Kidney Blood Pressure Research

Kidney Blood Press Res 2020;45:576–588
DOI: 10.1159/000506741
Received: May 15, 2019
Accepted: February 19, 2020
Published online: June 23, 2020

Research Article

Pulse Wave Analysis and Pulse Wave Velocity for Fistula Assessment

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Keywords
Arterial stiffness · Arteriovenous fistula · Dialysis · Duplex sonography · Haemodynamics and vascular regulation · Pulse wave analysis · Pulse wave velocity

Abstract
Background/Aims: Pulse wave analysis (PWA) and pulse wave velocity (PWV) provide information about arterial stiffness and elasticity, which is mainly used for cardiovascular risk stratification. In the presented prospective observational pilot study, we examined the hypothesis that radiocephalic fistula (RCF)-related changes of haemodynamics and blood vessel morphology including high as well as low flow can be seen in specific changes of pulse wave (PW) morphology. ***Methods:*** Fifty-six patients with RCF underwent local ambilateral peripheral PWA and PWV measurement with the SphygmoCor® device. Given that the output parameters of the SphygmoCor® are not relevant for the study objectives, we defined new suitable parameters for PWA in direct proximity to fistulas and established an appropriate analysing algorithm. Duplex sonography served as reference method. ***Results:*** Marked changes of peripheral PW morphology when considering interarm differences of slope and areas between the fistula and non-fistula arms were observed in the Arteria radialis, A. brachialis and arterialized Vena cephalica. The sum of the slope differences was found to correlate with an increased flow, while in patients with fistula failure no changes in PW morphology were seen. Moreover, PWV was significantly reduced in the fistula arm. ***Conclusion:*** Beside duplex sonography, ambilateral peripheral PWA and PWV measurements are potential new clinical applications to characterize and monitor RCF function, especially in terms of high and low flow.

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Introduction

Pulse wave analysis (PWA) and pulse wave velocity (PWV) measurements are useful clinical tools and provide comprehensive information about arterial stiffness [1–4]. Especially, the measurement of the central PWV is suggested by international guidelines in order to stratify the cardiovascular risk of individual patients with arterial hypertension [5–8] and to modify the risk estimation of patients with dyslipidaemias and moderate cardiovascular risk [9]. PWA applied at peripheral sites such as the Arteria radialis or Arteria brachialis is mainly used to estimate the shape of the central pulse wave (PW), i.e., the PW in the ascending aorta [10, 11]. To conduct the PWA, various types of non-invasive measurement devices have been developed and introduced into clinical practice [12, 13]. The assessment of the central PW focusses on the augmentation, i.e., the superposition of the antegrade PW being generated by the ventricular ejection and retrograde PWs being generated by the reflection of the antegrade PW at peripheral sites [14–16].

The placement of an arteriovenous fistula (AVF) in upper extremities as access for haemodialysis results in profound local haemodynamic changes [17]. A mature and well-working native AVF goes along with an increased volume load and altered pressure conditions in the peripheral blood vessels in the fistula arm [17–19]. Furthermore, these profound haemodynamic changes are always accompanied by structural remodelling of local arteries and veins in the fistula arm [17–19]. As an AVF might fail to mature or may malfunction in the long run (i.e., developing inadequately high or low flow), monitoring its function is of vital clinical interest and any technique that can be used in this context to improve fistula outcome in haemodialysis patients is of vital importance [20, 21]. At present duplex sonography is the monitoring method of choice. As peripheral PWA and PWV measurements in proximity to an AVF are most likely to provide useful information about the profound changes of haemodynamics and blood vessel morphology in the fistula arm [17–19], the aim of this clinical pilot study was to examine whether peripheral PWA and PWV measurements also have the potential to characterize and monitor AVF function.

Materials and Methods

Study Enrolment and Protocol

This prospective observational clinical pilot study included 56 haemodynamically stable patients with native radiocephalic fistula (RCF) at the forearm and without any vascular interventions on the opposite side (contralateral forearm). Patients underwent non-invasive local ambilateral peripheral PWA and ambilateral PWV assessments with the SphygmoCor® device (version 8.2) using applanation tonometry. Measuring points were located at the A. brachialis and at the A. radialis of both arms, at the fistula arm also, approximately at 1 cm proximal to the anastomosis in the arterialized Vena cephalica. For reference purposes, ambilateral duplex sonographic measurements in the A. brachialis were performed. An illustration of the measuring points and further details are provided in the online supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000506741) and in Figure 1.

The study was approved by the local ethics committee (Ethik-Kommission der Ärztekammer Westfalen-Lippe und der Medizinischen Fakultät der Westfälischen Wilhelms-Universität Münster, No. 2014-360-f-S).

Evaluation Algorithm and Analysed Parameters

So far, peripheral PWA and PWV measurements have not been used in areas close to an AVF. Given the haemodynamic differences between the AVF arm and the contralateral arm, it

