patients), followed by Bad Oeynhausen (93 patients) and Greifswald (24 patients). The present study is a sub-study of the invasive validation study of the Antares algorithm for calculation of PWV (ongoing) and central BP, of which the invasive validation of central BP calculation with Antares was published in 2019 [8]. In 27 patients, additional measurements with the Mobil-O-Graph (ARCSolver algorithm) were carried out in Bad Oeynhausen. This study was conducted in compliance with the Declaration of Helsinki. Ethics approvals including all experimental protocols were obtained from the local ethics committees. All participants gave informed consent for inclusion before they participated in this study.

Study setting: All measurements were performed following the expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity [9]. All measurements were done in a supine position, with constant temperature and humidity, without excessive ambient noise in the cardiac catheter laboratory. The patient was adapted to the environment and without disturbing influences. Data acquisition was made at a period of undisturbed rest, free from acute hemodynamic interventions, free from acute medication changes, and without talking. No particular medication was given closely before the recordings of the pulse waves.

Single-point aortic PWV measurement: All measurements were performed as described in the invasive validation study for central BP [8]. In all patients, non-invasive BP measurements were performed with the custo screen 400 device (custo med GmbH, Ottobrunn, Germany), with the integrated Antares algorithm to determine aortic PWV on a connected laptop. After placing the cuff at the bare left upper arm, the measurements were performed. When severe arrhythmia occurred during the recording of the pulse waves, a second recording was performed. If the second recording was disturbed by severe arrhythmia again, these recordings were not included in this analysis. After removing unacceptable measurements, each individual measurement could be analyzed without having to discard a single measurement. In a subset of 27 patients (patient characteristics are shown in Table 3) reference measurements using a single-point measurement system were performed with the Mobil-O-Graph device, with the integrated ARCSolver algorithm to calculate aortic PWV on a connected laptop as described elsewhere [10]. In these patients, the measurement was carried out on the same arm using the

Table 3 Patient characteristics of subset with Mobil-O-Graph (ARCSolver algorithm) examinations ($n=27$)

	Data
Gender (female/male)	13/14
Age (years)	51 ± 18 (26–84)
Heart rate (1/min)	78 ± 13 (58–113)
Height (cm)	170 ± 10 (149–190)
Weight (kg)	73 ± 13 (50–112)
BMI (kg/m^2)	25 ± 5 (19–38)

Data are presented as mean \pm standard deviation (min–max)

custo screen 400 device. It was started closely after reference measurement was finished.

The Antares software version 2.0 was applied in the oscillometric device. Again, the underlying principle of obtaining pulse waves remains the same as it was done in the invasive validation study for Antares central BP [8]: “The acquisition of the oscillometric pulse waves took place during the deflation of the cuff. Cuff deflation speed was 4 mmHg/s with a linear deflation via a regulated valve. Redwave Medical is patent holder for pulse wave analysis (PWA) in pulse waves that are recorded during inflation and deflation of a cuff (patent no DE 10 2017 117 337 B4). Generally speaking, it means that the pulse waves generated during a standard oscillometric BP measurement procedure can be taken for PWA with no need for altering the standard BP pump operation.” The recorded pulse waves were analyzed for determining aortic PWV using the Antares algorithm. In order to be independent of potential error of peripheral BP measurements as well as surrogate input values, Antares algorithm uses solely the raw signal of pulse waves during the deflation process provided by the oscillometric device and notably no other data. The integration of Antares in the software of a blood pressure monitor aims to enable a brachial cuff-based BP monitor to be a single-point measurement device with accurate aortic PWV values independently from secondary input data, such as patient age and BP.

As reference of aortic PWV with the use of equations for PWV estimation (ePWV), the calculation of ePWV was performed using the five equations with input from peripheral BP and/or age (Table 4).

