Aus dem CharitéCentrum für Innere Medizin, Medizinische Klinik m.S. Nephrologie und Internistische Intensivmedizin

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Habilitationsschrift

Der Stellenwert der Oszillometrie in der nicht-invasiven Beurteilung des physiologischen und strukturellen Zustandes des arteriellen Gefäßsystems

zur Erlangung der Lehrbefähigung
für das Fach Innere Medizin und Nephrologie

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von

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1 Inhaltsverzeichnis

2 Abkürzungen

A	*Querschnittsfläche*
C	*Compliance*
CAVI	*cardio ankle vascular index*
MAD	*mittlerer arterieller Druck*
P	*Blutdruck*
Pdia(t)	*diastolischer Druck zum Zeitpunkt t*
Pes	*endsystolischer aortaler Druck*
PiCCO	*Puls Contour Cardiac Output*
Pmittel,aortal	*mittelere aortaler Druck*
Pmittel,venös	*mittlerer venöser Druck*
PWV	*pulse wave velocity*
R	*Resistenz*
VSMC	*vascular smooth muscle cells*
Zc	*charakteristische Impedanz*
ΔP	*Druckdifferenz*
ΔV	*Volumendifferenz*
ρ	*Blutdichte*

3 Einleitung

3.1 Allgemeines

Vaskuläre Erkrankungen sind nach wie vor eine der Hauptursachen für die Morbidität und Mortalität der westlichen Population. Pathophysiologische Prozesse in unterschiedlichen Schichten der arteriellen Gefäßwand führen zu verschiedenen Entitäten von Gefäßerkrankungen. So werden die Veränderungen in der Intima bzw. Subintima, welche durch Inflammation, Fibrose und Lipidpartikelakkumulation verursacht sind, als

„Atherosklerose“ bezeichnet. Bekannte und „klassische“ Risikoerkrankungen wie arterieller Hypertonus, Adipositas, Lipidstoffwechselstörungen, Diabetes mellitus und Rauchen führen zur Entstehung und zum Voranschreiten der Atherosklerose. Die Veränderungen der arteriellen Gefäßmedia – die Arteriosklerose – beruhen hingegen pathophysiologisch auf anderen Prozessen: hier stehen vor allem Veränderungen in den glatten Muskelzellen der Media (vascular *smooth muscle cells=VSMC)* und die Kalzi- fizierung der Media im Vordergrund. Wesentliche Unterschiede ergeben sich auch bei den Risikofaktoren für die Arteriosklerose. Hier spielen vor allem Alter, chronische Nie- reninsuffizienz und Diabetes mellitus eine Rolle. Je nach dominierender Konstellation der Risikofaktoren überwiegt entweder die eine oder die andere Entität der strukturellen Gefäßwandveränderung. Allerdings laufen Atherosklerose und Arteriosklerose meist simultan ab, da häufig mehrere Risikofaktoren vorhanden sind und in unterschiedlicher Aktivität die Prozesse beeinflussen. Während die Atherosklerose im Zuge der Prävention von Myokardinfarkten und ischämischen Schlaganfällen in den letzten Jahrzehnten deutlich im Vordergrund stand, gewann das Interesse an Arteriosklerose mit steigender Lebenserwartung, insbesondere bei Patienten mit Diabetes mellitus und

chronischer Niereninsuffizienz.

3.2 Arteriosklerose

Die Arteriosklerose ist pathophysiologisch und biomechanisch ein komplexer Prozess, in dem die glatten Gefäßmuskelzellen (VSMC) eine sehr wichtige Rolle spielen. Es kommt zu einer Proliferation und akzelerierten Seneszenz der VSMC, außerdem zu einem veränderten Expressionsmuster mit Expression chondrozytärer, osteoblastischer und osteoklastischer Proteine, die den Prozess der Mediakalzifizierung in Gang setzen bzw. steuern.[1] Hinzu kommen die Endotheldysfunktion und Veränderungen der Extrazellularmatrix, welche die Elastin/Kollagen-Zusammensetzung und Zell-Matrixinteraktionen betreffen.[2]

Das hämodynamische Korrelat der Arteriosklerose ist die arterielle Gefäßsteifigkeit. Im klinischen Setting ist vor allem die Kenntnis der aortalen Gefäßsteifigkeit relevant, da die Arteriosklerose der Aorta mit erhöhter kardiovaskulärer Mortalität und Morbidität assoziiert ist.[3]

3.3 Physiologie der Hämodynamik im arteriellen Gefäßsystem

Das Interesse die hämodynamische Situation im arteriellen System im Detail zu verstehen und anhand eines Modells zu beschreiben ist seit Jahrhunderten groß. Hales hatte 1735 zum ersten Mal den Blutdruck beschrieben und stellte fest, dass dieser über die Dauer des Herzschlages und im Intervall bis zum nächsten Herzschlag variiert. Weber äußerte 1827 die erste Theorie nach der das Druckverhalten im arteriellen Gefäßsystem sich nach dem Prinzip des Windkessels verhält.[4] Otto Frank formulierte das bekannte Zwei-Element-Windkessel-Modell, wobei Resistenz (R) und Com- pliance als Elemente fungierten (Abbildung 1).[5] Nach dem Poiseuille's Gesetz ist R invers proportional zum Gefäßradius in vierter Potenz. Somit ist der Gesamt-R vor allem durch die peripheren Widerstandsgefäße (in erster Linie

Arteriolen) bestimmt. Die Compliance ist durch strukturelle Beschaffenheit der großen arteriellen Gefäße und vor allem der Aorta bestimmt (Abbildung 1).

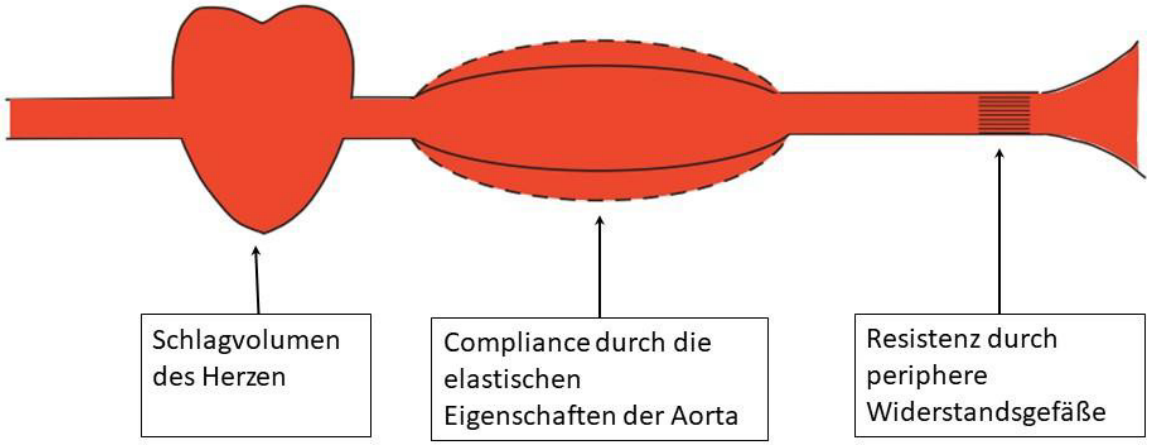

Abbildung 1: *Windkesselmodel; Abbildung in Anlehnung an Westerhof et al.*[6] *Verwendung mit freundlicher Genehmigung von Springer Nature im Rahmen der Open Access Nutzungsbedingungen*

Der gesamte periphere Widerstand kann mit folgender Formel berechnet werden:

$$R = (P_{mittel,aortal} - P_{mittel,venös})/CO \approx P_{mittel,aortal}/CO$$

Hierbei ist $P_{mittel,aortal}$ der mittlere Blutdruck in der Aorta, $P_{mittel,venös}$ der mittlere venöse Druck und CO das Herzminutenvolumen. Der mittlere venöse Blutdruck ist meist nahe null und vernachlässigbar. Die totale Compliance (C) ergibt sich aus dem Verhältnis der Druckänderung (ΔP) als Antwort auf Volumenänderung (ΔV)

$$C = \Delta V/\Delta P$$

Otto Frank konnte zeigen, dass R und C Einfluss auf den Druckverlauf in arteriellen Gefäßen haben. Somit konnte er mit seinem Zwei-Element Windkesselmodel den Verlauf des aortalen Druckes beschreiben. Folgende Gleichung hat er zugrunde gelegt:

$$P_{dia}(t) = P_{es}e^{-t/R*C}$$

Hierbei ist $P_{dia}(t)$ der diastolische aortale Druck zum Zeitpunkt (t) und der P_{es} der end-systolische aortale Druck. Somit kann bei gegebenen R und C die Druckkurve beschrieben werden (Abbildung 2)

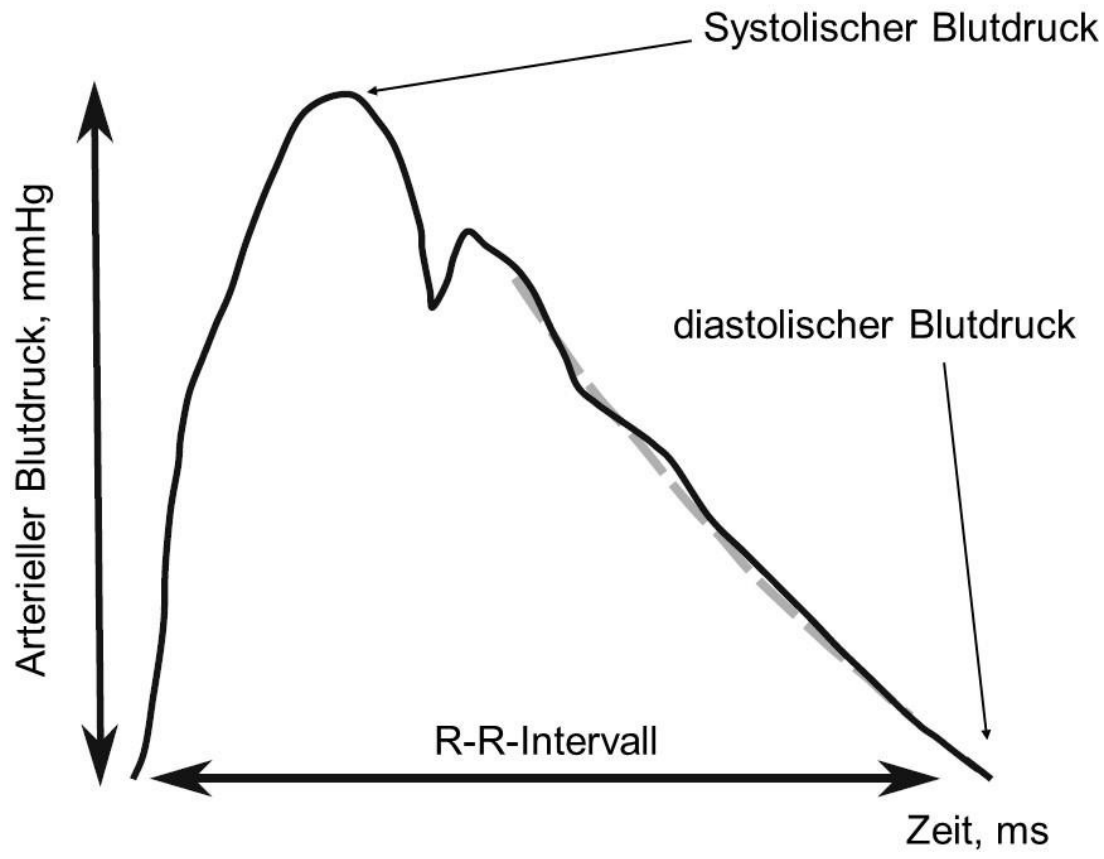

Abbildung 2: Der Abfall des aortalen Druckes in der Diastole kann durch die Exponentialkurve aus Resistenz und Compliance (graue gestrichelte Linie) angenähert werden (Windkesselmodel). Abbildung in Anlehnung an Westerhof et al.[6] Verwendung mit freundlicher Genehmigung von Springer Nature im Rahmen der Open Access Nutzungsbedingungen

Für die Anwendbarkeit des Zwei-Elemente-Windkesselmodels gibt es jedoch Limitationen: so geht Frank in seinem Model davon aus, dass der kritische Blutdruck,

bei demes zum Sistieren des Blutflusses kommt, bei null liegt. Experimentell wurde aber gezeigt, dass dieser kritische Blutdruck nicht null ist.[7] Eine weitere Annahme ist die Konstanz der Compliance. Bekannt ist allerdings, dass die Compliance sich in Abhängigkeit vom im Gefäß vorherrschenden Blutdruck ändert, wobei sie ihr Maximum bei niedrigen und ihr Minimum bei hohen arteriellen Drücken erreicht.[8] Die Entwicklung und der Einsatz des elektromagnetischen Durchflussmessers konnte zeigen, dass die Re- lation zwischen Druck- und Flusskurve durch das Zwei-Element-Windkesselmodel schlecht vorhergesagt wird.[9] Weitere Untersuchungen konnten zeigen, dass die Ergänzung der charakteristischen Impedanz (Zc) in dem Drei-Element-Windkesselmodel seine Prognose in Bezug auf die Prädiktion der Blutdruck- und Flusskurve verbessert.[10] Die charakteristische Impedanz verlinkt den Aspekt der Wellenfortbewegung mit dem klassischen Windkesselmodel. Sie wird mit folgender Formel zum Ausdruck gebracht:

$$Z_c = PWV \times \frac{\rho}{A}$$

Hierbei ist PWV die Pulswellengeschwindigkeit (*pulse wave velocity),* ρ die Blutdichte, A die Querschnittsfläche der Arterie (Aorta) und P der Blutdruck.

Das Windkesselmodell kann in der biophysikalischen Beschreibung der hämodynamischen arteriellen Gesamtsituation, dem sogenannten „Physiom“ verwendet werden.[11] Kann nun die Druckkurve erfasst werden, so ist es möglich mit Anwendung des Drei-Elemente-Windkesselmodels Rückschlüsse auf die aortale Compliance und somit auf die Aortensteifigkeit zu beziehen.[12] Allerdings berücksichtigen die Windkesselmodelle nicht die Pulswellentransmission und -reflexion im arteriellen System. Diese müssen in das Modell einbezogen werden, um ein vollständiges Bild der Druckkurve aber auch der Flusskurve zu bekommen. In einem weiteren Modell (Abbildung 3) werden deshalb folgende Punkte berücksichtigt: Die Reflektionswellen erreichen typischerweise die proximale Aorta in der mittleren bzw. späten Systole. Daher kann die frühe Systole als

eine von den Reflektionswellen unabhängige Zeitspanne betrachtet werden. Aus den hier bestimmten Druck- und Flusskurven kann die charakteristische Impedanz zuverlässig nach der Formel $\Delta P/\Delta V$ berechnet werden. Die Kenntnis der charakteristischen Impedanz erlaubt dann die Identifizierung des Reflektionsanteils (schwarz straffierte Fläche in der Abbildung 3) in der Summationskurve. Kann die aortale Druckkurve erfasst oder z.B. von der peripheren arteriellen Druckkurve abgeleitet werden, können durch die Zerlegung der Summationskurve in einzelne Anteile Rückschlüsse über die aortale Gefäßsteifigkeit oder den peripheren Gefäßwiderstand gezogen werden.