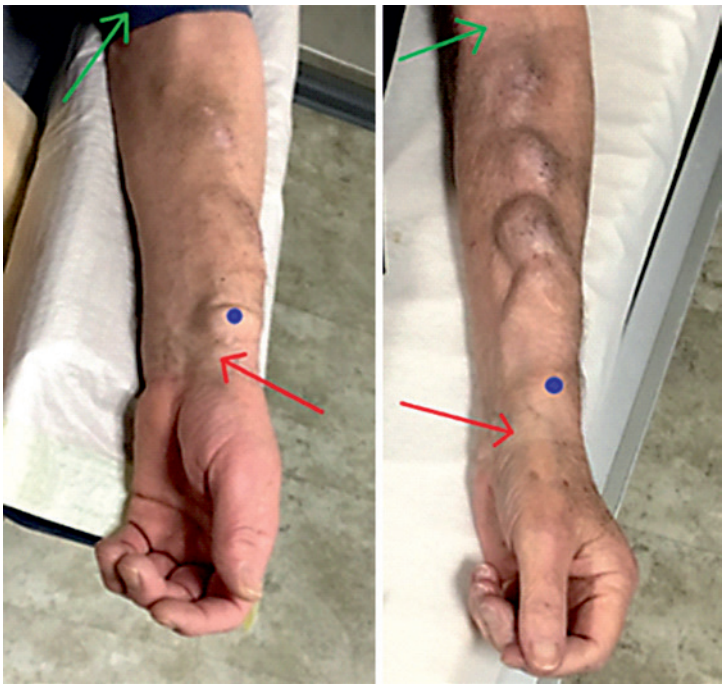

Fig. 1. Points of measurement at the fistula arm. Two different patients (written informed consent for publication was given) with native radiocephalic fistula are shown. The radial point of measurement (distal of the anastomosis, thumb side of the wrist joint) is marked with a red arrow, whereas the brachial point of measurement (proximal of the anastomosis, medial/ulnar in the antecubital fossa) is marked with a green arrow. The pulsatile buzz of the arterialized V. cephalica was recorded approximately 1 cm proximal of the anastomosis, i.e. downstream in the arterialized superficial part of the venous drainage system of the forearm, indicated with a blue spot.

is obvious that the output parameters computed by peripheral PWA algorithms implemented in commercially available devices, e.g., SphygmoCor®, are suitable only for measurements at the contralateral arm and not in direct proximity to the AVF. Moreover, parameters of the central PW are not suitable for characterizing AVF's haemodynamics in the periphery. In order to examine whether alterations related to fistula function can be seen in specific changes of peripheral PW morphology, appropriate measuring points at the fistula arm need to be identified and a new algorithm calculating suitable morphological parameters to characterize the peripheral PW morphology in direct proximity to AVFs has to be developed.

We used digitized curves recorded with the SphygmoCor® and processed them using MATLAB®. In order to take confounding by varying cardiac function into account, we considered heart rate and subendocardial viability ratio (SEVR) as calculated by the SphygmoCor® device for the non-fistula arm. SEVR is a functional cardiac parameter, which provides information about the quality of cardiac perfusion (ratio of diastolic and systolic area under the curve (AUC)). Also, all measured peripheral PWs were standardized prior to analysis in terms of peak blood pressure and duration of the systole and diastole (described in detail in the online suppl. material). After standardization, we considered the average slope in the four characteristic sections of the PW as well as the AUC of the first two sections (systole), the last two sections (diastole), and the whole curve as morphological parameters to be used in the statistical analyses (Fig. 2). Thereafter, interarm differences of corresponding parameters measured at the non-fistula and fistula arms, respectively, where calculated. In order to reduce the number of PW parameters to be tested and therefore simplify the analysis with regard to a potential clinical use, we calculated a sum parameter ($\Sigma\lambda^x$) by summing up the interarm slope differences in the four sections. More details, in particular precise definitions of all parameters, are provided in the online supplementary material and in supplementary Figures S1–S4.

For PWV the standard measurement and analysing procedure of the SphygmoCor® device was used in both arms. PWV was measured in 3 segments on each side: between A. carotis communis and A. radialis (segment cr), between A. carotis communis and A. brachialis (segment cb) and between A. brachialis and A. radialis (segment br). In addition to the PW

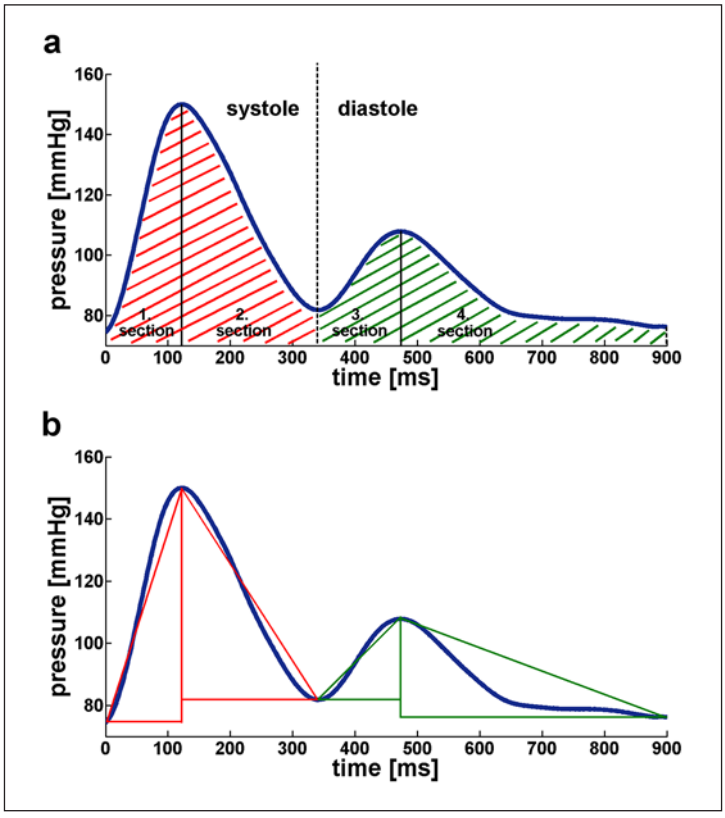

Fig. 2. Morphological parameters of peripheral pulse wave analysis. **a** A peripheral pulse wave of a healthy subject (radial point of measurement, after standardization) divided into 4 sections. The end of each of the 4 sections (computed using the standardized evaluation algorithm) is indicated by a vertical line. The dotted black vertical lines mark the border between the systolic and diastolic parts of the curve, i.e. the end of the second section, as well as the end of the diastolic part of the curve, i.e. the end of the fourth section. The areas are marked in red (systolic), green (diastolic) and red + green (total). **b** For the slopes, the 4 relevant slope triangles are marked in red (first and second segments) and green (third and fourth segments).

parameters, duplex sonographic parameters were considered. Further details are provided in the online supplementary material and in supplementary Table S1.