All data were saved in a database (Excel 2019, Microsoft Corp., Redmond, WA, USA) and analyzed with IBM SPSS Statistics 22 software (IBM Corp., Armonk, NY, USA). The data are reported as the mean \pm standard deviation. Distribution of data was analyzed with Shapiro–Wilk test. The Antares PWV was normally distributed, whereas the formula-based ePWV procedures did not. Therefore, Spearman’s rank correlation coefficient (r_s)

Table 4 Equations for pulse wave velocity (PWV) estimation with input from peripheral blood pressure (BP) and/or age

Method	Equation
Boutouyrie1 [7]	
BP category	
Optimal	$PWV = 0.000 \cdot \text{age} + 0.83 \cdot 10^{-3} \cdot \text{age}^2 + 5.55$
Normal	$PWV = 0.000 \cdot \text{age} + 0.99 \cdot 10^{-3} \cdot \text{age}^2 + 5.69$
High normal	$PWV = 0.000 \cdot \text{age} + 1.05 \cdot 10^{-3} \cdot \text{age}^2 + 5.91$
Grade I HT	$PWV = 0.000 \cdot \text{age} + 1.18 \cdot 10^{-3} \cdot \text{age}^2 + 6.17$
Grade II/III HT	$PWV = 0.044 \cdot \text{age} + 0.85 \cdot 10^{-3} \cdot \text{age}^2 + 5.73$
Boutouyrie2 [7]	
Age category (years)	
< 30	$PWV = 0.0472 \cdot MBP + 2.20$
30–39	$PWV = 0.0423 \cdot MBP + 2.20$
40–49	$PWV = 0.0646 \cdot MBP + 1.41$
50–59	$PWV = 0.0731 \cdot MBP + 1.35$
60–69	$PWV = 0.0715 \cdot MBP + 3.16$
≥ 70	$PWV = 0.0676 \cdot MBP + 5.46$
Salvi [5]	$PWV = \text{age}^2 / 1.000 + 0.034 \cdot SBP$
Greve1 [11]*	$PWV = 9.5875 - 0.4025 \cdot \text{age} + 4.5602 \cdot 10^{-3} \cdot \text{age}^2 - 2.6208 \cdot 10^{-5} \cdot \text{age}^2 \cdot MBP + 3.1762 \cdot 10^{-3} \cdot \text{age} \cdot MBP - 1.8321 \cdot 10^{-2} \cdot MBP$
Greve2 [11]*	$PWV = 4.60 - 0.13 \cdot \text{age} + 0.0018 \cdot \text{age}^2 + 0.0006 \cdot \text{age} \cdot MBP + 0.0284 \cdot MBP$

MBP mean blood pressure, SBP systolic blood pressure, HT hypertension

*Data are presented in the supplemental file

was used to assess the correlation between ePWV methods and Antares PWV. In addition, scatter plots were created for a graphical overview. Agreement between the different PWV methods was evaluated using Bland–Altman plots with limits of agreement (± 1.96 SD). Significance level was set at $P < 0.05$.

3 Results

The Bland–Altman plots and scatter plots for the Antares PWV to ePWV, that are based on age (Boutouyrie1), mean BP (Boutouyrie2), and on age and systolic BP (Salvi), and the plots for Antares PWV to ARCSolver are shown in Figs. 1, 2, 3 and 4. The plots for the Greve1, 2 formulas (based on age and mean BP) are shown in the supplemental file (Figs. S1, S2). The trend lines illustrate the over- or underestimations for Antares PWV, which are not present in case of Antares PWV to Salvi. Spearman's rank correlation analysis revealed a significant relation between Antares PWV with Boutouyrie1 ($r_s = 0.829$, $P = 0.000$, $n = 219$), Boutouyrie2 ($r_s = 0.763$, $P = 0.000$, $n = 219$), Salvi ($r_s = 0.805$, $P = 0.000$, $n = 219$), Greve1 ($r_s = 0.810$, $P = 0.000$, $n = 219$), Greve2 ($r_s = 0.802$, $P = 0.000$, $n = 219$), and ARCSolver ($r_s = 0.854$, $P = 0.000$, $n = 27$). Analysis of age groups and BP categories [12] showed an age- and BP-dependent pattern of increase in Antares PWV in patients, with the lowest PWV at optimal or normal BP and the youngest age category (Fig. 5).