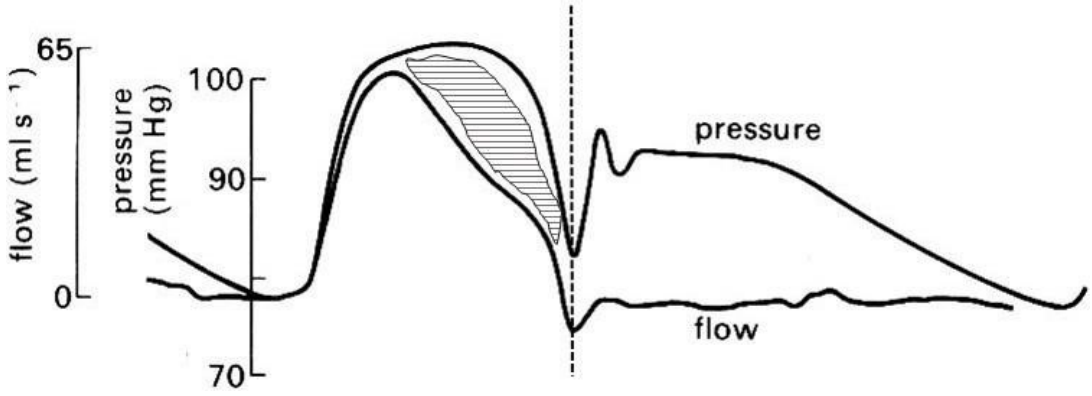

Abbildung 3: Die Überlagerung der Druckkurve und Flusskurve in der frühen Systole erlaubt die Identifizierung der Druckkurvenfläche, die durch Reflektionswellen verursacht wird (grau straffierte Fläche). Die gestrichelte Linie markiert das Ende der Systole. Abbildung in Anlehnung an Kouchoukos et al.[13] Verwendung mit freundlicher Genehmigung von Wolters Kluwer Health

3.4 Hämodynamische Parameter zur Erfassung der Arteriosklerose

Der hämodynamische Ausdruck der Arteriosklerose ist die arterielle Steifigkeit. Führender etablierter Surrogatparameter der arteriellen Steifigkeit ist die PWV. Klinische Endpunktstudien zeigen einen unabhängigen prädiktiven Wert der PWV hinsichtlich kardiovaskulärer Ereignisse.[14]

Die PWV kann regional oder lokal gemessen werden. Typischerweise wird die regionale PWV basierend auf den Zwei-Punkt-Messungen in der ipsilateralen A.

carotis undA. femoralis durchgeführt. Daraus wird die so genannte carotis-femorale PWV (cf PWV) ermittelt, welche den Mittelwert der PWVs in der Aorta zwischen A. carotis und A. femoralis darstellt. cfPWV wird als Goldstandard in der Messung der arteriellen Steifigkeit akzeptiert.[15]

3.5 Methoden zur Messung der PWV

Für die Bestimmung der PWV ist die Visualisierung der Pulskurven an unterschiedlichen anatomischen Punkten (z.B. A. carotis und A. femoralis für die Bestimmung der cfPWV) notwendig. Obwohl die invasive Messung der Pulskurven und die direkte Distanzmessung sicherlich die zuverlässigsten Ergebnisse bieten, ist die invasive Messung in der klinischen Routine zu aufwendig und in der Risiko-Nutzen-Abwägung dem Patienten nicht zumutbar. Daher haben sich mehrere Methoden der nicht-invasiven Messung der arteriellen Steifigkeit entwickelt. Die transkutane Tonometrie bzw. piezoelektrische Mechanotransduktion ist die häufigste nicht-invasive Methode zur Erfassung der Pulskurven. Hier werden jeweils die Fußpunkte des systolischen Druckanstieges in der A. carotis und A. femoralis angeschaut. Der zeitliche Unterschied zwischen den Fußpunkten ergibt die Transitzeit Δt (Abbildung 4). Der Abstand zwischen den Messpunkten kann oberflächlich gemessen werden (Distanz). Die PWV kann dann mit der Formel $PWV = \frac{Distanz}{\Delta t}$ berechnet werden.[16] Die ultraschallbasierte und MRT-basierte Pulskurvendetermination wurden ebenfalls in Studien angewandt. [17,18] Da diese Methoden kosten- und personalintensiver sind, gibt es im Vergleich zu Tonometrie/Mechanotransduktion weniger Studien, die diese Methoden anwenden.

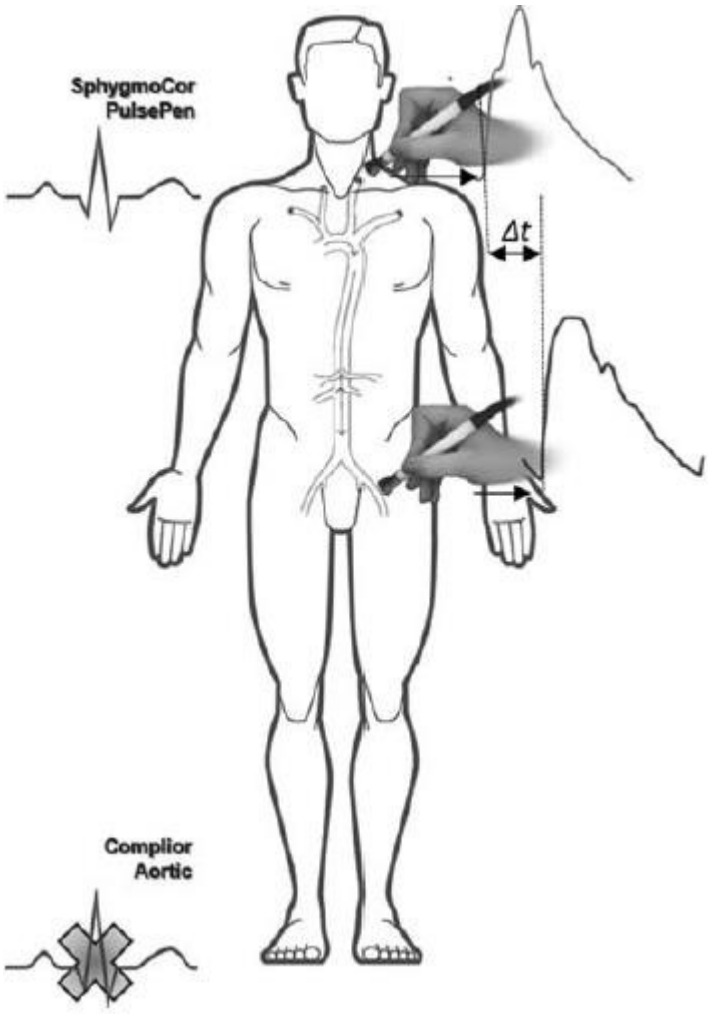

Abbildung 4:Bestimmung der Pulswellengeschwindigkeit anhand der Pulskurvenanalyse mit der Fuß-zu-Fuß-Methode. Verwendung mit freundlicher Genehmigung von Wolter Kluwer Health aus Milan A, et al.[16]

Die Knöchel-Arm-PWV ist eine weitere Möglichkeit der nicht-invasiven PWV-Bestimmung, welche in Asien populär ist. Die Ermittlung der Pulskurve erfolgt oszillometrisch simultan am Oberarm und Unterschenkel. Die Transitzeit und die PWV werden wie bei der tonometrischen Methode berechnet.[19]

Der Arteriograph (TensioMed, Ingolstadt, Deutschland) als weitere Möglichkeit verwendet einen Algorithmus, der nur eine Ein-Punkt-Messung der arteriellen Pulskurve in der A. brachialis notwendig macht. In der mit Hilfe der Druckrezeptoren generierten Pulskurve wird die Zeit zwischen dem Auftreten des systolischen Volumenejektionspeak durch die Aorta (P1) und des durch die Rückkehr der Reflektionswellen bedingten

zweiten Peaks (P2) ermittelt. Diese wird als Transitzeit genommen. Als Distanz wird der Abstand zwischen Jugulum und Symphyse genommen.[20] Die aortale PWV wird nach folgender Formel berechnet:

$$PWV = \frac{d\ \ jugulum - symphyse}{0{,}5 * Transitzeit}$$

3.6 Oszillometrisch-basierte Kalkulation der aortalen PWV

Als weitere Methode steht eine oszillometrische Messmethode zur Verfügung, die anhand der erfassten Pulskurve in der A. brachialis eine Schätzung der aortalen PWV vornimmt. Hierbei handelt es sich um eine Ein-Punkt-Messung.

Der in der Manschette eingebaute hochsensible Drucksensor erfasst die Pulskurve in der A. brachialis. Als nächstes erfolgt die Modellierung der zentralen aortalen Pulskurve mit Hilfe der Transferfunktion basierend auf den Berechnungen im *three layer feed forward back propagation* artifiziellen neuronalen Netzwerk.[21]

Die zugrundeliegende Physik basiert auf Überlegungen von Womersley, der eine lineare Lösung zur Beschreibung des Flüssigkeitsverhaltens im elastischen Rohr vorgeschlagen hat. Die Grundidee von Womersley ist, dass jegliches Fluss- und Druckprofil mit Hilfe der aggregierten harmonischen Funktionen beschrieben werden kann.

Die erste Ableitung aus der anhand der Transferfunktion generierten aortalen Druckkurve kann als Grundlage für die Fourieranalyse genommen werden. So können basierend auf dieser Kurve Fourier-Reihen bis zur 5. Ordnung berechnet werden. Diese können neu zusammengesetzt werden und dadurch die Flusskurve generiert werden. Aus der Relation zwischen Druck- und Flusskurve kann die charakteristische Impedanz, die dem Young-Modulus entspricht, berechnet werden.[22]

Grundsätzliche mathematische Korrelation zwischen PWV in elastischen Rohren und dem Grad der Wandsteifigkeit kann mit Hilfe der Moens-Korteweg Gleichung beschrieben werden:

$$PWV = \sqrt{\frac{E * h}{2 * R * \rho}}$$

Wo *E*– Young-Konstante, h– Wanddicke, R-Radius und ρ –Blutdichte ist. Die Young-Konstante ist dimensionslos und reflektiert die elastischen Eigenschaften der Gefäßwand.

Oben genannte physikalische Prinzipien liegen einem mathematischen Algorithmus zugrunde, welcher der Berechnung der PWV mit den in den Studien verwendeten Geräten zugrunde liegt.

3.7 Oszillometrie-basierte Kalkulation des Herzminutenvolumens

Zunächst ist es notwendig die vorwärts gerichtete Druckwelle von den Reflexionswellen in der Summationskurve zu trennen, da nur die vorwärts gerichtete Druckkurve die Ejektionsarbeit des Herzens abbildet. Im verwendeten Algorithmus wird derDruckkurveninflektion (Abbildung 5) als Orientierung genommen um den Punkt des Aortenklappenschlusses und somit das Ende des systolischen Blutflusses zu bestimmen. Dieser Punkt der Druckkurveninflektion wird mit Hilfe der Spline-Interpolation bestimmt. Die Applikation des Levenberg-Marquardt Algorithmus erlaubt die Bestimmung des Schlagvolumens als Integral der Blutflusskurve über die Zeit bis zum Aortenklappenschluss (braune Fläche in der Abbildung 5)

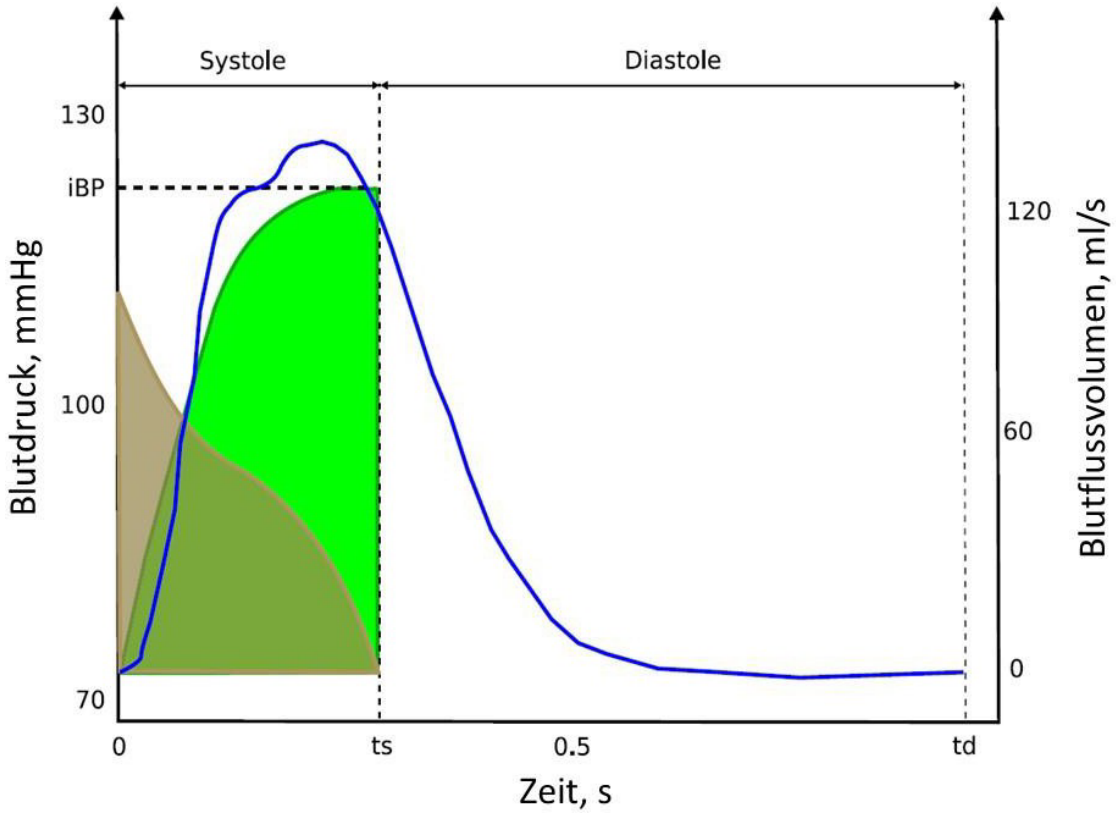

Abbildung 5: Bestimmung des Schlagvolumens in der oszillometrie-basierten nicht-invasiven Kalkulation. ts – Zeitpunkt, wo die Systole endet und der Blutfluss zum Sistieren kommt. Dieser wird basierend auf dem Inflektion-Blutdruck (blood pressure)- iBP bestimmt (gestrichelte Linien). Grüne Fläche markiert die generierte vorwärts gerichtete Pulskurve. Braune Fläche markiert den systolischen ejektionsbedingten Blutfluss. Verwendung mit freundlicher Genehmigung des Elsevier Verlages in Anlehnung an Wassertheurer et al.[21]

3.8 Fragestellungen

Das Bestreben möglichst genau und nicht-invasiv den Zustand des Kreislaufsystems und der arteriellen Gefäßwand abzubilden war schon immer von großem Interesse. Mit der Messung des arteriellen Blutdruckes steht uns ein zuverlässiger und nicht-invasiver Parameter zur Verfügung. Allerdings erlauben solche Parameter wie arterielle Gefäßsteifigkeit und Herzminutenvolumen ein deutlich profunderes Verständnis der Veränderungen im Gefäßsystem und der arteriellen Wandstruktur und können somit die Prognose der kardiovaskulären Ereignisse präzisieren und eine Markerfunktion in den Therapiekonzepten übernehmen. Der Ruf nach einfacher nicht-invasiver Bestimmung dieser Parameter, die ohne größeren personellen, apparativen und finanziellen

Aufwand erfolgen kann, ist dementsprechend groß. Die oszillometrische Messmethode eröffnet solche Möglichkeiten, obwohl sie auf komplexen mathematischen Modellen und Annahmen basiert. Somit könnte sie die tonometrische Methode gerade im klinischen Alltag ersetzen. Ziel der vorliegenden Arbeit war es Validität und Zuverlässigkeit der Methode in unterschiedlichen Kollektiven und unter verschiedenen Umständen zu überprüfen, den blutdruckunabhängigen-Wert der PWV zu untersuchen sowie die Limitationen, die sich daraus ergeben können, näher zu beleuchten.