Statistical Analyses

To describe demographic and clinical parameters, standard univariate statistical analyses were used. All continuous variables were tested for normal distribution using graphical methods (histograms and Q-Q plots) and statistical methods (Kolmogorow-Smirnov-Lilliefors tests and Shapiro-Wilk tests). Normal-distributed continuous variables were analysed by Student's *t* tests and are shown as means ± standard deviation. Non-normal-distributed continuous variables were analysed by Wilcoxon signed-rank tests. Variables are shown with their 95% confidence intervals, and the associated two-sided *p* values are given. In order to test the correlation between PW and duplex sonographic parameters, Pearson correlation was used. Correlation coefficients *r* and associated two-sided *p* values are given, and a linear regression was performed in case of significant testing (two-sided test). Significance refers to local, unadjusted *p* value <0.05. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA, released 2019).

Results

Study Population

The patients' cohort (m/f: 2.3, age: 55.3 ± 13.5 years, BMI: 26.30 ± 4.89) consists of 56 persons with RCF (Table 1 and online suppl. Table S2). The overall majority (47 patients) had at least one kidney transplant and due to transplant failure, 4 of them were on haemodialysis

Table 1. Patients' characteristics

	Patients' cohort
Number	56 (100%)
Gender ratio (m/f)	2.29
Age, years	55.29±13.45
BMI	26.30±4.89
Patients with dRCF; pRCF	44 (78.6%); 12 (21.4%)
Patients with RCF at the left arm; right arm	46 (82.1%); 10 (17.9%)
Patients with former fistula (same arm)	7 (12.5%)
Patients with glomerulopathy	24 (42.9%)
Patients with diabetic kidney disease	7 (12.5%)
Patients with hypertensive kidney disease	5 (8.9%)
Patients with polycystic kidney disease	7 (12.5%)
Patients with haemolytic-uraemic syndrome	1 (1.8%)
Patients with hepatorenal syndrome	2 (3.6%)
Patients with other primary renal disease	2 (3.6%)
Patients with unknown primary renal disease	8 (14.3%)
Patients with renal transplant	47 (83.9%)
Patients with current haemodialysis	13 (23.2%)
Dialysis vintage, months	57.46±41.78

Variables are reported as absolute and relative frequencies or means ± standard deviation. m, male; f, female; BMI, body mass index; RCF, radiocephalic fistula; dRCF, distal RCF; pRCF, proximal forearm RCF.

Table 2. Peripheral pulse wave analysis (PWA) and pulse wave velocity (PWV) measurements

	N	Min.	Max.	m	μ	σ	CI_l	CI_u	p_t
$\lambda^r{}_1$	56	−0.20	0.40	0.0527	0.0579	0.1237	0.0248	0.0910	0.001
$\lambda^r{}_2$	56	−0.14	0.04	−0.0351	−0.0447	0.0393	−0.0552	−0.0342	0.000
$\lambda^r{}_3$	56	0.00	0.27	0.0738	0.0830	0.0558	0.0681	0.0980	0.000
$\lambda^r{}_4$	56	−0.03	0.04	0.0068	0.0075	0.0136	0.0039	0.0112	0.000
$\Sigma\lambda^r$	56	−0.18	0.66	0.1289	0.1463	0.1680	0.1000	0.1926	0.000
$\Lambda^r{}_{sys}$	56	−5.17	1.77	−1.6272	−1.4687	1.4445	−1.8556	−1.0819	0.000
$\Lambda^r{}_{dia}$	56	−6.66	6.41	−0.7298	−0.7668	2.9045	−1.5446	0.0110	0.053
$\Lambda^r{}_{tot}$	56	−10.38	8.12	−2.1582	−2.2355	3.9884	−3.3036	−1.1674	0.000
$\lambda^b{}_1$	56	−0.18	0.34	0.0430	0.0472	0.1165	0.0160	0.0783	0.004
$\lambda^b{}_2$	56	−0.18	0.06	−0.0279	−0.0372	0.0507	−0.0508	−0.0236	0.000
$\lambda^b{}_3$	56	−0.03	0.17	0.0595	0.0590	0.0450	0.0469	0.0710	0.000
$\lambda^b{}_4$	56	−0.03	0.04	0.0061	0.0067	0.0135	0.0030	0.0103	0.001
$\Sigma\lambda^b$	56	−0.17	0.77	0.1626	0.1827	0.18457	0.1318	0.2336	0.000
$\Lambda^b{}_{sys}$	56	−6.16	2.40	−0.9667	−0.7736	1.5272	−1.1826	−0.3647	0.000
$\Lambda^b{}_{dia}$	56	−10.74	7.21	−0.9786	−1.0088	3.5933	−1.9711	−0.0465	0.040
$\Lambda^b{}_{tot}$	56	−16.89	8.82	−1.9473	−1.7824	4.8674	−3.0859	−0.4789	0.008
$\tau^{crnS,\ crS}$	49	−3.10	3.20	0.9000	0.6990	1.2772	0.3321	1.0658	0.000
$\tau^{cbnS,\ cbS}$	44	−3.20	3.40	0.4500	0.5417	1.5207	0.0793	1.0040	0.023
$\tau^{brnS,\ brS}$	23	−2.93	3.90	1.5500	1.2558	1.7051	0.5184	1.9932	0.002

Results of Student's *t* test (two-sided, significance level 5%) of radial and brachial slope and area differences (peripheral PWA, slope differences $\lambda^x{}_k$ in mm Hg/ms for $k \in (1,2,3,4)$, corresponding sum differences $\Sigma\lambda^x$ in mm Hg/ms, and area differences $\Lambda^x{}_j$ in s × mm Hg for j ∈ {sys, dia, tot}, with $x \in \{r, b\}$) as well as PWV differences (considered in three different segments, $\tau^{xnS,\ xS}$ in m/s for $x \in$ {cr, cb, br}) between the non-fistula and fistula arms. Due to quality control, only PWV measurements with an uncertainty of maximally ±1.2 m/s were accepted (see suppl. material, subsection measuring points). Therefore, not all 56 patients could be included in the analysis of the PWV differences. *N*, total number of patients; min., minimal value; max., maximal value; m, median; μ, mean; σ, standard deviation; CI_l, lower 95% confidence interval; CI_u, upper 95% confidence interval; p_t, significance value.