4 Discussion

The main result is that Antares PWV, integrated into a regular upper arm oscillometric BP monitor, presented a high correlation and acceptable comparability to age- and BP-dependent equations for estimation of aortic PWV as well as ARCSolver PWV algorithm. Moreover, the present study reports the first results of Antares PWV, raising the hypothesis that Antares is able to recapitulate the derived age and BP pattern with a single-point measurement device previously observed with two-point measurement devices without imputation of age and BP.

The five ePWVs ranged between 4.7 and 15.5 m/s (mean: 10.3 ± 2.1 m/s) and the Antares algorithm between 4.3 and 13.7 m/s (mean: 9.0 ± 1.7 m/s). Therefore, the measurements covered the relevant diagnostic range of PWV. For Antares PWV, we found a correlation of $r_s > 0.76$ with equations based on BP, and $r_s > 0.80$ for equations based on age. Based on the mean differences found, the agreement with ePWV was highest for the “Salvi” formula and lowest for “Boutouyrie1.” Salvi et al. compared the PWV calculation by Mobil-O-Graph (ARCSolver algorithm) and BPLab (v.5.03 and v.6.02) with a non-invasive two-point device SphygomoCor (carotid-femoral PWV) and the invasive PWV. They found that the ePWV was highly correlated with invasive PWV and carotid-femoral PWV (both, $r > 0.70$) but showed a negative proportional bias at Bland–Altman

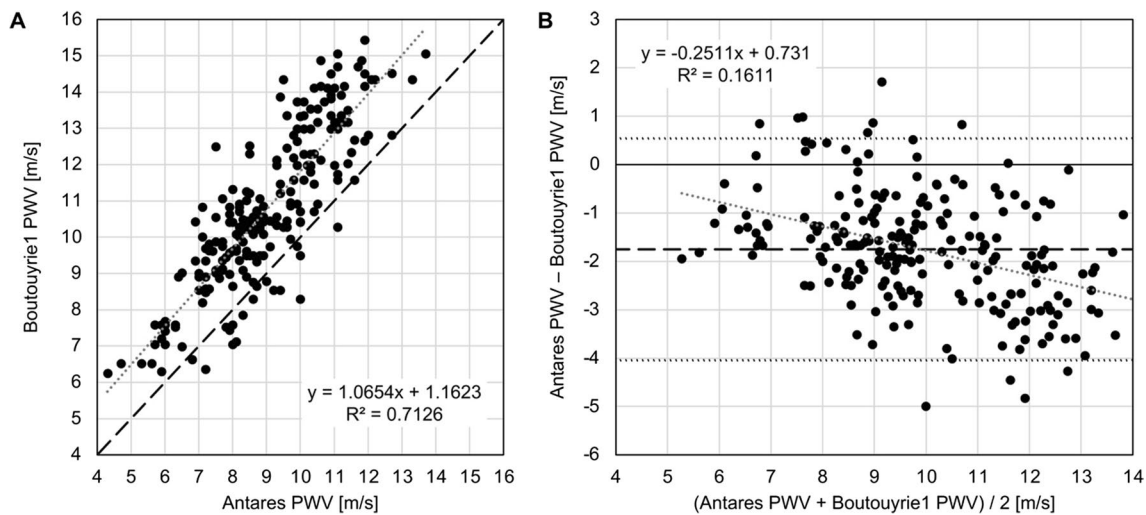


Fig. 1 Relationship between pulse wave velocity (PWV) values ($n = 219$) acquired by Antares algorithm (Antares PWV) and estimated pulse wave velocity (ePWV), based on age (Boutouyrie1). **A** Scatter plot for Antares PWV and ePWV (Boutouyrie1). Gray dotted line: linear regression line. Black dashed line: identity line. R^2 , coefficient of determination. **B** Bland–Altman plot for Antares PWV and ePWV (Boutouyrie1) with the representation of mean difference (black dashed line) and limits of agreement (black dotted line), from ± 1.96 SD. Mean difference \pm SD: -1.75 ± 1.17 m/s. Gray dotted line: linear regression line