Im Einzelnen wurden folgende Fragestellengen bearbeitet:

- Sind die verfügbaren Geräte mit der Möglichkeit der PWV- und HZV-Kalkulation in der Lage eine präzise periphere Blutdruckmessung durchzuführen? (Manuskript 1);
- Kann die nicht-invasive oszillometrische Kalkulation der PWV zuverlässige Messergebnisse im Vergleich zur tonometrischen Messung als Goldstandard liefern? Sind diese Messergebnisse präzise und robust unter verschiedenen Untersuchungsbedingungen? (Manuskript 2)
- Ist der neu entwickelte Algorithmus anhand mehrfacher simultaner PWV- und Blutdruckmessungen in der Lage blutdruckunabhängige PWV darzustellen und welchen Stellenwert hat diese blutdruckunabhängige PWV in klinischen Studien? (Manuskripte 3 und 4)
- Wie ist die Zuverlässigkeit der nicht-invasiven oszillometrisch kalkulierten HZV-Werte? (Manuskripte 5 und 6)

4 Eigene Arbeiten

4.1 Übersicht der vorgelegten Manuskripte

1. Reshetnik A, Gohlisch C, Tolle M, Zidek W, Van Der Giet M. Oscillometric assessment of arterial stiffness in everyday clinical practice. Hypertens Res 2017; 40:140-5;
2. Reshetnik A, Gohlisch C, Zidek W, Tölle M, van der Giet M. Validation of the Tel-O-GRAPH, a new oscillometric blood pressure-measuring device, according to the British Hypertension Society protocol. Blood Press Monit. 2016 Oct; 21(5):307-9;
3. Reshetnik A, Tölle M, Eckardt KU, van der Giet M. Would Oscillometry be Able to Solve the Dilemma of Blood Pressure Independent Pulse Wave Velocity - A Novel Approach Based on Long-Term Pulse Wave Analysis? Front Physiol 2020; 11:579852;
4. Reshetnik A, Wrobel D, Wirtz G, Tölle M, Eckardt KU, van der Giet M. True Arterial Stiffness Does Not Change between Dialysis Sessions during 1 Week in Outpatients on Intermitted Hemodialysis, Kidney and Blood Pressure Research 2020; 45(1):51-60;
5. Reshetnik A, Compton F, Scholzel A, Tolle M, Zidek W, Giet MV. Noninvasive oscillometric cardiac output determination in the intensive care unit - comparison with invasive transpulmonary thermodilution. Sci Rep 2017; 7:9997.
6. Reshetnik A, Gjolli J, van der Giet M, Compton F. Non-invasive Oscillometry-Based Estimation of Cardiac Output - Can We Use It in Clinical Practice? Front Physiol 2021; 12:704425.

4.2 Oszillometrische Kalkulation der PWV in der klinischen Praxis

4.2.1 Validierung der peripheren oszillometrischen Blutdruckmessung

Reshetnik A, Gohlisch C, Zidek W, Tölle M, van der Giet M. Validation of the Tel-O-GRAPH, a new oscillometric blood pressure-measuring device, according to the British Hypertension Society protocol. Blood Press Monit. 2016 Oct; 21(5):307-9 (Manuskript 1) https://doi.org/10.1097/MBP.0000000000000195

Wie in der Einleitung beschrieben, ist eine zuverlässige Erfassung der peripheren Blutdruckwerte und der peripheren Druckkurve eine Voraussetzung für die präzise PWV-Kalkulation. In dieser Arbeit validierten wir daher die Präzision der oszillometrischen peripheren Blutdruckmessung mit TEL-O-GRAPH der Firma I.E.M. im Vergleich zur auskultatorischen Messung als Referenzmethode. Sowohl der TEL-O-GRAPH als auch der Mobil-O-GRAPH verfügen über die Berechnungs-Software für den Algorithmus zur PWV- und HZV-Kalkulation, welcher unter Punkt 1.6 beschrieben ist. Hierzu wurden nach strengen Kriterien des Validierungsprotokolls der *British Society of Hypertension* 85

Proband:innen eingeschlossen.[23] Es waren dezidierte Angaben zu der erforderlichen

Anzahl der Proband:innen in unterschiedlichen Blutdruckgruppen zu er- füllen, welche breite Bereiche der systolischen und diastolischen Blutdruckwerte ab- gedeckt haben. In unserer Arbeit deckten wir bei der Validierung den systolischen Be- reich von 70 bis 232 mmHg und den diastolischen Bereich von 40 bis 136 mmHg ab. Die mittlere Differenz zwischen dem Testgerät und der auskultatorischen Messung be- trug -0,2±6,6 mmHg für den systolischen und 0,2±6,6 mmHg für den diastolischen Blutdruck. Wir konnten entsprechend den Protokollvorgaben eine sehr hohe Messgenauigkeit feststellen, so dass von einer präzisen Messung der periphere Blutdruckwerte mit dem TEL-O-

GRAPH auszugehen ist.

Validation of the Tel-O-GRAPH, a new oscillometric blood pressure-measuring device, according to the British Hypertension Society protocol

Alexander Reshetnik, Christopher Gohlisch, Walter Zidek, Markus Tölle and Markus van der Giet

4.5.2 **Oszillometrische PWV-Messung unter Alltagsbedingungen**

Reshetnik A, Gohlisch C, Tolle M, Zidek W, Van Der Giet M. Oscillometric assessment of arterial stiffness in everyday clinical practice. Hypertens Res 2017;40:140-52.2 (Manuskript 2)
https://doi.org/10.1038/hr.2016.115

Diese Arbeit untersucht die Zuverlässigkeit der oszillometrischen PWV-Kalkulation im Vergleich zu der tonometrischen Messung in einem Kollektiv der ambulanten Patient:innen aus der nephrologisch-hypertensiologischen Hochschulambulanz. Zudem beleuchtet sie die Robustheit der oszillometrischen PWV-Messung unter unterschiedlichen Bedingungen: Vergleich der Messergebnisse zwischen sitzender und liegender Position und Vergleich der Messergebnisse, wenn das Gerät durch jemand Unerfahrenen (Proband/in) oder Erfahrenen (Studienpersonal) bedient wird. Für die oszillometrischen Messungen wurde der Tel-O-GRAPH der Firma I.E.M. verwendet und für die tonometrischen Messungen wurde Sphygmocor der Firma AtCor Medical verwendet. Zur Validierung der nicht-invasiven oszillometrischen PWVKalkulation wurden 89 Probanden eingeschlossen. Der Validierungsprozess erfolgte nach den gültigen Kriterien der *ARTERY Society* unter Verwendung vom BlandAltman-Algorhythmus.[25] Bei einem mittleren Bias von 0,49 mit *limits of agreement* von ±1,26 m/s und einem Per- son-Korrelationsindex von 0,86 konnten wir eine präzise PWV-Kalkulation im Vergleich zur tonometrischen Messung als etablierten Goldstandard in der nicht-invasiven PWV-Messung nach Vorgaben der *ARTERY Society* zeigen. Es zeigte sich eine hohe Präzision der Einzelmessungen mit dem Tel-O-GRAPH bei einem ermittelten Intraklassen-Korrelationskoeffizienten von 0,99.

Im weiteren Schritt überprüften wir in einem Teil unseres Studienkollektivs die Variabilität der kalkulierten PWV- Werte abhängig von der Lage der Probanden und der Person, die das Gerät bedient. Wir konnten keine Abweichung der kalkulierten Werte voneinander feststellen.

Zusammenfassend haben wir zum ersten Mal neben dem üblichen

Validierungsprozess umfassend die Robustheit und Präzision der oszillometrischen PWV-Messung untersucht. Unsere Daten zeigten valide und robuste PWV-Messungen bei gleichzeitig sehr einfacher Bedienung. Somit konnte diese Arbeit zeigen, dass die oszillometrische Messung als Methode eine zuverlässige Einschätzung der PWV unter verschiedenen Bedingungen liefert.

Hypertension Research (2016), 1–6

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4.3 Blutdruckunabhängige Bewertung der PWV als Marker der Gefäßsteifigkeit

Reshetnik A, Tölle M, Eckardt KU, van der Giet M. Would Oscillometry be Able to Solve the Dilemma of Blood Pressure Independent Pulse Wave Velocity - A Novel Approach Based on Long-Term Pulse Wave Analysis? Front Physiol 2020; 11:579852 (Manuskript 3)

Es gibt eine physiogische Assoziation zwischen der PWV und dem im Gefäß vorherrschenden arteriellen Blutdruck: Die PWV steigt mit steigendem arteriellen Blutdruck und fällt mit sinkendem Blutdruck.[27] Somit ist eine erhöhte PWV nicht sofort gleichzusetzen mit dem bestehenden arteriellen Gefäßschaden, sondern ist immer in Relation zum dazugehörigen arteriellen Blutdruck zu setzen. Eine auf dem individuellen Niveau ermittelte Relation zwischen PWV und dem arteriellen Blutdruck würde die physiologische Reaktion der PWV auf die Änderung des Blutdruckes von der pathologischen Erhöhung der PWV als Ausdruck der voranschreitenden Arteriosklerose unterscheiden können.

In dieser Arbeit entwickelten wir einen mathematischen Algorithmus, welcher basierend auf der mehrfachen simultanen Messung der PWV und des arteriellen Blutdruckes eine individuelle Relation zwischen PWV und dem Blutdruck mathematisch beschrieb. Hierzu werteten wir die Langzeit-Blutdruck und -PWV-Messungen von 507 Patient: innen aus. Wir haben gesehen, dass es eine lineare Korrelation zwischen dem Blutdruck und den kalkulierten PWV-Werten besteht. Der „statische“ Teil der PWV (*PWVbaseline*) korrelierte mit bekannten Einflussfaktoren wie Alter, Nierenfunktion und Blutdruck. Hingegen konnten wir keine Assoziation der PWV-Reaktion – als eine „dynamische“ PWV-Komponente (*PWVslope*) – auf sich ändernden Blutdruck mit diesen Faktoren feststellen. Zum ersten Mal konnten wir durch eine mathematische Beschreibung die Blutdruckkomponente der PWV heraustrennen. Der Einsatz des oben genannten Algorithmus ermöglicht somit die Darstellung der blutdruckunabhängigen PWV beispielsweise als eine PWV, die auf einen bestimmten Blut- druckwert normiert ist.

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ORIGINAL RESEARCH
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Would Oscillometry be Able to Solve the Dilemma of Blood Pressure Independent Pulse Wave Velocity – A Novel Approach Based on Long-Term Pulse Wave Analysis?

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The utility of pulse wave velocity (PWV) as a surrogate parameter of arterial vessel damage (AVD) beyond the traditional brachial blood pressure (BP) measurement may be questioned as changes in BP are often accompanied by the corresponding changes in PWV. We sought to establish a new way for BP-independent estimation of AVD with PWV. We retrospectively analyzed data from 507 subjects with at least one available 24 h ambulatory BP- and pulse wave analysis, performed with Mobil-O-Graph (I.E.M., Stolberg, Germany). Individual relationship between eaPWV and central systolic BP (cSBP) was analyzed for every 24 h recording. The analysis revealed linear relation between eaPWV and cSBP in all subjects, which is described by equation eaPWV = a∗cSBP + b. We termed "a" as PWVslope and "b" as PWVbaseline. All available demographic parameters and clinical data were correlated with eaPWV, PWVslope and PWVbaseline. 108 subjects had repeated 24 h recordings. Mean age was 60.7 years and 48.7% were female. 92.5% had hypertension, 22.9% were smoker, 20.5% had diabetes mellitus and 29.6% eGFR < 60 ml/min/1,73 m^2. Direct correlation was observed between age, SBP and eaPWV, while diastolic BP (DBP) and eGFR correlated inversely with eaPWV. PWVbaseline correlated directly with age and inversely with DBP, while PWVslope didn't correlate with any inputted parameter. Using simple mathematical approach by plotting eaPWV and cSBP values obtained during ABPM, it is possible to visualize unique course of individual PWV related to BP. Using PWVslope and PWVbaseline as novel parameters could be a feasible way to approach BP-independent PWV, though their clinical relevance should be tested in future studies. Our data underline the importance of BP-independent expression of PWV, when we use it as a clinical surrogate parameter for the vascular damage.

Keywords: aortic pulse wave velocity, vascular damage, non-invasive oscillometric measurement, vascular stiffness, arteriosclerosis

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INTRODUCTION

Aortic stiffness (AS) is considered to be associated with increased cardiovascular risk. Thus, European Society of Hypertension recommends screening for elevated AS in hypertension (Mancia et al., 2013). Pulse wave velocity (PWV) and in particular carotid-femoral PWV (cfPWV) is an established non-invasive standard to assess AS (Van Bortel et al., 2012). It has been shown to be

associated with increased cardiovascular mortality and morbidity independent from established cardiovascular risk factors (Ben-Shlomo et al., 2014). One of the main problems about establishing PWV as an independent surrogate parameter for arterial vessel damage (AVD) is its physiological intrinsic relationship to blood pressure (BP) level. Higher BP results in a stiffer artery and higher PWV, yet without any change in anatomical structure and physiologic properties of the vessel wall. In contrast, AS represents persistent structural changes in arterial vessel walls. It is thus matter of discussion whether increased PWV reflects persistent damage of the arterial wall or is an expression of elevated BP. Establishment of BP-independent PWV would probably better reflect real vessel damage.