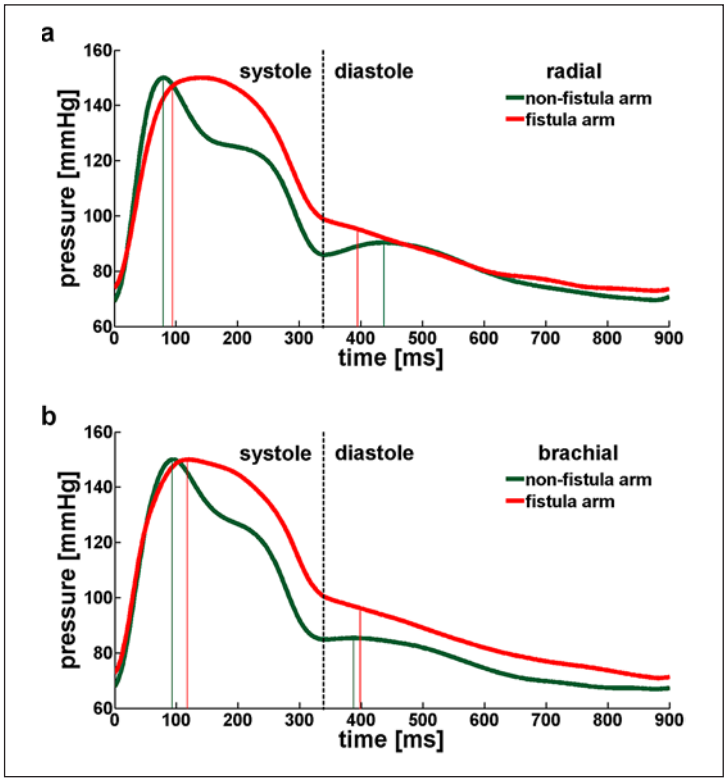

Fig. 3. Standardized peripheral pulse waves of patient No. 10 (online suppl. Table S2) recorded at the radial (**a**) and brachial (**b**) points of measurement at the fistula (red) and non-fistula arms (green). These are shown in direct comparison. The end of the first and third sections is indicated by a vertical line marked in the colour of the curve, whereas the dotted black vertical line marks the border between the systolic and diastolic parts of the curve, i.e. the end of the second section. For the definition of the sections and in particular an explanation why the end of the first section does not always coincide with the first maximum of the curve, see online supplementary material, subsection evaluation algorithm.

in addition to the remaining 9 non-transplanted patients (Table 1 and online suppl. Table S2). The 4 most common primary kidney diseases in this cohort in decreasing order were glomerulopathy, diabetic nephropathy, polycystic kidney disease and hypertensive kidney disease (Table 1 and online suppl. Table S2). The cumulative time spent on dialysis was 57.5 ± 41.8 months in the patients' cohort (Table 1). Comorbidities of patients are presented in online supplementary Table S2. Moreover, 2 exemplary patients with fistula failure (F1 and F2, not part of the analysed cohort) were considered (online suppl. Table S2).

Peripheral PWA

The slope differences and their sum between the non-fistula and fistula arms were significantly different from zero, independently from the point of measurement (Table 2). In detail, the slope was greater for the non-fistula arm than for the fistula arm in the first 3 sections, whereas in the fourth section the absolute value of the slope was smaller for the non-fistula arm than for the fistula arm (Fig. 3, online suppl. Fig. S1, Table 2, and online suppl. Table S3).

The mean AUC difference between the non-fistula and fistula arms was negative and differed significantly from zero in each of the 3 parts (systole, diastole, total) of the PW, independently from the point of measurement, except for the diastole at the A. radialis (Table 2, Fig. 3 and online suppl. Table S3).

Similar results in every section of the PW were obtained for measurements in the arterialized V. cephalica when compared to the values recorded at the A. radialis of the non-fistula arm (online suppl. Tables S4 and S6). In contrast, when parameters of measurements in the arterialized V. cephalica were compared to values measured at the A. radialis of the fistula arm, almost no significant differences were found (online suppl. Tables S5 and S6). Finally, for the measurements in the arterialized V. cephalica compared to the values at the brachial measuring points, conclusive results were not found (online suppl. Tables S4–S6).

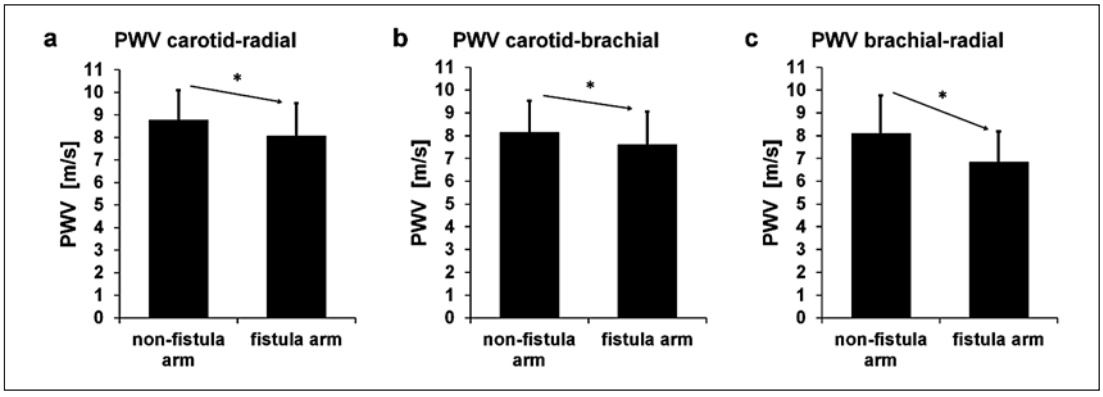

Fig. 4. Pulse wave velocity (PWV) measurements. Bars represent PWVs in metres per second measured in 3 different corresponding segments of the non-fistula and fistula arms expressed as means with standard deviation. PWVs between the carotid and radial points of measurement (**a**), the carotid and brachial points of measurement (**b**) and the brachial and radial points of measurement (**c**) are shown as means ± standard deviation. * $p < 0.05$, paired sample t test.