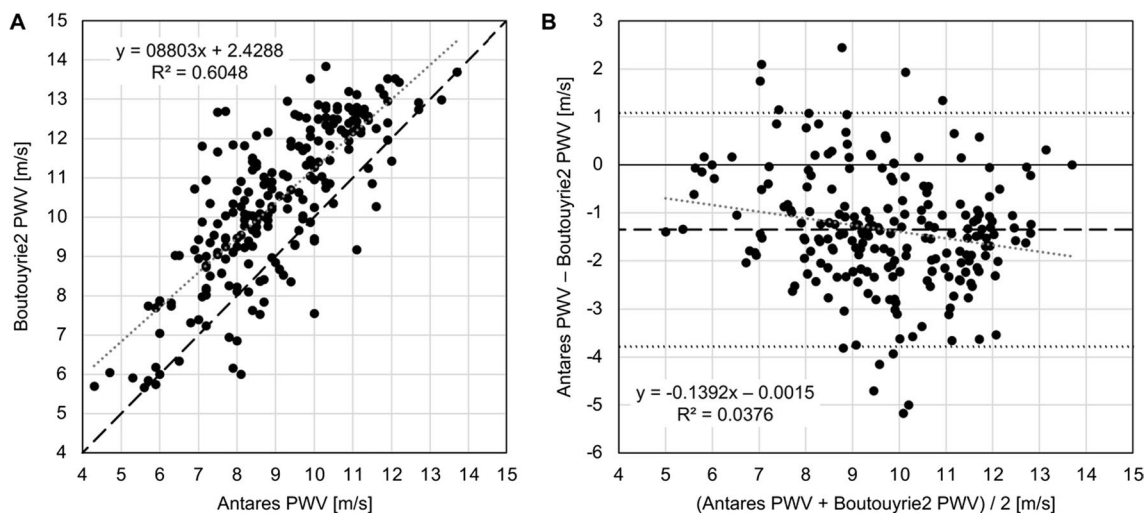


Fig. 2 Relationship between pulse wave velocity (PWV) values ($n = 219$) acquired by Antares algorithm (Antares PWV) and estimated pulse wave velocity (ePWV), based on mean blood pressure (MBP, Boutouyrie2). **A** Scatter plot for Antares PWV and ePWV (Boutouyrie2). Gray dotted line: linear regression line. Black dashed line: identity line. R^2 , coefficient of determination. **B** Bland–Altman plot for Antares PWV and ePWV (Boutouyrie2) with the representation of mean difference (black dashed line) and limits of agreement (black dotted line), from ± 1.96 SD. Mean difference \pm SD: -1.35 ± 1.24 m/s. Gray dotted line: linear regression line

plot. Some proportional bias could also be observed in our data when comparing Antares PWV with ePWVs (Table 4) and ARCSolver PWV, with “Boutouyrie1” and ARCSolver PWV being the most pronounced (Figs. 1,4). The Mobil-O-Graph was chosen as a reference single-point measurement device because of its existing invasive validations [5, 6] and use in several studies.

Aortic PWV provided by currently available ePWV equations or cuff-based single-point measurement devices BPLab and Mobil-O-Graph with their proprietary algorithms are significantly dependent on age and BP. However, as these estimates of aortic PWV are derived mainly from two classic risk factors (age and SBP), these approaches may provide less additional