Emerging non-invasive oscillometric devices use mathematical approaches and are able to deliver an estimated aortic PWV (eaPWV) based on pulse wave analysis and wave separation analysis, whereby major clinical determinants are age, central systolic BP (cSBP) of the patient and aortic characteristic impedance (Wassertheurer et al., 2008). Validation studies have shown this eaPWV be in good correlation with non-invasively determined cfPWV and invasively determined aortic PWV (Weber et al., 2015; Reshetnik et al., 2017). eaPWV role as a predictor of cardiovascular and all-cause mortality has been shown recently (Sarafidis et al., 2017). Such devices allow easy and quick calculation of eaPWV (Reshetnik et al., 2017), which can be repeated plenty of times under varying BP and patient position. In the present retrospective study we sought to establish new BP-independent PWV using mathematic analysis of the repeated eaPWV measurements during 24 h ambulatory BP and pulse wave monitoring. We hypothesized that establishing of BP-independent PWV would be first step on the way to demonstrate real vascular damage.

MATERIALS AND METHODS

All included subjects received long-term (24 h) ambulatory BP and pulse wave monitoring as a part of clinical routine in our Department of Nephrology at Campus Benjamin Franklin, Charité University Berlin. Charité University Berlin review board approved the study (EA4/112/18). No informed consent was required for the study purpose. We screened all available recordings from our database, which comprised time period from August 2012 to February 2018, and included all subjects with at least one representative 24 h recording of peripheral BP, central BP and PWV. All available demographic and clinical data were collected. Smoker status was missing in 50%, exact protein-creatinine ratio in 64% and albumin-creatinine ratio in 65% of study subjects. Other demographic and clinical parameters were completely present in all subjects. We could analyze 648 long-term BP and pulse wave analysis recordings from 507 patients with 43,567 single measurements. Available demographic and clinical data were summarized and analyzed. For the purpose of the study "hypertension" was defined, when the diagnosis "hypertension" has been mentioned in the medical record, subject had antihypertensive medication or the BP level was higher than 130/80 mmHg in the ambulatory BP monitoring. Due to retrospective study design the diagnosis "hyperliproteinemia" and smoking status were based on data from the medical record. All implemented procedures were in accordance with institutional guidelines.

BP-Monitoring and Pulse Wave Analysis

All recordings were performed with Mobil-O-Graph (I.E.M., Stolberg, Germany) and data analysis was performed with HMS Client Software, Version 5.1. The Mobil-O-Graph is a non-invasive oscillometric device, which combines ambulatory blood pressure monitoring with long-term pulse wave analysis (**Supplementary Figure 1**). The cuff was applied at the left or right upper arm after the circumference of the arm was measured and appropriate cuff size was chosen (size 1: 24–34 cm or size 2: 32–42 cm). First, brachial SBP and diastolic BP (DBP) were obtained. Thereafter, the cuff was again inflated maintaining the diastolic pressure level for 10 s for assessment of the pulse waveform using high fidelity pressure sensor. The mathematic method for pulse wave analysis in Mobil-O-Graph is based on the algorithm used in ARCSolver (Wassertheurer et al., 2008). Using generalized transfer functions (Fourier analysis and de-compensation into wave harmonics) aortic pressure waveform can be modulated. Central flow curve can be calculated by the means of an adopted, multi-dimensional Windkessel model. The time-lag between pressure and flow curve is generally referred to as "characteristic impedance (Zc)," in which the flow curve follows the pressure curve. Zc, together with the input variables of central systolic and diastolic blood pressure and age allows the device the estimation of aortic PWV (Wassertheurer et al., 2010). Single recordings were done every 20 min during the day (0600–2,200 h) and every 30 min during the night (2,200–0600 h). A 24 h recording with $\geq$80% valid single measurements of SBP, DBP, central BP and PWV was considered representative. For each parameter of a single 24 h recording, mean value of all valid single measurements was obtained and included in the statistical analysis.

Correlation Between Central SBP and eaPWV

In order to assess the course of eaPWV depending on change in BP, we used scatter plots to visualize a possible correlation. All single measurements of cSBP and corresponding eaPWV from each of the 648 24-h readings were included in separate scatter plots. The relationship between cSBP and eaPWV was linear and could be described with following equation: eaPWV = a*cSBP + b. We termed factor "a" as "PWVslope" and factor "b" as "PWVbaseline." **Figure 1** presents scatter plots with appropriate equations for three individuals from different age ranges.

Correlation Between Available Demographic and Clinical Data and eaPWV, PWVslope, and PWVbaseline

We tested the impact of each available demographic and clinical parameter on eaPWV, PWVslope, and PWVbaseline using

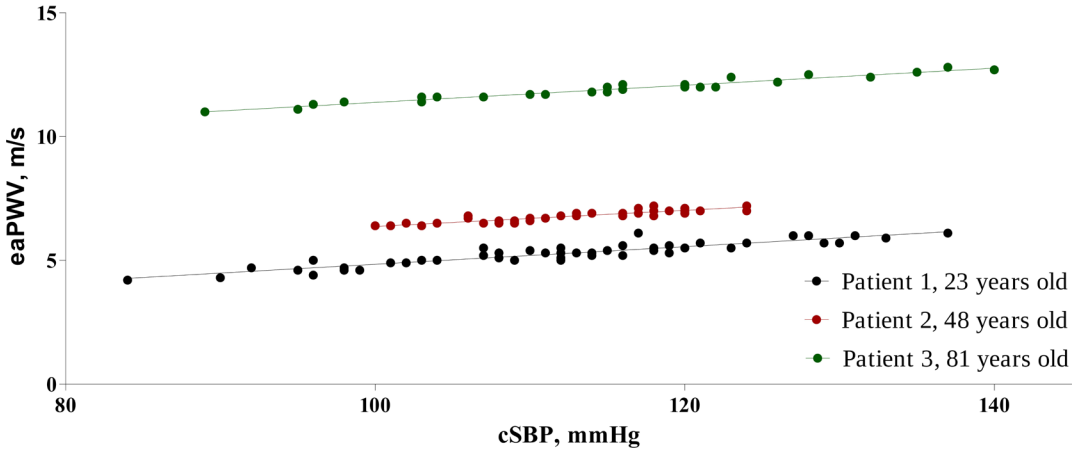

FIGURE 1 | Correlation between central blood pressure and pulse wave velocity in individual patients in three different age ranges; A < 25 years; B- 40–50 years; C > 75 years.

single regression analysis. Those with significant result in single regression analysis were included in multiple regression analysis.

Repeated Measurements

For a part of the study collective repeated measurements were recorded. One hundred and eight patients had two recordings. Twenty five patients had three recordings. Five subjects had four recordings and one patient had five recordings. Data from at least one follow up recording were compared to the initial measurement, respectively. The change of eaPWV, PWVslope, and PWVbaseline between recordings was assessed and possible factors impacting this change were evaluated.

Statistics

This study is retrospective. For each continuous variable mean and standard deviation were calculated. For each dichotomous variable number of affected subjects and the ratio related to the whole study collective in per cent were determined. Normal distribution of parameters was proofed with Kolmogorov-Smirnov-Test. In order to compare parameters from repeated measurements paired *T*-Test was used in case of proven normal distribution and Wilcoxon paired test in case of non-normal distribution. A multiple regression approach was used to determine relationship between available parameters. Two-sided *p*-values lower than 0.05 were considered as statistically significant. Statistic analysis was performed with SPSS Statistics 23.0 (IBM, New York, United States).

RESULTS

Five hundred and seven patients were included in the analysis. Approximately half of the study collective was female (48.7%). The mean age was 60.7 [18–92] years and the mean body-mass index was 27.4 kg/m^2. 92.5% of patients had established diagnosis of hypertension, 33.7% of hyperlipoproteinemia and 22.9% were smoker. Approximately a fifth had DM (20.5%) and 29.6% have had chronic kidney disease with an estimated glomerular flow rate (eGFR) below 60 ml/min/1,73 m^2 according to creatinine-based CKD-EPI equation with the mean protein/creatinine-ratio of 363 ± 1,025 mg/g and the mean albumin/creatinine-ratio of 248 ± 792 mg/g. The mean brachial SBP was 133 mmHg and DBP 80 mmHg with the mean heart rate of 69.5 beats/min. The mean cSBP was 121.6 ± 13.4 mmHg and the mean eaPWV was 9.2 ± 2.2 m/s. The mean PWVslope was 0.035 with the range from 0.026 to 0.050 m/s*mmHg and the mean PWVbaseline was 4.9 with the range from −0.21 to 11.2 m/s. Further details regarding demographic and clinical parameters as well as details about medication can be found in **Table 1**.

eaPWV and PWVbaseline increased with rising BP and age (**Figures 2**, **3**). PWVslope increased numerically with increasing age und SBP. This association was without statistical significance (**Table 2**). eaPWV and PWVbaseline were significantly higher in women compared to men (9.5 ± 2.2 vs. 8.9 ± 2.2, $p = 0.001$; and 5.2 ± 2.2 vs. 4.6 ± 2.1 m/s; $p < 0.001$). No differences in PWVslope were observed between female and male subjects.

In the single regression analysis we observed statistically significant correlation between eaPWV and age, SBP, DBP, mean BP, PP, heart rate, sex, DM, hyperlipoproteinemia, eGFR, history of hypertension, coronary artery disease, myocardial infarction, stroke, peripheral arterial disease, medication with ACE-Inhibitor/Angiotensin receptor blocker, calcium channel blocker, thiacids, beta blockers and central alpha-agonists. Multiple regression analysis revealed independent significant influence of age, SBP, DBP, eGFR and history of myocardial infarction on the eaPWV. Increased age and SBP were associated with increasing in eaPWV, while decreased DBP and eGFR were associated with the rise in eaPWV. Study patients with history of myocardial infarction had higher eaPWV than patients without previous myocardial infarction. Using the same demographic and clinical parameters inputted in single and multiple regression analyses we showed independent influence of DBP and age on PWVbaseline (**Table 3**). In contrast, we observed

TABLE 1 | Main characteristics and medication of the study collective (n = 507).

Sex	
Male, n(%)	260 (51.3)
Female, n(%)	247 (48.7)
Age, years	60.7 ± 16.3
Body mass index, kg/m^2	27.4 ± 5.3
Hypertension, n (%)	469 (92.5)
Hyperlipoproteinemia, n (%)	171 (33.7)
Smoker, n (%)*	116 (22.9)
Previous stroke, n (%)	26 (5.1)
Coronary heart disease, n (%)	123 (24.3)
Previous myocardial infarction, n (%)	36 (7.1)
Peripheral vascular disease, n (%)	22 (4.3)
Diabetes mellitus, n (%)	104 (20.5)
Chronic kidney disease (eGFR < 60 ml/min/1.73 qm CKD-EPI-Equation), n (%)	150 (29.6)
eGFR, ml/min/1.73 qm	70.4 ± 26.0
Protein/Creatinin-Ratio, mg/g#	363 ± 1025
Albumin/Creatinin-Ratio, mg/g$	248 ± 792
ABPM brachial systolic blood pressure, mmHg	133.0 ± 14.8
ABPM brachial diastolic blood pressure, mmHg	80.0 ± 10.7
ABPM mean blood pressure, mmHg	101.2 ± 11.3
ABPM pulse pressure, mmHg	52.9 ± 11.3
ABPM heart rate, beats/min	69.5 ± 10.3
ABPM central systolic blood pressure, mmHg	121.6 ± 13.4
ABPM central diastolic blood pressure, mmHg	81.7 ± 10.9
ABPM estimated aortic pulse wave velocity, m/s	9.2 ± 2.2
ABPM PWVslope, m/s*mmHg	0.035 ± 0.003
ABPM PWVbaseline, m/s	4.9 ± 2.2
Medication	
Antiplatelet therapy, n(%)	113 (22.3)
Oral anticoagulation, n(%)	30 (5.9)
Cholesterol reducing therapy, n(%)	180 (35.5)
Statins, n (%)	168 (33.1)
RAAS blocker, n(%)	355 (70)
Calcium-channel blocker, n(%)	275 (54.2)
Aldosterone antagonists, n (%)	37 (7.3)
Thiacid diuretics, n (%)	151 (29.8)
Loop diuretics, n (%)	80 (15.8)
Betareceptor-blocker, n (%)	266 (52.5)
Alphareceptor-blocker, n(%)	63 (12.4)
Central alpha-agonists, n (%)	67 (13.2)
Direct vasodilators, n(%)	15 (3)

Available in 253 subjects; #available in 181 subjects; $available in 175 subjects.

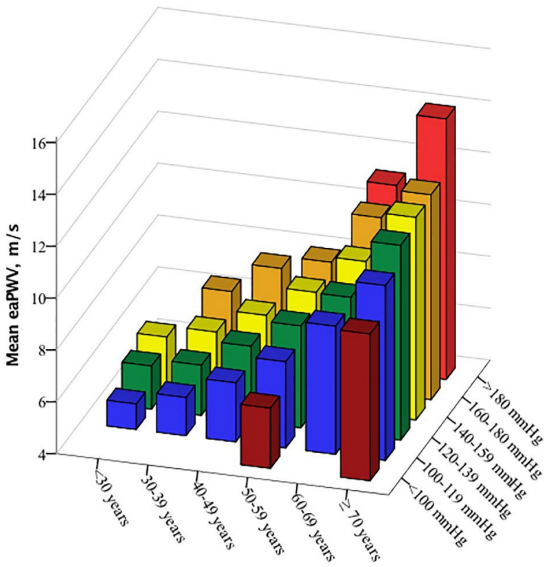

FIGURE 2 | Mean estimated aortic pulse wave velocity (eaPWV) values according to age and blood pressure categories.

no statistically significant correlation between any available demographic and clinical parameter and PWVslope, although it increased numerically with increasing age and SBP level.