Table 3. Duplex sonography

	N	Min.	Max.	m	μ	σ	CI_l	CI_u	p_t	CT	p_w
ΔV	55	–7.59	–0.51	–2.67	–2.95	1.64				–	0.000
ΔV_{CS}	55	–3.79	–0.25	–1.34	–1.47	0.82				–	0.000
ΔA	55	–119.60	2.30	–27.40	–32.57	23.16	–38.83	–26.31	0.000		
Δ_{Xmax}	51	–179.30	6.80	–61.90	–68.38	42.96	–80.47	–56.30	0.000		
Δ_{Xmin}	51	–129.30	–17.10	–61.80	–68.20	27.84	–76.03	–60.37	0.000		
Δ_{Xend}	51	–129.40	–17.10	–61.00	–67.97	27.28				–	0.000
Δ_{X^-}	51	–179.20	–17.70	–73.40	–80.52	36.03				–	0.000
$\Delta_{Xmax/end}$	51	2.01	36.04	11.70	12.07	6.88	10.14	14.01	0.000		
Δl_p	51	1.12	4.59	2.92	2.82	0.82	2.59	3.05	0.000		
Δl_Ω	51	0.13	0.59	0.39	0.39	0.10	0.36	0.41	0.000		
$\Delta d_\updownarrow$	51	–6.80	0.60	–2.50	–2.67	1.51	–3.09	–2.24	0.000		
$\Delta d_\leftrightarrow$	51	–10.50	–0.10	–3.00	–3.32	1.92	–3.86	–2.78	0.000		
ΔU	51	–27.20	1.10	–9.00	–9.65	5.47				–	0.000

Results of Student's t test (two-sided, significance level 5%) and Wilcoxon signed-rank test (significance level 5%) for brachial duplex sonographic parameters' differences between the non-fistula and fistula arms. Differences in flow ΔV in L/min, cross-sectionally averaged flow ΔV_{CS} in L/min, cross-section ΔA in mm^2, flow velocities Δ_{Xx} in cm/s for $x \in \{max, min, end\}$, average flow velocity Δ_{X^-} in cm/s, systolic-diastolic ratio $\Delta_{Xmax/end}$, pulsatility index Δl_p, resistance index Δl_Ω, diameters Δd_x in mm for $x \in \{\updownarrow, \leftrightarrow\}$, and perimeter ΔU in mm are shown. In 4 patients, a superficial brachial artery was detectable; therefore, flow and cross-section of A. brachialis and A. brachialis superficialis were measured independently and added up afterwards. All other parameters could not be quantified in these patients (see online suppl. material, subsection measuring points). N, total number of patients; min., minimal value; max., maximal value; m, median; μ, mean; σ, standard deviation; CI_l, lower 95% confidence interval; CI_u, upper 95% confidence interval; p_t, significance value (Student's t test); CT, central tendency; p_w, significance value (Wilcoxon signed-rank test).

It has to be mentioned that, due to varying anatomical conditions and turbulent flow, measuring in the arterialized V. cephalica was more cumbersome and less standardized than at the arterial measuring points. Also, the standard deviations of the AUC und slope parameters were greater and the accuracy of measurement on the arterialized V. cephalica was lower than at the arterial measuring points. Measuring quality was even insufficient in 6 out of 56 patients (online suppl. Tables S4–S6).