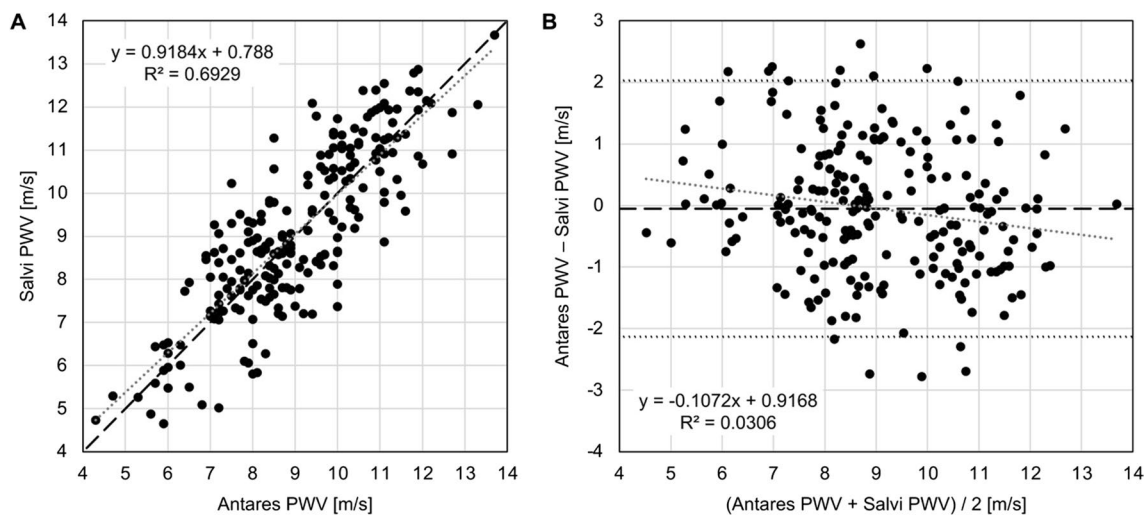


Fig. 3 Relationship between pulse wave velocity (PWV) values ($n = 219$) acquired by Antares algorithm (Antares PWV) and estimated pulse wave velocity (ePWV), based on age and systolic blood pressure (Salvi). **A** Scatter plot for Antares PWV and ePWV (Salvi). Gray dotted line: linear regression line. Black dashed line: identity line. R^2 , coefficient of determination. **B** Bland–Altman plot for Antares PWV and ePWV (Salvi) with the representation of mean difference (black dashed line) and limits of agreement (black dotted line), from ± 1.96 SD. Mean difference \pm SD: -0.05 ± 1.06 m/s. Gray dotted line: linear regression line