One hundred and eight patients have had repeated recordings. The mean between-recording time was 4.5 ± 5.8 months. The mean age of these patients was 60 years and the BMI was 27.8 kg/m^2. 42% were female. The mean eGFR was 72.1 ml/min/1.73 m^2 according to creatinine-based CKD-EPI equation with ca. 29% of the patients having chronic kidney disease with an eGFR < 60 ml/min/1.73 m^2. The mean brachial BP was 134.9/80.1 mmHg with the mean heart rate of 67.3 beats/min. The mean eaPWV was 9.2 m/s with the mean PWVslope of 0.035 and PWVbaseline of 4.9 m/s. **Supplementary Table 1** denotes further information about the subgroup of patients with repeated recordings.

eaPWV was adjusted to the SBP level of 120 mmHg. We observed statistically significant difference in eaPWV$_{120}$, while SBP, DBP, PP and heart rate didn't change significantly between recordings (**Table 4**). We then investigated change in eaPWV$_{120}$ (delta-eaPWV$_{120}$) across the range of change in SBP, DBP, heart rate and PP as well as change in eaPWV$_{120}$ related to absolute level of initial SBP, DBP, heart rate and eaPWV$_{120}$. Increase in DBP between the measurements was statistically significant associated with decrease in eaPWV$_{120}$ (Spearman $R^2 = 0.048$, $p < 0.01$). Higher absolute value of initial PP was statistically significant associated with increase in follow-up eaPWV$_{120}$ (Spearman $R^2 = 0.038$, $p < 0.05$). We did not observe any statistically significant correlation between the change in SBP, heart rate and PP, absolute level of initial SBP, DBP, heart rate, eaPWV120 and change in eaPWV120 between the measurements (**Supplementary Figures 2, 3**).

DISCUSSION

In our study analysis of the relationship between eaPWV and cSBP based on multiple single measurements from simultaneous 24 h BP monitoring and pulse wave analysis was essential to describe individual relationship between PWV and BP.

In 2010, a landmark study was published by Arterial Stiffness' Collaboration, where reference and normal values for PWV (measured as cfPWV) were established. The authors observed a linear relationship between BP and PWV and quadratic

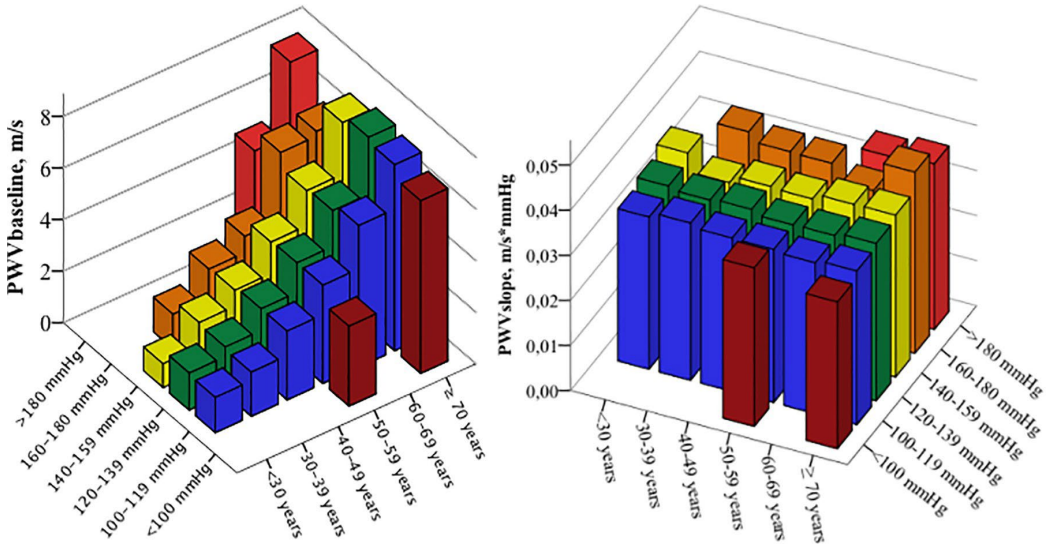

FIGURE 3 | Mean pulse wave velocity baseline (PWVbaseline) values (right graph) and PWVslope (left graph) according to the age and blood pressure categories.

TABLE 2 | Distribution of estimated aortic pulse wave velocity (eaPWV), PWVslope, and PWVbaseline in the study population according to age and blood pressure category.

Age category, years	systolic blood pressure category, mmHg					
	<100	100–119	120–139	140–159	160–180	>180
eaPWV as mean ± standard deviation, m/s						
<30		5.0 ± 0.1	5.7 ± 0.8	6.0 ± 0.2		
30–39		5.5 ± 0.2	5.9 ± 0.2	6.4 ± 0.2	7.2*	
40–49		6.3 ± 0.3	6.9 ± 0.4	7.3 ± 0.4	8.3 ± 0.2	
50–59	6.3*	7.3 ± 0.4	7.9 ± 0.4	8.4 ± 0.4	8.8 ± 0.2	
60–69		8.9 ± 0.5	9.2 ± 0.5	9.9 ± 0.6	10.8 ± 0.4	11.2*
≥70	9.7*	10.7 ± 0.9	11.5 ± 1.0	11.8 ± 0.8	11.9 ± 1.3	14.1*
PWVslope as mean ± standard deviation						
< 30		0.034 ± 0.002	0.035 ± 0.004	0.037 ± 0.005		
30–39		0.035 ± 0.003	0.035 ± 0.002	0.033 ± 0.004	0.039*	
40–49		0.034 ± 0.003	0.035 ± 0.003	0.034 ± 0.003	0.037 ± 0.002	
50–59	0.035*	0.034 ± 0.001	0.034 ± 0.002	0.035 ± 0.002	0.037 ± 0.003	
60–69		0.033 ± 0.001	0.034 ± 0.003	0.035 ± 0.003	0.034 ± 0.004	0.036*
≥70	0.033*	0.034 ± 0.002	0.035 ± 0.002	0.036 ± 0.004	0.040 ± 0.007	0.037*
PWVbaseline as mean ± standard deviation, m/s						
<30		1.4 ± 0.3	1.4 ± 0.9	0.9 ± 0.6		
30–39		1.7 ± 0.2	1.8 ± 0.3	1.9 ± 0.6	1.3*	
40–49		2.7 ± 0.4	2.7 ± 0.4	2.5 ± 0.6	2.5 ± 0.2	
50–59	3.1*	3.8 ± 0.5	3.8 ± 0.5	3.7 ± 0.5	3.1 ± 0.8	
60–69		5.5 ± 0.5	5.2 ± 0.6	5.1 ± 0.5	5.7 ± 1.0	4.9*
≥ 70	6.7*	7.2 ± 0.9	7.4 ± 1.0	7.1 ± 1.0	5.9 ± 0.8	7.7*

Standard deviation not available.

relationship between PWV and age (Reference Values for Arterial Stiffness' Collaboration, 2010). The strength of the study was that all PWV values were measured. However, only few single measurements per patient were obtained and detection of individual relationship between PWV values and corresponding BP level was not possible. Analysis of over 11,000 patients allowed to draw general conclusions about PWV course with change in age and BP in whole study collective. However, individual impact of BP-level on PWV in single patients could not be determined. This point represents a current dilemma in interpreting PWV as an additional cardiovascular risk marker.

TABLE 3 | Significant influence parameters on estimated aortic pulse wave velocity (eaPWV) and PWVbaseline in multiple regression analysis.

	Dependent parameter: eaPWV		
Independent parameter	Regression coefficient	R^2-value	*p*-value
Age	0.13	0.86	<0.001
Systolic blood pressure	0.03	0.05	0.007
eGFR	0.002	0.0007	0.02
Myocardial infarction	0.21	0.0006	0.02
Dependent parameter: PWVbaseline			
Age	0.12	0.88	<0.001
Diastolic blood pressure	-0.018	0.007	<0.001

TABLE 4 | Comparison between initial and follow-up recording (*n* = 108).

	Initial recording	Follow up recording	*p*-value
Systolic blood pressure, mmHg	134.4 ± 14.3	135.6 ± 15.6	0.35#
Diastolic blood pressure, mmHg	80.0 ± 10.7	80.5 ± 11.6	0.59#
Pulse pressure, mmHg	54.4 ± 11.3	55.2 ± 11.3	0.34*
Heart rate, beats/min	67.8 ± 9.7	67.4 ± 10.5	0.57#
PWV_{120}, m/s	8.9 ± 2.1	9.0 ± 2.1	<0.001#
PWVslope	0.0347 ± 0.00297	0.03495 ± 0.00324	0.37#
PWVbaseline, m/s	4.79 ± 2.11	4.81 ± 2.08	0.56#

*$eaPWV_{120}$- estimated aortic pulse wave velocity for the systolic blood pressure of 120 mmHg according following equation: PWV_{120} = 120 mmHg*PWVslope + PWVbaseline; #paired t-test; *paired Wilcoxon-test.*

In our study, we used a device, which is able to estimate aortic PWV using oscillometric approach. Currently required parameters for the eaPWV calculation are age, measured brachial BP and data from pulse wave analysis (Wassertheurer et al., 2008). Approaching the dilemma of the BP-independent PWV we analyzed individual relationship between eaPWV and SBP based on the data coming from ABPM. Based on our findings the relationship can be described with an individual linear equation. According to determined equation PWVslope could represent individual reaction of PWV to an increase in BP, while PWVbaseline could probably reflect baseline status of the arterial vessels. Though we observed increasing PWVslope values with increasing age and BP, this association was not statistically significant. Additionally, we did not show association between PWVslope and any other clinical parameter. Thus, the clinical relevance of the PWVslope as a separate parameter is still to be proofed. A possible explanation could be a high impact of age in the determination of the eaPWV in the algorithm. Recently, the clinical relevance of the eaPWV beyond the impact of age and SBP has been questioned (Schwartz et al., 2019). Despite the known shot-cuts of the oszillometric PWV estimation this method is valid, feasible and easy to apply in the clinical practice. It is able to capture multiple PWV changes with corresponding changes in BP. Previously to the era of oszillometric PWV measurement multiple PWV recordings were sophisticated and such relationships as obtained in our study could not be established. Based on the mathematical analysis of derived data we were able to reach a "standardization" of the PWV using novel parameters PWVbaseline und PWVslope and in such a way to separate the BP-impact on it. The standardization to a particular BP level is also useful to compare PWV between the patients but also to compare PWV values in the same individual over a time course as we have done in a part of our study collective with available repeated measurements.

To our knowledge, this is the first time serial BP and corresponding PWV changes have been reported. Greve et al. (2016) assessed the performance of estimated PWV, calculated from age, mean arterial pressure, using equations published by Arterial Stiffness' Collaboration. Though estimated PWV performed well in healthy subjects, it did not add any predictive value in patients with diabetes mellitus or on antihypertensive drugs. As mentioned above, this might be due to high individual variability, which cannot be addressed by using equations coming from another study collective (Greve et al., 2017). Lim et al. (2015) observed intraindividually increasing cfPWV with increasing mean BP in healthy subjects. However, they did not describe individual relationship between cfPWV and BP in their study collective.

The relation between cSBP and eaPWV can readily be translated to the relation between obtained brachial SBP and eaPWV, as we observed well known strong correlation between SBP and cSBP in our data (Pearson correlation coefficient 0.96). We choose cSBP as an independent variable based on the original publication of the method, where authors described cSBP as one of the major determinants needed for the calculation of the eaPWV (Hametner et al., 2013).

We observed well-known association between eaPWV with age and SBP. As in the study published 2010 by Arterial Stiffness' Collaboration (Reference Values for Arterial Stiffness' Collaboration, 2010) the correlation between eaPWV and SBP was linear and the correlation between eaPWV and age was better explained by quadratic equation. Furthermore, we saw significant increase in eaPWV with a decreasing kidney function and decreasing DBP. The influence of age, SBP and chronic kidney disease on AS and PWV is well known and could be demonstrated in previous studies (Tolle et al., 2015). The impact of DM on AS (De Angelis et al., 2004) and PWV (Cardoso and Salles, 2016) as its surrogate parameter is also well known. However, we could not show significant independent influence of DM on eaPWV in our collective. One possible explanation could be a relatively low prevalence of DM in our study collective as only circa 20% of patients had DM, which was non-insulin-dependent in the majority of cases. One can speculate that changes in vascular structure might have been only moderate. Furthermore, the impact of BP, age and kidney function had statistically higher impact on eaPWV compared to DM in our analysis. Higher prevalence of isolated systolic hypertension in subjects with DM has been shown previously (Os et al., 2006). Observed increase in eaPWV with lower DBP in our study could thus been interpreted as an indirect link between DM and eaPWV. Supporting this hypothesis, diabetics showed significantly lower DBP compared to non-diabetics in our collective.

Recent data pointed out that changes in heart rate could also contribute to significant changes in PWV (Tan et al., 2016) and adjustment of PWV to a heart rate would also be necessary. We did not see any significant independent effect of heart rate on PWV in our data.

Many studies demonstrated severe differences in PWV between female and male subjects (DuPont et al., 2019). We observed higher eaPWV120 in women. However, we did not show any independent effect of sex on PWV in multiple regression analysis. Additionally, women were significantly older (63.2 ± 15.9 vs. 58 16.4 years) than men in our study collective, which is probably the major reason for higher eaPWV.

Many studies demonstrated significant influence of smoking on AS (Doonan et al., 2010). We did not observe any significant independent effect of smoking on eaPWV. This result is, however, limited as data on smoking status were available in only 50% of the study subjects due to retrospective study design.

Comparison of repeated ABPM readings, which were performed on average 4.5 months apart, revealed statistically significant change in eaPWV120. However, the mean difference of 0.1 m/s is not relevant from the clinical point of view. We observed no clinically relevant impact of any hemodynamic parameter on eaPWV120, no matter whether the amount of difference between initial and follow up recording or absolute value of the initial recording were considered (**Supplementary Figures 2, 3**), although single variables (e.g., PP) indeed showed statistically significant impact on change in eaPWV120.

Assuming that remodeling of vessel wall is a very slow process, the period of 4.5 months is likely to be too short to reveal a real change in the architecture of the vessel wall explaining why the individual BP-adjusted eaPWV did not change in our study. Thus far, published studies compared initial and follow up PWV-values without individual BP-adjustment. For instance, 2011 published study by Ignace et al. compared cfPWV before and after kidney transplantation (Ignace et al., 2011). Though cfPWV was adjusted to the reduction in mean BP, individual adjustment to the particular level of BP is missing and individual degree of BP-impact on cfPWV cannot be obtained. Whether observed reduction in cfPWV of mean 0.5 m/s 3 months after transplantation in patients still on comparably high level of immunosuppression really reflects improvement in AS is debatable.

CONCLUSION

In conclusion, using simple mathematical approach by plotting eaPWV and cSBP values obtained during ABPM, it is possible to visualize unique course of individual PWV related to BP. Using PWVslope and PWVbaseline as novel parameters could be a feasible way to approach BP-independent PWV, though clinical relevance should be tested in future studies. Our data underline the importance of BP-independent expression of PWV, when we use it as a clinical surrogate parameter for the vascular damage.

We acknowledge several limitations of our study: Attributable to the oscillometric method, which we used, obtained PWV-values were not measured but estimated based on pulse wave analysis and utilization of age and central BP. BP-adjustment of eaPWV using obtained individual PWVslope could thus represent the extent of arterial damage. However, the clinical potential of the obtained novel parameters PWVbaseline and PWVslope is not yet established and the next necessary step would be to correlate these parameters to relevant clinical endpoints.