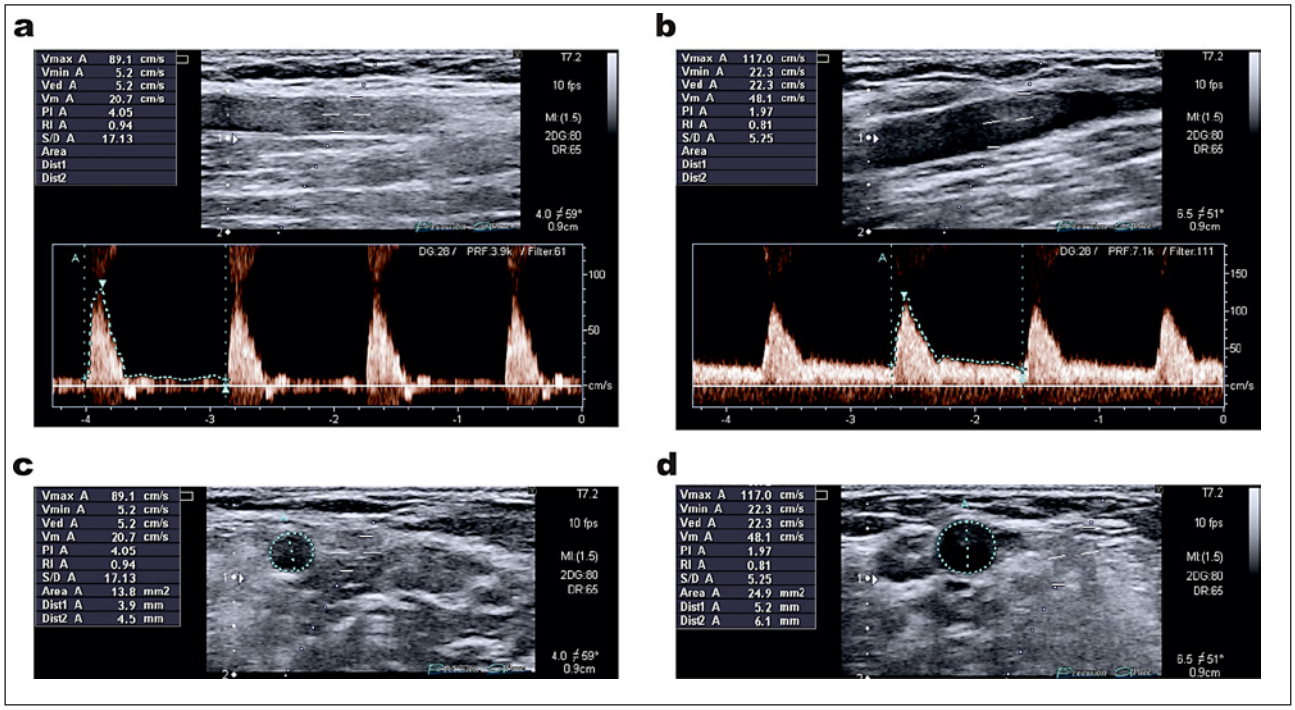

Fig. 5. Exemplary sonographic images of patient No. 30. The images were taken at the non-fistula (**a**, **c**) and fistula arms (**b**, **d**). **a**, **b** Doppler spectra of the A. brachialis recorded in the duplex mode. **c**, **d** The cross-sections of the A. brachialis as measured in B-mode. For patients' characteristics, see online supplementary Table S2.

Pulse Wave Velocity

PWV was significantly reduced in the forearm with RCF irrespective of PWV measurement being restricted to the forearm or extended to more proximal parts of the upper limb and the cervical region (Fig. 4, Table 2, and online suppl. Table S3). The greatest interarm PWV difference was measured in segment br, but measuring quality was low (Table 2 and online suppl. Table S3).

Duplex Sonography

The flow, all flow velocities, the cross-section, the perimeter and all diameters were found to be significantly increased at the fistula arm (Table 3 and online suppl. Table S1). An exemplary Doppler spectrum of the flow in the A. brachialis at the fistula and non-fistula arm, both with an exemplary B-mode image to demonstrate the diameter, are shown in Figure 5. Moreover, in the fistula arm, the values for the resistance and pulsatility index as well as for the systolic-diastolic ratio were found to be significantly reduced (Table 3 and online suppl. Table S1).

Correlations and Clinical Outcomes

The sum of the slope differences correlated with flow and peak flow velocity differences (Fig. 6, online suppl. Fig. S5). A similar effect was found when considering each section separately (online suppl. Table S7). In contrast, no such correlation was found between the sum of the slope differences and the artery diameters (online suppl. Fig. S6). The same applies to the sum of the slope differences and the heart rate as well as the SEVR (online suppl. Fig. S7). Moreover, in the two exemplary patients with fistula failure (F1 and F2, online suppl. Table