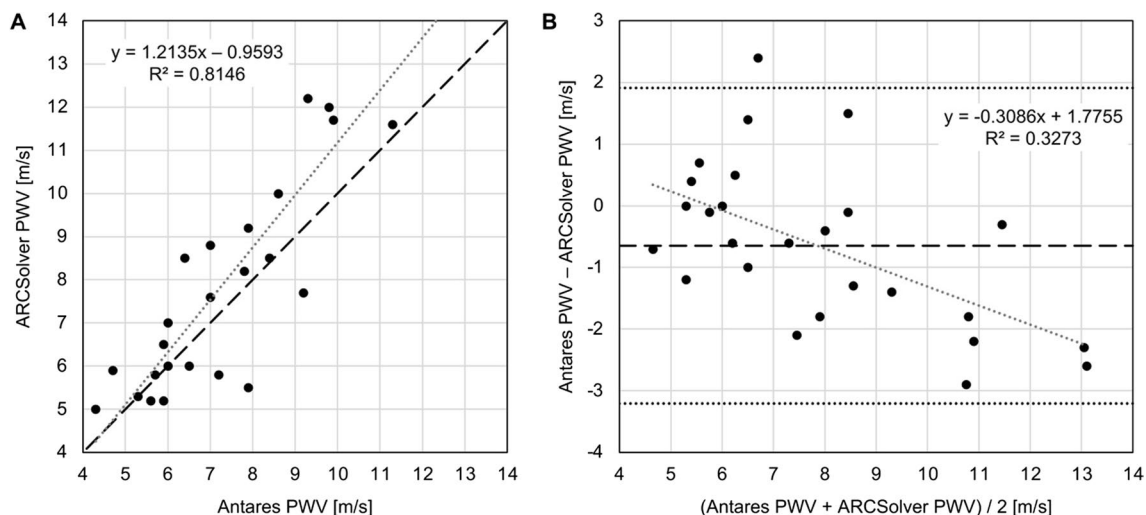
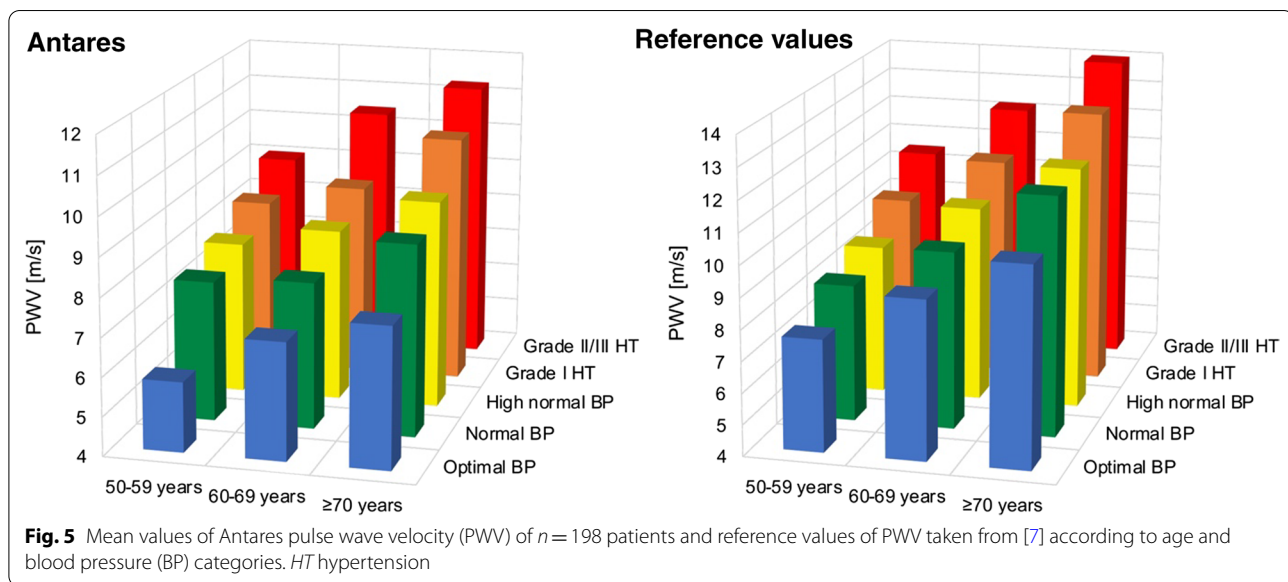


Fig. 4 Relationship between pulse wave velocity (PWV) values ($n = 27$) acquired by Antares algorithm (Antares PWV) and PWV based on ARCSolver algorithm (Mobil-O-Graph). **A** Scatter plot for Antares PWV and ARCSolver PWV. Gray dotted line: linear regression line. Black dashed line: identity line. R^2 , coefficient of determination. **B** Bland–Altman plot for Antares PWV and ARCSolver with the representation of mean difference (black dashed line) and limits of agreement (black dotted line), from ± 1.96 SD. Mean difference \pm SD: -0.65 ± 1.31 m/s. Gray dotted line: linear regression line

prognostic information and limit the assessment of arterial stiffness, as the estimates of PWV may not faithfully reflect factors beyond age and BP [5].

Currently, an increase in aortic PWV derived by invasive or non-invasive two-point measurement is considered an independent predictor of coronary heart disease and stroke, in addition to the traditional risk factors. The key strength of PWV might be lost

if algorithms or equations for PWV estimation are based on surrogate input, such as age and BP, instead of independently assessing the vascular function. Furthermore, because of intrinsic properties, BP-based PWV algorithms may induce misleading results when investigating PWV changes in specific conditions characterized by BP changes (e.g., pharmacological treatment, physical activity) [5]. Based on our data, it can be



hypothesized that the Antares PWV algorithm, which relies solely on brachial cuff-based waveform features, has the potential to assess a wider range of individually available vascular function manifestations independent of surrogate input data.