Worth mentioning is the fact that pulse wave analysis is done in the brachial artery, which is a muscular artery, used as a surrogate for PWV in the aorta, which is an elastic vessel. As the anatomy of elastic and muscular arteries is different, they could stiffer in distinct manner (Shirwany and Zou, 2010).

Retrospective design of the study precludes inferences about causal relationships. All available demographic and clinical parameters were included, however, unidentified confounders cannot be ruled out. For instance, no information about the cuff position was available, which is known to be potential influence factor on the PWV. The study population was limited to a specific group of non-severe ill subjects, with a majority having hypertension, mild kidney disease and obesity. Thus, further studies are needed in other populations to confirm and generalize our findings. Low prevalence of diabetes mellitus and advanced kidney disease might have diminished the known effect of these influence factors on PWV. Small part of the subjects with repeated measurements and short follow up period could be a reason for clinically non-relevant change in eaPWV120, obtained in the study.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethic Review Board Charité University Berlin. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

AR and MG: conceptualization. AR: methodology, formal analysis, writing—original draft preparation. K-UE and MG: writing—review and editing. MG: project administration. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphys.2020.579852/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

4.4 Kurzfristige Veränderung der blutdruckunabhängigen PWV bei Hämodialyse-Patient:innen

Reshetnik A, Wrobel D, Wirtz G, Tölle M, Eckardt KU, van der Giet M. True Arterial Stiffness Does Not Change between Dialysis Sessions during 1 Week in Outpatients on Intermitted Hemodialysis, Kidney and Blood Pressure Research 2020;45(1):51-60 (Manuskript 4)

Wie bereits weiter oben erwähnt, kann die blutdrucknormierte PWV einen geeigneteren Parameter für die Erfassung des wahren Gefäßschadens darstellen. In dieser Arbeit schauten wir uns die Veränderung der konventionellen PWV und die Veränderung der blutdrucknormierten PWV im Verlauf einer Woche in einem Kollektiv von ambulanten Hämodialyse-Patient: innen an. Dieses Kollektiv ist besonders gut geeignet, da die Hämodialyse-Patient: innen eine relevante Arteriosklerose aufweisen und gleichzeitig die Blutdruckwerte von Dialysesitzung zu Dialysesitzung durch den variierenden Volu- menstatus und variierende Medikamentenspiegel schwanken. Insgesamt wurden 54 Hämodialyse-Patient: innen eingeschlossen. Für jede/n wurden beginnend ab Dialyse- start und in 15minütigen Abständen bis zum Ende der Dialysesitzung mit dem Mobil- O-GRAPH der Firma I.E.M der Blutdruck und PWV ermittelt. Anhand dieser Werte wurde, wie oben beschrieben, die individuelle Korrelation zwischen der PWV und dem Blutdruck ermittelt. Als eine blutdrucknormierte PWV wurde dann PWV_{120} (PWV normiert auf den zentralsystolischen Blutdruck von 120 mmHg) verwendet. Wir konnten zeigen, dass während die konventionell gemessene PWV zwischen den einzelnen Hämodialysesitzungen schwankte, die PWV_{120} stabil blieb. Unsere Daten deuten darauf hin, dass die PWV-Schwankungen in diesem Patientenkollektiv die intrinsische Blutdruckabhängigkeit widerspiegeln, während die blutdrucknormierte PWV den wahren Gefäßstatus widerspiegelt und erwartungsgemäß stabil bleibt. Die Ergebnisse unterstreichen die Notwendigkeit der individuellen Blutdruck-Adjustierung bei der Bewertung der PWV in klinischen Studien und der klinischen Routine.

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Research Article

True Arterial Stiffness Does Not Change between Dialysis Sessions during 1 Week in Outpatients on Intermitted Hemodialysis

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Keywords
Arterial stiffness · Pulse wave velocity · Blood pressure dependence · Dialysis · End-stage renal disease

Abstract
Introduction: End-stage renal disease (ESRD) is associated with exponentially elevated cardiovascular mortality. Arterial stiffness (AS) – usually expressed with pulse wave velocity (PWV) – is an established independent predictor of cardiovascular risk beyond the traditional risk factors. Higher PWV values are frequently observed in patients with ESRD. Due to the intrinsic physiologic relationship between PWV and prevailing arterial pressure, PWV can change without relevant changes in the arterial wall structure, and thus an individual pressure-independent expression of PWV is essential. ***Methods:*** The study is a single-center observational study. Repeated measurements of blood pressure (BP) and pulse wave analysis were performed during each dialysis session of 1 week. Aortic PWV was then adjusted to 120 mm Hg central systolic BP (PWV120) based on individually determined relationship. PWV120 values were compared between single sessions. Calculation of the PWV120 was performed retrospectively. ***Results:*** Fifty-four subjects were included, 61.1% of whom were male. The median age was 75.5 years, and median dialysis vintage was 33.1 months. Mean systolic/diastolic BP was 121.4/70.5 mm Hg, and the median heart rate was 64.6 beats/min. Mean PWV was 10.9 m/s, and mean PWV120 was 11.3 m/s. PWV120 did not change across single dialysis session during 1 week, while systolic, diastolic BP, PWV, and ultrafiltration volume differed

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significantly. ***Discussion/Conclusions:*** Our data suggest that true AS does not change in the short-term course in dialysis patients. The observed changes in PWV are rather associated with BP change due to intrinsic pressure dependence. Our analytical approach represents a novel method for this purpose, which is easy in performance and also applicable for large interventional trials and clinical practice.

Introduction

Arterial stiffness (AS) reflects the damage of the arterial vessel wall [1]. Its association with increased cardiovascular morbidity and mortality has been shown in different populations [2, 3]. Chronic kidney disease (CKD) has been associated with increased AS [4]. The cardiovascular disease burden is disproportionally high in patients with CKD and particularly in end-stage renal disease [5]. Thus, assessment of the AS and developing of the treatment strategies to decrease AS in these patients are of significant clinical relevance. However, one of the relevant caveats about AS, which is usually characterized by pulse wave velocity (PWV), is its intrinsic dependence from prevalent blood pressure (BP) [6–8]. As a consequence, change in the BP causes a change in PWV without any change in the arterial wall structure. Specifically, cyclic changes in BP and hydration status in hemodialysis patients could alter PWV values. Whether "true" PWV reflecting the real change in arterial wall structure changes remains unknown.

Available modern oscillometric devices can perform pulse wave analysis and reliably calculate aortic PWV in the clinical routine, which is proofed to be valid compared to tonometric and invasive measurements [9, 10]. Multiple PWV measurements can easily be performed using this technique. Based on the analysis of the multiple PWV measurements in a single patient, we developed a method to obtain an individual BP-independent PWV, which would better reflect the true change in the arterial wall structure. We hypothesized that individual BP-independent PWV would not alter between dialysis sessions in 1 week.

Materials and Methods

Study Collective

Adult persons (age ≥18 years) on stable hemodialysis or hemodiafiltration regimen were recruited from the outpatient dialysis unit in Kamen, Germany, from March to April 2017. Exclusion criteria were pregnancy, arterial stenosis proximal or at the measurement site, former dialysis fistula at the measurement site, active infection, arrhythmias making peripheral oscillometric BP measurement, and/or pulse wave analysis impossible. All included subjects performed written informed consent. The Ethical Committee of the medical association Westphalia-Lippe and the University of Muenster, Germany, approved the study. All dialysis procedures were performed with Surdial X dialysis machines (Nipro, Osaka, Japan). Clinical data, including comorbidities, concurrent medication, and laboratory data, were obtained from the electronic and paper-based patient records. We considered patients having hypertension when they have had already a previously established diagnosis of hypertension or have been taking antihypertensive drugs. We considered patients having hyperlipoproteinemia when they have had a previously established diagnosis of hyperlipoproteinemia or have been taking cholesterol-lowering drugs. The study schematic is shown in Figure 1.

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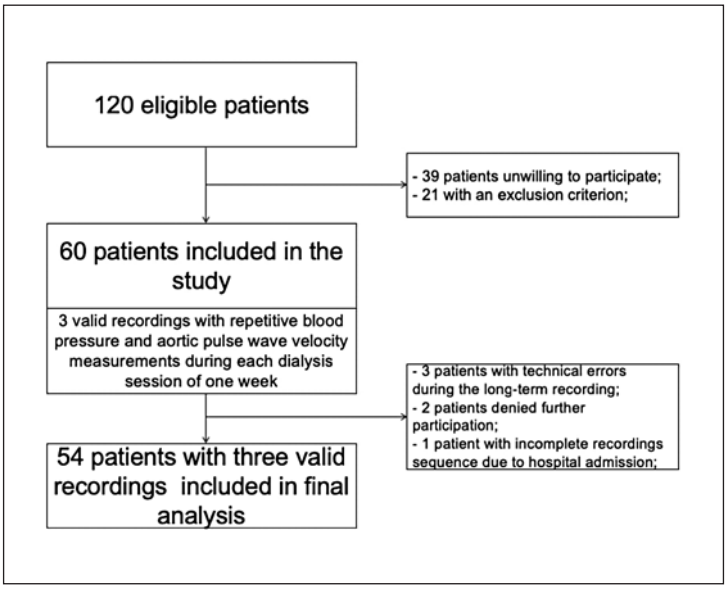

Fig. 1. Study schematic. BP, blood pressure; PWV, pulse wave velocity;

Hemodynamic Measurements

All BP and pulse wave analysis measurements were performed with Mobil-O-Graph-24 h-pulse wave analysis Monitor (I.E.M. GmbH, Stolberg, Germany), and data analysis was performed with HMS Client Software, version 5.2. Mobil-O-Graph uses ARCSolver method to calculate aortic PWV [11]. Upper arm circumference was measured before the measurement to apply appropriate cuff (Size S: 20–24 cm, M: 25–32 cm, L: 33–38 cm, XL: 39–55 cm). The recordings were performed at the non-fistula arm. The first measurement was started when a patient has taken a comfortable position in the dialysis chair. The device repeated the measurement automatically every 15 min until the dialysis session ended. Additional on-demand measurements were started manually. Single point measurements of the aortic PWV and central systolic BP were plotted together, and individual change in aortic PWV related to the change in central systolic BP was visualized (online suppl. Figure, see www.karger.com/doi/10.1159/000504138). A linear equation was generated based on the point cloud. The point of interception with Y-axis was defined as PWVbaseline and the slope of the line as PWVslope. Consequently, PWV at 120 mm Hg central systolic BP (PWV120) was calculated as PWVslope × 120+ PWVbaseline. Calculation of the PWVbaseline and PWVslope has been performed retrospectively.

Statistics

SPSS version 25.0 (IBM, Armonk, NY, USA) was used for the statistical analysis. Normally distributed parameters are reported as mean and SD. Nonnormally distributed parameters are reported as median and interquartile range. Definition of normal distribution was based on the results of the Kolmogorov-Smirnov test. All categorical data were presented as the total number and percentage of the total study population. To describe the hemodynamic values of the single dialysis days in a week, Friedman-test and Friedmans ANOVA post hoc test were used. Hemoglobin A1c values were available for 36 patients. Two-sided p value below 0.05 was considered as statistically significant.

Table 1. Baseline characteristics of the study collective

Age, years	75.5 (64–85)
Gender, men	33 (61.1)
Height, mean (SD), cm	170.8 (9.3)
Dry weight, mean (SD), kg	79.8 (19.8)
Smokers	12 (22.2)
Presence of diabetes	33 (61.1)
History of hypertension	52 (96.3)
Hyperlipoproteinemia	35 (64.8)
History of coronary heart disease	27 (50.0)
History of stroke	11 (20.4)
History of peripheral artery disease	26 (48.1)
History of myocardial infarction	11 (20.4)
History of atrial fibrillation	16 (29.6)
Dialysis vintage, months	33.1 (4.7–61.5)
Dialysis catheter patients	12 (22.2)
Effective time of dialysis per session, h*	4.25 (4.00–4.50)
sp Kt/V, mean (SD) (–)	1.55 (0.16)
Diuresis, mL	500 (50–950)

* Mean of 3 dialysis sessions.

Normally distributed parameter reported as mean and SD; nonnormally distributed parameter reported as median and interquartile range; categorical data as total number (percentage).

spKt/V, single pool Kt/V.

Results

Fifty-four subjects were included in the analysis, 33 (61.1%) of whom were male. The median age was 75.5 years, and the mean dry weight of the patients was 79.8 kg. The median dialysis vintage was 33.1 months, and the mean single pool Kt/V was 1.55. Almost all study participants (96.3%) had an established diagnosis of arterial hypertension, diabetes mellitus (61.1%), and hyperlipoproteinemia (64.8%). About 22.2% of the patients were dialyzed via an indwelling central venous catheter, and others were dialyzed via a fistula. Baseline characteristics of the study collective are further described in Table 1. People with diabetes were well controlled with the mean hemoglobin A1c of 6.4%. Median cholesterol level was 157 mg/dL. Almost 76% of the study collective was on a renin-angiotensin blocker. The same percentage of patients was on a loop diuretic, and the median residual diuresis was 500 mL/day. In total, 51.9% took a statin. The detailed information regarding laboratory parameters and comedication is given in Table 2. Mean systolic and diastolic BP of the study population was 121.4/70.5 mm Hg, and the median heart rate was 64.4 beats/min. PWV adjusted to 120 mm Hg central systolic BP was 11.3 m/s compared to PWV, which was 10.9 m/s. Table 3 gives extended information about the hemodynamic parameters of the patients.

Systolic, diastolic, central systolic, central diastolic BP, PWV, and ultrafiltration volume are significantly higher on the first dialysis session during the week compared to second and third dialysis sessions. In contrast, PWVslope, PWVbaseline, and PWV120 did not differ significantly between the dialysis sessions within 1 week (Fig. 2). Univariable linear regression analysis showed diastolic BP, mean arterial BP, age, smoker status, and intact parathyroid hormone (iPTH) as significant impact parameters on PWV120. These parameters were entered in the multiple linear regression analysis, which revealed age as only independent, statistically significant impact parameter on PWV120. The change in PWV120 was not predictable by the change in systolic, diastolic BP, heart rate, and ultrafiltration volume between the dialysis sessions during 1 week (Fig. 3). Table 4 gives a comparison of hemody-

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Table 2. Relevant laboratory parameters and comedication

HbA1c, mean (SD), %	6.4 (1.3)*
Hb, mean (SD), g/dL	10.8 (1.1)
Total protein, g/dL	6.6 (6.2–6.9)
Albumin, g/dL	55.5 (52.0–59.1)
Cholesterol, mg/dL	157 (126–189)
High-density lipoprotein, mean (SD), mg/dL	43.9 (13.2)
Low-density lipoprotein, mean (SD), mg/dL	91.1 (36.8)
iPTH, ng/L	228 (105–424)
Calcium phosphate product, mean (SD), $mmol^2/L^2$	3.6 (1.1)
Renin-angiotensine-system blockade	41 (75.9)
Calcium channel blocker	28 (51.9)
Aldosterone antagonists	5 (9.3)
Thiazids	12 (22.2)
Loop diuretics	41 (75.9)
Betablockers	40 (74.1)
Alpha blockers	3 (5.6)
Central alpha-agonists	8 (14.8)
Nitrates	5 (9.3)
Direct vasodilators	1 (1.9)
Platelet aggregation inhibitors	32 (59.3)
Anticoagulation	15 (27.8)
Statins	28 (51.9)

* Data from 36 patients available.