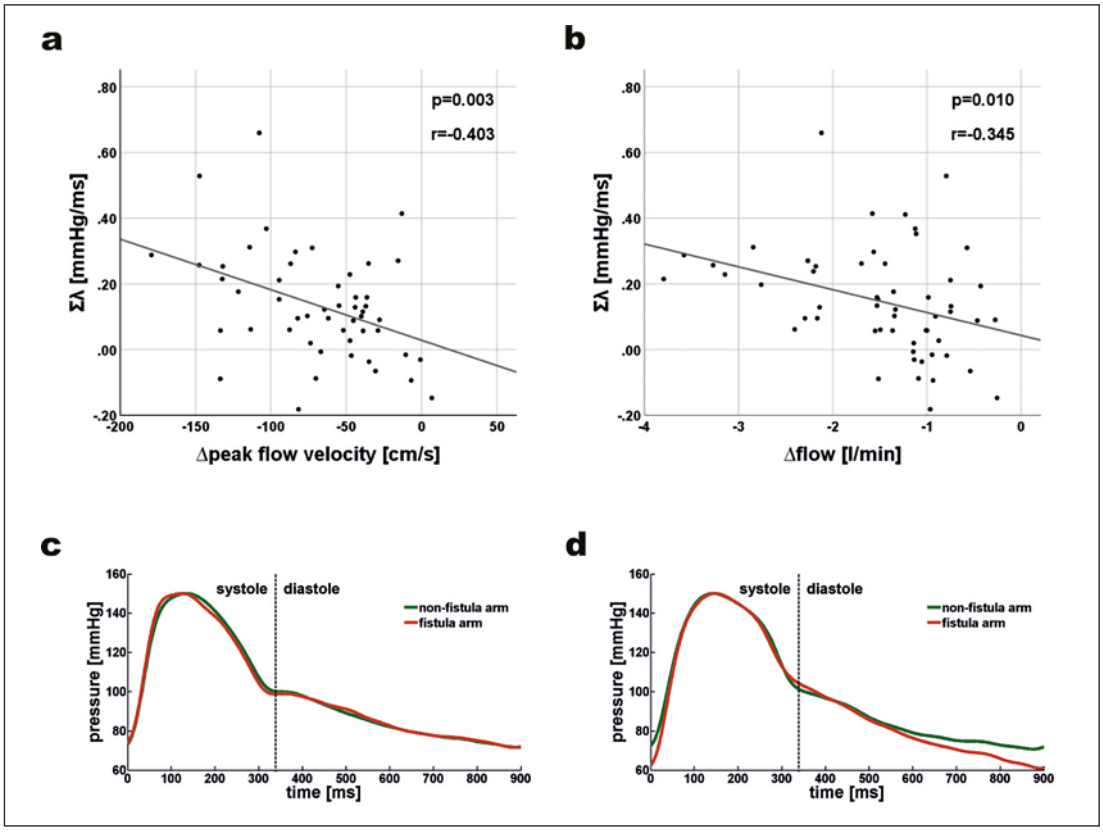

Fig. 6. Peripheral pulse wave analysis and fistula function, brachial measuring point. Scatter plots of interarm differences in peak flow velocity Δ_{Xmax} in centimetres per second (**a**) and flow ΔV_{cs} in litres per minute (**b**) versus the sum of interarm slope differences $\Sigma\lambda^b$ in millimetres Hg per millisecond in the A. brachialis are shown with Pearson correlation coefficient *r* and the associated two-sided *p* value. As significant correlations were given, grey regression lines were added to the scatter plots. Standardized peripheral pulse waves of patient F1 (**c**) and F2 (**d**) with complete fistula failure (online suppl. Table S2) recorded at the brachial point of measurement at the fistula (red) and non-fistula arms (green) are shown in direct comparison. The dotted black vertical line marks the border between the systolic and diastolic parts of the curve.

S2) virtually no changes in PW morphology, flow, peak flow velocity, cross-section and diameters at the fistula in comparison to the non-fistula arm could be detected (Fig. 6, online suppl. Fig. S5, and suppl. Table S8). Furthermore, a significant inverse correlation between PWV in the segment cr and flow as well as cross-sectional area at the fistula arm was shown (online suppl. Fig. S8).

Discussion

In this pilot study, which included 56 patients with mature and well-working native RCF, we observed noticeable changes in the peripheral PW morphology and PWV in the fistula compared to the non-fistula arm. Independently of the point of measurement on the arteries, the sum of the slope differences was found to correlate with flow and peak flow velocity, which is relevant for high and low flow RCFs. In contrast, alteration of the artery diameters seems to have only a minor influence on PW morphology changes. In 2 patients with fistula failure virtually no changes in PW morphology, flow and peak flow velocity were seen. In

order to minimize potential differences in PW morphology simply caused by blood pressure and heart rate alterations, all measured peripheral PWs were standardized prior to analysis. As expected, according to standardization no significant influence of heart rate could be observed when considering the sum of the slope differences. Furthermore, there was no significant correlation of SEVR and the sum of the slope differences. Therefore, an influence of cardiac function on our findings could not be verified.

We suggest using primarily the radial or brachial point for assessment. Similar, if not more pronounced effects were observed in the arterialized V. cephalica when compared to radial measurements in the non-fistula arm. Nevertheless, PWA in the arterialized V. cephalica is limited due to the lack of a directly corresponding point of measurement at the non-fistula arm. Furthermore, despite arterialization of the V. cephalica [17, 18], peripheral PWA, all in all, is not validated for venous measurements [12, 14]. Finally, the measurement quality is impaired by the pulsatile buzz and the possible turbulent flow in the arterialized V. cephalica [17, 18].

PWV was significantly reduced in the fistula arm. Based on the Bramwell-Hill equation, PWV depends on parameters characterizing the local haemodynamics and arterial stiffness [22, 23]. More precisely, this equation postulates an inverse relationship between the PWV and the local arterial elasticity (vascular compliance) [22, 23]. Additional factors influencing the PWV are the local arterial diameter and total peripheral resistance [6, 7, 23]. Overall, PWV is a direct measure of local arterial stiffness and an appropriate biomarker for vascular age determination [7, 8]. Under physiological conditions the arterial vessels show a reduction of arterial elasticity and cross-section by following their course from the heart to the periphery and the concurrent gain of arterial stiffness towards the periphery is associated with a sustained rise of PWV [22]. In contrast to that, the placement of an RCF is associated with local arterial dilation and therefore reduced arterial stiffness as well as reduced peripheral resistance in the fistula arm, consistent with our duplex sonographic findings [24]. Therefore, based on the Bramwell-Hill equation a significantly reduced PWV in the fistula in comparison to the non-fistula arm can be explained. In addition, our findings are supported by the results of an already published study investigating the alteration of the arterial stiffness among the patients with native AVF by performing PWV measurements between the carotid and brachial points of measurement [25]. Moreover, our data support this idea by showing a significant inverse correlation between PWV and flow as well as cross-sectional area at the fistula arm. Due to RCF placement at the forearm, the largest PWV reduction was observed between the brachial and radial points of measurement, but the fistula's influence on more proximal parts of the upper limb was still measurable. In terms of validity and reliability, the PWV measurement between the carotid and radial points of measurement is the most appropriate one as in direct proximity of the native RCF (between A. brachialis and A. radialis) a non-negligible rise of measurement inaccuracy was observed.

As a consequence of a rise in volume flow in the AVFs there is an overall increase in the peripheral arterial elasticity (vascular compliance) and Windkessel function [26], i.e., the peripheral arteries (A. radialis and A. brachialis) at the fistula arm gain aortic qualities [17, 19, 27]. Simultaneously, a reduced arterial stiffness and an overall decrease in the total peripheral resistance can be observed at the fistula arm [25, 27]. The duplex sonographic examination of the fistula arm confirmed those haemodynamic changes, and thus, the intact shunt function for the patients under study. The flow, flow velocity, cross-section, perimeter and the diameter increased while the resistance and pulsatility index declined in comparison to the non-fistula arm.