Two-point devices, like SphygmoCor, Complior, or PulsePen, follow the principle of pulse wave travel distance divided by time with strongly convincing results in terms of prognostic value of PWV, and therefore, carotid-femoral PWV was called non-invasive gold standard for measurement of PWV [1]. In view of the age- and BP-dependent pattern of PWV determined with 2-point measurement devices in healthy people within a large multicenter PWV reference value study [7], the Antares algorithm was able to display this pattern in patients undergoing cardiac catheterization (Fig. 5), but exclusively on the basis of the waveform characteristics of an oscillometric BP measurement with a 1-point measurement system.

A major disadvantage of two-point measurement devices is that the measurement procedures are more complex than with single-point devices, which impedes their use in the clinical application field. Based on the scientific criticism of algorithm-based systems (Mobil-O-Graph and BPLab) that mainly use SBP and age to calculate PWV and the associated limitation for use in clinical or epidemiological studies [5, 6], the novel Antares algorithm could overcome this potential limitation due to its independence from surrogate parameters. However, the Antares PWV algorithm has yet to be validated invasively and tested for its ability to combine a single-point device with additional high prognostic value.

4.1 Limitations

This study is a cross-sectional study in a patient population designed to assess the feasibility of the novel Antares PWV algorithm in a 1-point measurement device by comparing it with different ePWV equations and the ARCSolver algorithm. Therefore, this study does not claim to be a validation study. However, validation of the Antares PWV algorithm is required and subject of ongoing efforts.

The circumstance that the underlying measurements for determining the PWV were carried out on patients during a clinically indicated cardiac catheterization led to the fact that, due to the generally rare indication in younger patients, only three patients with an age of less than 30 years could be included in this study. However, 78 patients (35.6%) were between 30 and 60 years old and 138 patients (63%) were older than 60 years. Thus, we were able to cover a clinically relevant range for PWV diagnosis above the age of 30 years.

Due to the small sample sizes in the different age and BP categories of patients under 50 years, only the averaged Antares PWV data for patients over 50 years could be used to show an age- and BP-dependent pattern of PWV (Fig. 5). Future studies with substantially larger sample sizes are needed to confirm the data as well as to map additional age ranges.

Another limitation is the small number of female study participants, who made up only 28.3% of the study population.

For the comparison of the Antares PWV with the Mobil-O-Graph (ARCSolver algorithm), only a small number of patients ($n = 27$) could be evaluated.

Therefore, this comparison should only be considered as hypothesis generating.

5 Conclusion

This study demonstrates the feasibility of the Antares algorithm to use an oscillometric BP monitor as a single-point measurement device for the calculation of aortic PWV with acceptable comparability and high correlation to both estimated PWV and ARCSolver PWV. Thereby, Antares achieved comparable results based solely on the analysis of pulse wave characteristics without requiring secondary input data, such as BP or age.

By integrating the Antares PWV into commercially available BP monitors, PWV could be measured in every physician's office in the future, allowing broader application of aortic PWV measurement in clinical practice.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1007/s44200-021-00009-3>.

Below is the link to the electronic supplementary material. Supplementary file1 (DOCX 417 kb)

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Author Contributions

JB and AS performed data management and analysis, manuscript writing and editing; MD, EG, M-AO, SR, and SE performed data collection and data management; SE helped in manuscript editing; SE and MD provided editorial assistance and scientific oversight for the manuscript. All the authors have read and approved the final manuscript.

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Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest

J.B. has interest in Redwave Medical GmbH, and has received equipment and lecture fees from IEM GmbH, BPLab, SMT medical GmbH & Co., SOT Medical Systems and Tensiomed. M.D. has received equipment for research projects from custo med and funding for research projects from Redwave Medical GmbH. S.R. has received equipment for research projects from custo med and funding for research projects from Redwave Medical GmbH. A.S. has part-time obligations in Redwave Medical GmbH. E.G., M.-A.O., and S.E. have no conflict of interest to state. Redwave Medical GmbH had no role in the design, execution, or interpretation of the study. Redwave Medical GmbH provided information about the algorithm requested by the authors.

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