Normally distributed parameter reported as mean and SD; non-normally distributed parameter reported as median and interquartile range; categorical data as total number (percentage).

iPTH, intact parathyroid hormone; HbA1c, hemoglobin A1c.

Table 3. Hemodynamic parameters of the study collective

Systolic BP, mean (SD), mm Hg	121.4 (15.7)
Diastolic BP, mean (SD), mm Hg	70.5 (10.9)
Pulse pressure, mm Hg	49.3 (42.2–56.5)
Mean arterial pressure, mean (SD), mm Hg	93.8 (12.3)
Heart rate, b/min	64.4 (58.6–70.2)
Central systolic BP, mean (SD), mm Hg	108.5 (13.8)
Central diastolic BP, mm Hg	70.1 (62.3–78.0)
PWV, m/s	10.9 (9.1–12.7)
PWVslope, m/s × mm Hg	0.0350 (0.0322–0.0378)
PWVbaseline, m/s	7.1 (5.2–9.0)
PWV120, m/s	11.3 (9.5–13.1)

Parameters reported as mean/median of 3 dialysis sessions during 1 week; PWV120, pulse wave velocity adjusted to the level of 120 mm Hg central systolic BP and calculated as PWVbaseline + 120 mm Hg × PWVslope; normally distributed parameter reported as mean and SD; non-normally distributed parameter reported as median and interquartile range.

BP, blood pressure; PWV, pulse wave velocity; PWV120, PWV adjusted to 120 mm Hg central systolic BP.

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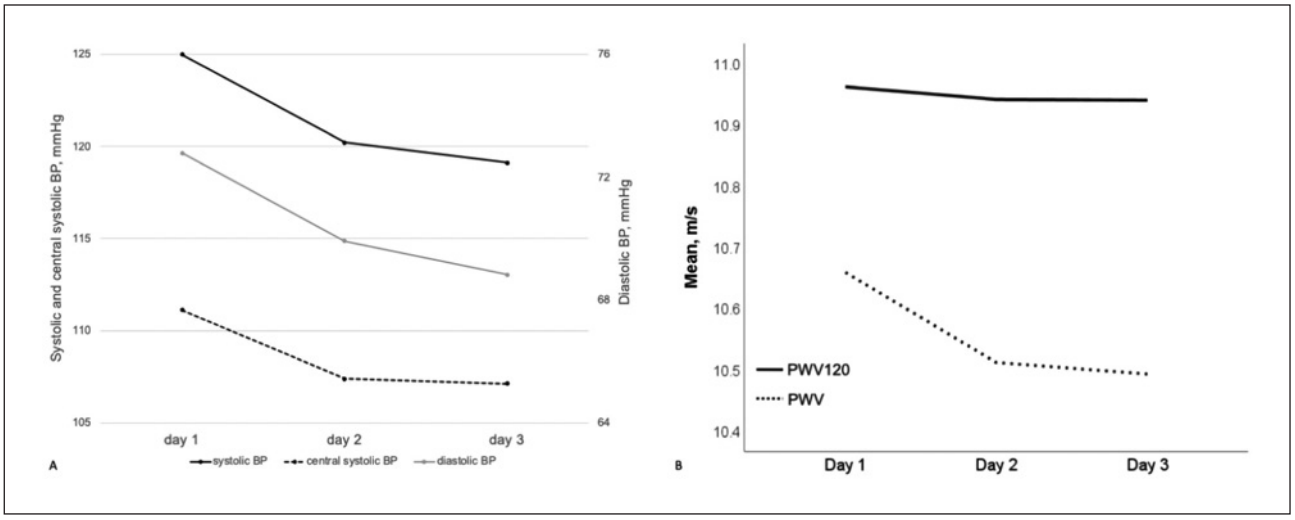

Fig. 2. Change in (**A**) systolic, diastolic, central systolic BP and (**B**) PWV and PWV120 between the dialysis days of 1 week. BP, blood pressure; PWV, pulse wave velocity; PWV120, PWV adjusted to 120 mm Hg central systolic BP.

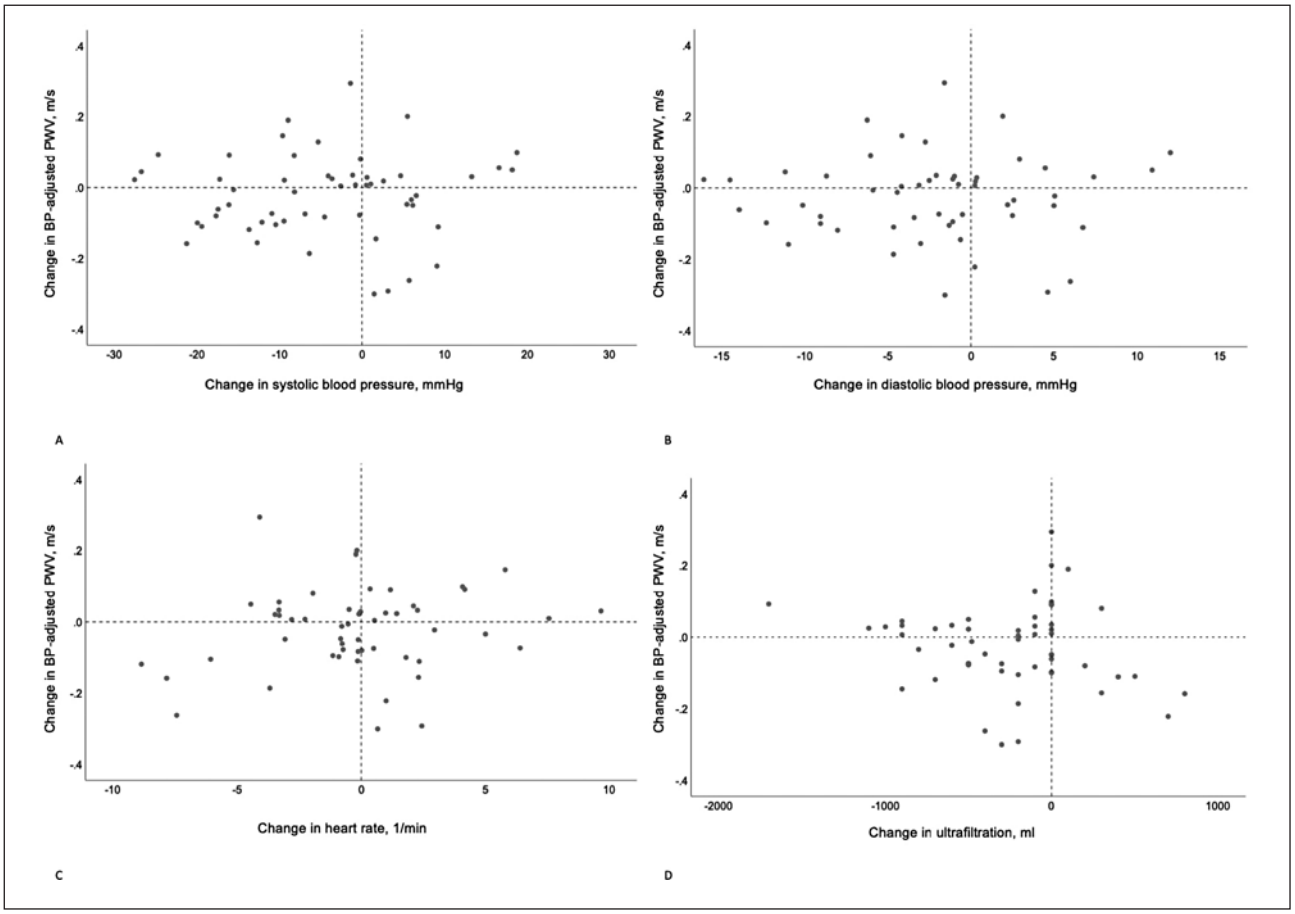

Fig. 3. Change in BP-adjusted PWV related to change in (**A**) systolic BP; (**B**) diastolic BP; (**C**) heart rate; and (D) ultrafiltration between the dialysis sessions during 1 week. BP, blood pressure; PWV, pulse wave velocity.

Table 4. Comparison of hemodynamically relevant parameters between 3 dialysis days of the week

	Day 1	Day 2	Day 3	*p* value, Friedman-test
Systolic BP, mean (SD), mm Hg	125.0 (17.6)	120.2 (14.0)	119.1 (15.0)	0.005*
Diastolic BP, mean (SD), mm Hg	72.8 (12.1)	69.9 (10.4)	68.8 (10.0)	<0.001#
Pulse pressure, mean (SD), mm Hg	52.2 (11.3)	48.9 (42.5–55.3)	50.3 (10.1)	0.486
Mean arterial pressure, mean (SD), mm Hg	96.7 (13.8)	93.0 (11.2)	91.9 (11.5)	0.001*
Heart rate, b/min	63.2 (56.8–69.7)	64.1 (58.7–69.6)	65.7 (59.7–71.1)	0.595
Central systolic BP, mean (SD), mm Hg	111.1 (15.5)	107.4 (12.7)	107.1 (12.8)	0.014*
Central diastolic BP, mean (SD), mm Hg	74.1 (12.1)	69.9 (64.1–75.8)	70.1 (10.1)	<0.001#
PWV, mean (SD), m/s	10.7 (2.4)	10.5 (2.5)	10.5 (2.5)	0.003*
PWVslope, mean (SD), m/s × mm Hg	0.0350 (0.0050)	0.0348 (0.0053)	0.0355 (0.0045)	0.946
PWVbaseline, m/s	7.2 (5.1–9.3)	6.8 (2.6)	6.7 (2.6)	0.786
PWV120, mean (SD), m/s	11.0 (2.6)	10.9 (2.6)	10.9 (2.6)	0.703
Ultrafiltration volume, mean (SD), mL	2,819 (1,021)	2,545 (1,102)	2,511 (1,115)	0.002#

* Statistically significant difference days 1–3.

Statistically significant difference days 1–2 and days 1–3.

PWV120, pulse wave velocity adjusted to the level of 120 mm Hg central systolic BP and calculated as PWVbaseline + 120 mm Hg × PWVslope; normally distributed parameter reported as mean and SD; nonnormally distributed parameter reported as median and interquartile range.

BP, blood pressure; PWV, pulse wave velocity; PWV120, PWV adjusted to 120 mm Hg central systolic BP.

Table 5. Independent statistically significant impact parameters on PWV, PWVbaseline, and PWVslope based on multivariable linear regression analysis

	PWV	PWVbaseline	PWVslope
Independent parameters	Systolic BP$ Diastolic BP$ Age$ Residual diuresis# Loop diuretic# PAD#	Systolic BP* Diastolic BP* Age§ Residual diuresis#	Systolic BP*

PWV, pulse wave velocity; BP, blood pressure; PAD, peripheral artery disease. * $p < 0.05$. # $p < 0.01$. $ $p < 0.001$.

namically relevant parameters between 3 dialysis days of the week. Table 5 shows independent statistically significant influence parameters on PWV, PWVbaseline, and PWVslope based on the results of multiple linear regression analysis.

Discussion

In this study, we observed no change in PWV120 between dialysis sessions within 1 week in stable outpatients of the single center dialysis unit. PWV and BP parameters varied significantly between the dialysis sessions. The change in BP-adjusted PWV could not be predicted by any parameter, which varied between the dialysis sessions. Though, wide variation ranges were observed for systolic and diastolic BP, heart rate, and ultrafiltration amount between

the dialysis sessions. Our mathematical approach allows the adjustment of the PWV to a particular BP-level (in this study 120 mm Hg central systolic BP) and as a consequence possible BP-independent reflection of the true AS as an indicator of the arterial wall damage. Our findings support the expected presumption that the arterial wall structure does not change during 1 week in dialysis patients. The supposed changes in AS are based on the physiologic PWV change due to changes in BP [7]. This conclusion is of direct importance for the interpretation of the studies using PWV either as a cardiovascular risk marker or a PWV change as a therapeutic target. For example, a recently published study reported an association between volume overload and increased AS in patients with moderate to severe CKD [12]. However, volume overload usually causes an increase in BP (also observed in the study). An increased BP can cause increase in AS without any true changes in arterial wall structure. The authors of the study suggested an existing relationship between volume expansion and AS in the discussion. However, this link is confounded by the occurred change in BP.

Two main approaches exist in the literature to convert PWV in a BP-independent parameter: (1) generation of a dimensionless variable as implemented in cardio-ankle vascular index [13] and (2) general adjustment of the PWV values to BP performed on the statistical basis usually employing regression analysis techniques. While cardio-ankle vascular index is not as much substantiated with evidence as conventional aortic PWV, general adjustment of the PWV to BP is not individualized and applicable for study populations or for single subjects [14]. Moreover, the comparability of the values between different studies or during follow-up is difficult. To the best of our knowledge, no studies using individual BP-adjustment of the PWV in dialysis patients have been published so far. Di Iorio et al. [15] studied changes in BP-adjusted PWV in 20 dialysis patients in 1 week. The authors used normalization of the PWV as a method for BP-adjustment – corresponding to a general BP-adjustment approach [15] – and reported no significant change in normalized PWV during 1 week. Noteworthy, carotid-femoral PWV- and BP-measurements have been performed with different devices and the time point of BP- and carotid-femoral PWV-measurement has not been specified further. In case the measurements were not performed simultaneously, the direct link between the particular BP level and measured PWV would be difficult, as the BP varies continuously. Thus, compared to the Di Iorio et al. [15] work our methodological (oscillometry based) approach is possibly more accurate as the method delivers PWV and BP simultaneously. Overall, our data support their findings and extend the evidence that BP-adjustment is necessary to differentiate between physiologic reaction of PWV to a change in BP and true PWV as a reflection of arterial wall damage.