Our analyses mainly relied on the time domain of PWs [11, 28]. Among other things, PWs are also characterized by their frequency and amplitude [29]. They can be superposed, enhanced or damped [30, 31]. A peripheral PW is not a harmonic sinusoidal wave but consists

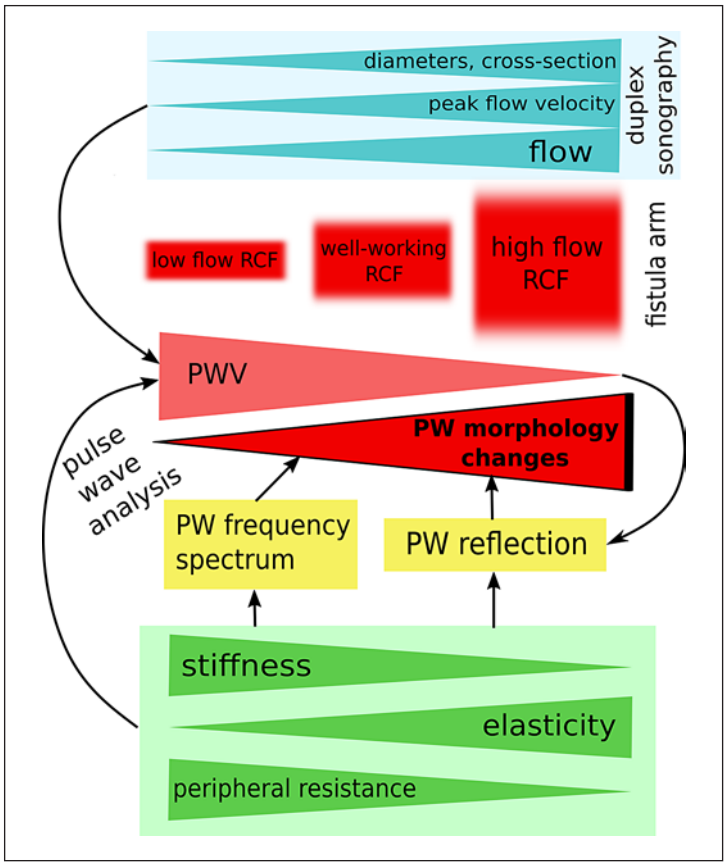

Fig. 7. Summary figure. Graphically summarized interpretation of changes in peripheral pulse wave (PW) morphology and pulse wave velocity (PWV) in relation to radiocephalic fistula (RCF) function characterized by flow. Details and further explanations are provided in the discussion section of the paper.

of summed ante- and retrograde waves of different frequencies [30–33]. PWs running through peripheral arteries of reduced elasticity show a gain of high-frequency wave components due to weaker damping, whereas in case of an increased arterial elasticity (vascular compliance) it is the other way around [30, 31]. Having that in mind, a mature and well-working native RCF, from a theoretical point of view, increases damping of high-frequency wave components due to increased arterial elasticity (vascular compliance) at the fistula arm [17, 19, 27]. Therefore, altered composition of the frequency spectrum could contribute to an adequate explanation for the observed morphological differences of the peripheral PWs recorded at the fistula and non-fistula arms. Also, it must be postulated that the reduced flow resistance results in a quantitatively lower PW reflection in the fistula arm. Due to damped amplitudes of the reflected wave components, this may also affect the observed PW morphology changes at the fistula arm. The same applies to a delayed PW reflection in the fistula arm due to an overall reduced PWV. The future evaluation of the frequency domain of PWs close to AVFs (e.g., using Fourier or wavelet analysis) and of PW reflection will have to analyse these phenomena at the fistula arm. This might yield an improved characterization of PWs close to AVFs.

In our study, all the mandatory blood pressure measurements were restricted to the non-fistula arm to avoid AVF thrombosis. This meant that the possible lowering of the distal local arterial blood pressure close to the AVF as a result of the reduced vascular resistance was not considered. From a clinical point of view, it has to be mentioned that the majority of the patients included in this study had a functioning kidney transplant, i.e., their RCFs were currently not in use. Finally, it is noteworthy that the cumulative dialysis duration of all 56 patients was heterogeneously distributed.

As the early detection of fistula failure is of vital clinical importance in haemodialysis patients, the search for new fistula monitoring methods is essential. We herein show that beside duplex sonography ambilateral peripheral PWA using applanation tonometry is able to characterize RCF function and therefore has the potential to serve as a new monitoring method to improve fistula outcome in haemodialysis patients. However, before our findings enter the stage of clinical application, the findings should be verified in prospective studies, in which patients with chronic kidney disease ideally undergo peripheral PWA and PWV measurements in comparison with duplex sonography prior to the initial RCF application surgery and periodically afterwards, especially in case of shunt complications. Examination should no more be restricted to RCFs but be expanded to other anatomical locations and types of arteriovenous dialysis access. Those future trials should confirm whether the new parameters can be used to predict clinical outcomes, such as mal-maturation, high flow fistula or fistula failure. Also, alternative measuring methods for PWA, like invasive recording after punctuating the venous parts of an AVF, oscillometry and plethysmography are of interest.

In summary, for the first time, this clinical pilot study was able to show that peripheral PWA and PWV measurements using applanation tonometry are feasible in a fistula arm and are promising tools to characterize fistula function (Fig. 7). For this purpose, suitable and robust parameters were defined, and a newly established standardized evaluation algorithm was applied.

Acknowledgement

We acknowledge support by the German National Academic Foundation (Studienstiftung des Deutschen Volkes). The foundation had no role in study design; collection, analysis and interpretation of data, writing the report and the decision to submit the report for publication. We also acknowledge support by the Open Access Publication Fund of the University of Münster.

Statement of Ethics

We complied with the guidelines for human studies and declare that the research was conducted ethically in accordance with the declaration of Helsinki.

The study was approved by the local ethics committee (Ethik-Kommission der Ärztekammer Westfalen-Lippe und der Medizinischen Fakultät der Westfälischen Wilhelms-Universität Münster, No. 2014-360-f-S). Written informed consent was obtained from all participants.

Disclosure Statement

The authors have no conflicts of interest to declare.

Author Contributions

N.M., H.P., S.R. and V.B. conceived and designed the study. N.M. acquired the data. J.S. and T.F. programmed the evaluation algorithm. N.M., S.M. and V.B. analysed and interpreted the data. N.M., S.M. and V.B. wrote the main article text. All authors reviewed the paper.

DOI: 10.1159/000506741

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