Considering the separate variables in the linear equation created from the point clouds, we defined the line interception point with the Y-axis as a PWVbaseline. This is a virtual parameter because the precondition for interception of the Y-axis would be the BP of 0 mm Hg, which is, of course, impossible in real life. However, this parameter seems to reflect the baseline status of the arterial wall as a static component. In our study, PWVbaseline was predicted by systolic and diastolic BP as well as patient age. All factors are known to be the main affecting factors of the AS [6]. Another variable in the linear equation – PWVslope – reflected the intensity of PWV change due to change in BP. This parameter would probably represent the dynamic component of AS or "true" stiffness as is described by the key physical principles [16]. Only systolic BP was able to predict PWVslope in multiple regression analysis of our study collective. Both PWVbaseline and PWVslope might depict different components of AS, which is a reflection of histopathological changes in arterial wall structure such as deterioration of elastin network, vascular smooth muscle hypertrophy, and transformation and increased collagen deposition [17–19]. iPTH was also reported as a main determinant of AS progression [20]. Though the impact of iPTH was significant in the univariate test, in the multivariate analysis, iPTH lost its statistical significance as an independent impact factor on PWV120.

In conclusion, our data suggest that true AS does not change in the short-term course in dialysis patients and observed changes in PWV are rather associated with BP change due to the intrinsic pressure-dependence. Since PWV has been an acknowledged predictive parameter for cardiovascular risk in non-CKD [21] and CKD population [22], it is essential to determine true changes in PWV and exclude the pressure-dependence component. Our analytical approach represents a novel method for this purpose, which is easy in performance and applicable for large interventional trials and clinical practice. Further studies should be performed to establish the link between BP-adjusted PWV and cardiovascular outcomes.

Though the study has its strengths, we acknowledge several limitations: Due to the device used, the aortic PWV was calculated and not measured. We have previously shown that calculated PWV measured by the Mobil-O-Graph is in a very good agreement with direct measurement of PWV [9]. The observational design of the study allows the description of associations but preclude any causal relationships. Single-center approach resulted in a given participants number. However, this is the largest study describing PB-adjuster PWV individually in dialysis patients so far. Further studies should be conducted to examine the validity of BP-adjusted PWV in other collectives.

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Mobil-O-Graphs were kindly provided by the manufacturer.

Statement of Ethics

The research was conducted in accordance with the World Medical Association Declaration of Helsinki and comply with the guidelines for human studies.

Disclosure Statement

M.G. has consultancy agreement with IEM (manufacturer of Mobil-O-Graph). There is no conflict of interest for the other authors.

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Author Contributions

A.R.: conception of design, analysis and interpretation of the data, drafting the article, final approval of the version to be published. D.W.: conception of design, analysis and interpretation of the data, drafting the article. G.W.: analysis and interpretation of the data. M.T. and K.-U.E.: providing intellectual content of critical importance. M.G.: interpretation of the data, revising the article, final approval of the version to be published.

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4.5 Oszillometrische Kalkulation des HZV

Das HZV ist ein wichtiger Parameter in der Beurteilung der Hämodynamik und der Organperfusion. Ein klinisch etabliertes Verfahren zur Messung des HZV ist die intermittierende Thermodilution welche mit einem Pulmonalis-Katheter oder einer transpul- monalen Methode mit der Indikatordetektion im arteriellen Kreislauf (Puls Contour Car- diac Output- PiCCO-System) durchgeführt wird.[30,31] Beide Verfahren sind invasiv und ihr Einsatz ist somit auf wenige Settings wie Intensivstation oder Operationssaal beschränkt. Nachfolgende Arbeiten untersuchten die oszillometrisch ermittelten HZV- Werte im Vergleich zur transpulmonalen Thermodilution.

4.5.2 **Pilotstudie**

Reshetnik A, Compton F, Scholzel A, Tolle M, Zidek W, Giet MV. Noninvasive oscillometric cardiac output determination in the intensive care unit - comparison with invasive transpulmonary thermodilution. Sci Rep 2017;7:9997. (Manuskript 5)

Es wurden 38 kritisch kranke und hämodynamisch instabile Patienten einer internistischen Intensivstation eingeschlossen. Zur oszillometrischen HZV-Kalkulation wurde der TEL-O-GRAPH der Firma I.E.M und für die transpulmonale Dilution das PiCCO-System der Firma Pulsion Medica Systems verwendet. Die Oszillometrie unterschätzte im Mittel das HZV deutlich (2,7±0,5 L/min*m^2 vs. 3,8±1,2 L/min*m^2). Auch die Bland-Altman-Statistik zeigte einen klinisch relevanten Bias von 1,08 L/min*m^2 und einen *percentage error* von 68,3%. Mit steigendem absoluten HZV-Wert änderte sich das Verhältnis zwischen dem kalkulierten und gemessenen Wert: zunächst überschätzte die oszillometrische Kalkulation und dann unterschätze sie den gemessen Wert. Auch die HZV-Veränderung nach Volumengabe wurde untersucht und in 69,5% der Messungen ein konkordantes Ergebnis gezeigt.

Zusammenfassend zeigte sich in dieser ersten Studie die grundsätzliche Machbarkeit der nicht-invasiven oszillometrischen HZV-Kalkulation in einem Kollektiv der kritisch kranken bei noch nicht ausreichender Zuverlässigkeit der oszillometrischen HZV-

Werte. Wir haben aufgrund unserer Ergebnisse eine Anpassung des Algorithmus vorgeschlagen.

4.5.2 **Folgestudie nach Weiterentwicklung des Algorithmus**

Reshetnik A, Gjolli J, van der Giet M, Compton F. Non-invasive Oscillometry-Based Estimation of Cardiac Output - Can We Use It in Clinical Practice? Front Physiol 2021;12:704425. (Manuskript 6)

Basierend auf den Ergebnissen der Pilotstudie hat die Firma den Algorithmus geändert. In dieser Studie haben wir die Performance der HZV-Kalkulation in der nachfolgenden Arbeit erneut untersucht. Es wurden 48 kritisch kranke und hämodynamisch instabile Patienten einer internistischen Intensivstation eingeschlossen. Zur oszillo- metrischen HZV-Kalkulation wurde das Mobil-O-GRAPH der Firma I.E.M und für die transpulmonale Dilution das PiCCO-System der Firma Pulsion Medica Systems verwendet. Auch in dieser Arbeit unterschätze die Oszillometrie das HZV im Mittel (2.6 vs. 3.2 L/min*m^2). Die Bland-Altman-Analyse zeigte einen besseren mittleren Bias von 0,7 L/min*m^2 und einen schlechteren *percentage error* von 83,6% im Vergleich zur ersten Arbeit. Die Erfassung der HZV-Änderung nach einer Volumen- gabe ergab nur in 50% eine Kongruenz zwischen Oszillometrie und der Referenzme- thode. In dieser Arbeit untersuchten wir zusätzlich noch die Trends der HZV-Profile über 6 Stunden. Auch hier zeigte sich lediglich in 50% eine Kongruenz der Ergebnisse mit der Referenzmethode.

Zusammenfassend zeigte sich auch nach der Veränderung des Algorithmus keine höhere Zuverlässigkeit der kalkulierten HZV-Werte im Kollektiv der hämodynamisch instabilen und kritisch kranken Patient: innen. Die Methode sollte daher außerhalb klinischer Studien noch nicht eingesetzt werden.

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Noninvasive oscillometric cardiac output determination in the intensive care unit – comparison with invasive transpulmonary thermodilution

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Assessment of the cardiac output (CO) is usually performed with invasive techniques requiring specialized equipment in the intensive care unit (ICU). With TEL-O-GRAPH (TG), CO can be derived from the oscillometrically obtained brachial pulse wave during the measurement of brachial blood pressure. CO and stroke volume (SV) determinations with TG were compared with transpulmonary thermodilution measurements with the PICCO system (PICCO) in 38 haemodynamically unstable ICU patients with a total of 84 comparison measurements performed. SV (33.3 ± 9.0 ml/m² vs. 44.3 ± 14.4 ml/m², $p < 0.001$) and CO (2.7 ± 0.5 l/min/m² vs. 3.8 ± 1.2 l/min/m², $p < 0.001$) were underestimated significantly with TG and oscillometric brachial systolic blood pressure (BP) was significantly lower and diastolic BP significantly higher than invasive femoral artery pressure. A linear correlation was found between CO dimension and CO underestimation with TG. Correct tracking of CO changes with a fluid challenge was possible in 69.5% of measurements. Oscillometric noninvasive CO is possible in the ICU, but accuracy and precision of this new method are lacking. Implementation of a correction factor accounting for the linear increase in CO underestimation observed with increasing CO could improve CO assessment with TG in haemodynamically unstable patients.

Cardiac output (CO) is a major determinant of organ perfusion, and CO monitoring therefore an integral part of the care for haemodynamically compromised patients in the intensive care unit (ICU). Clinical gold standard for CO determination is intermittent thermodilution measurement either performed via a pulmonary artery catheter, or, less invasively, with the PICCO system using the transpulmonary approach with indicator detection in the systemic arterial circulation[1,2]. Beat-to-beat CO monitoring is possible using CO calculation algorithms derived from the arterial pulse wave, and can either be performed invasively or noninvasively[2,3]. To date, noninvasive pulse wave recordings have only been established for distal blood pressure measurement sites such as the finger (volume clamp technique) and the radial artery (applanation tonometry)[4,5]. Distal blood pressure, though, is known to underestimate central arterial pressure in haemodynamically compromised patients, and noninvasive pulse wave derivation is not always possible in patients on vasopressor therapy[6]. With the Tel-O-GRAPH (TG) oscillometric brachial artery blood pressure measuring device, proximal noninvasive arterial pulse wave determination and CO estimation is possible, and the device has been evaluated clinically for the measurement of brachial blood pressure and calculation of central blood pressure and pulse wave velocity in haemodynamically stable patients[7–9]. In the present study, we therefore compared noninvasive CO determination with TG with invasive thermodilution CO measurement in haemodynamically unstable ICU patients to evaluate whether oscillometric TG CO is suitable for use in the ICU.

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	number of patients	number of measurements	number of measurements with fluid challenge[#]
single measurement	7	7	
single measurement on two separate days	5	10	
two measurements before and after fluid challenge on the same day	20	40	20
two measurements before and after fluid challenge on two separate days	4	16	8
two measurements before and after fluid challenge on four separate days	1	8	4
two measurements before and after fluid challenge on day one, single measu-rement on day two	1	3	1
	38	84	33
total			

Table 1. TG/PICCO comparison measurements (n = 84). [#]fluid challenge: 100 ml normal saline intravenously.

age, mean ± SD, years	68.2 ± 12.3
male gender, n (%)	26 (68.4%)
body surface area, mean ± SD, m^2	1.9 ± 0.2
body mass index mean ± SD, kg/m^2	26.4 ± 4.8
arm circumference, mean ± SD, cm	29.2 ± 4.3
mortality, n (%)	
at 28-days	18 (47.4%)
at 3 month	24 (63.2%)
SAPS on ICU admission, mean ± SD	57.7 ± 20.6
SOFA at study entry, mean ± SD	11.2 ± 3.9
mechanical ventilation, n (%)	34 (89.5%)
on ICU admission	34 (89.5%)
at study entry	36 (94.7%)
vasopressor therapy at study entry, n (%)	29 (76.4)
acute kidney injury at study entry, n (%)	28 (73.7)
on renal replacement therapy	23 (60.5)
chronic illness, n (%)	
hypertension	17 (44.7)
smoker	7 (18.4)
stroke	10 (26.3)
coronary heart disease	10 (26.3)
myocardial infarction	8 (21.1)
congestive heart failure	7 (18.4)
peripheral vascular disease	5 (13.2)
diabetes mellitus, insulin-dependent	4 (10.5)
diabetes mellitus, non-insulin-dependent	10 (26.3)

Table 2. Patient characteristics (n = 38). SD = standard deviation, ICU = intensive care unit, SAPS = simplified acute physiology score, SOFA = sepsis-related organ failure score.

Results

A total of 84 TG/PICCO comparison measurements were performed in 38 patients (Table 1). More than one comparison measurement was carried out in 31 patients, and in 33 instances measurements were performed before and immediately after a fluid challenge of 100 ml normal saline intravenously. Demographic data of the patients are displayed in Table 2. At time of study entry, 95 percent of patients were mechanically ventilated, and 76 percent were on continuous vasopressor support because of haemodynamic instability.

Mean cardiac index (CI) and stroke volume index (SVI) determined by noninvasive oscillometric TG calculation both were significantly and clinically relevantly lower than PICCO-CI and PICCO SVI measured with transpulmonary thermodilution (TG-CI 2.7 ± 0.5 $l/min/m^2$ vs. PICCO-CI 3.8 ± 1.2 $l/min/m^2$, $p < 0.001$ and TG-SVI 33.3 ± 9.0 ml/m^2 vs. PICCO-SVI 44.3 ± 14.4 ml/m^2, $p = 0.001$) (Table 3). Kolmogorov-Smirnov-Test revealed normal distribution for CI- and SVI- between-method bias. Bland-Altman analysis yielded a bias of 1.08 $l/min/m^2$ between noninvasive TG- and invasive PICCO-CI measurements, respectively (Fig. 1, panel A). Limits of agreement were ± 1.96 $l/min/m^2$ with a percentage error of 68.3%. Differences between TG-CI and PICCO-CI increased in a linear fashion (slope = 1.14) with increasing CI as shown by the dashed line in the

parameter	PICCO mean ± SD	TG mean ± SD	p value#
heart rate*, /min	86.9 ± 19.9	85.9 ± 19.8	0.72
systolic blood pressure, mmHg	123.6 ± 17.4	117.5 ± 16.0	0.006
diastolic blood pressure, mmHg	61.7 ± 10.7	70.6 ± 9.9	<0.001
cardiac output, l/min	7.34 ± 2.30	5.26 ± 0.93	<0.001
cardiac index, l/min/m^2	3.80 ± 1.22	2.73 ± 0.50	<0.001
stroke volume, ml	85.2 ± 27.2	63.9 ± 16.3	<0.001
stroke volume index, ml/m^2	44.3 ± 14.4	33.3 ± 9.0	<0.001

Table 3. Comparison of haemodynamic parameters measured noninvasively with TEL-O-GRAPH (TG) and invasively with the PICCO system (PICCO). SD = standard deviation #Wilcoxon matched pairs test, *heart rate determined with electrocardiography monitoring and TG, respectively.

Bland-Altman plot (Pearson's r = 0.75). For SVI, bias was 11 ml/m^2 with limits of agreement of ±25.5 ml/m^2 (percentage error 65.7%).

Figure 2 illustrates the mean differences in blood pressure measured noninvasively with TG and invasively with the femoral artery catheter used for PiCCO-CI determination. Systolic blood pressure was significantly lower when measured with TG (117.5 ± 16.0 vs. 123.6 ± 17.4, p = 0.006), whereas diastolic blood pressure was significantly higher with TG than measured intraarterially (70.6 ± 9.9 vs. 61.7 ± 10.7, p < 0.001).

When CI changes before and after a fluid challenge of 100 ml normal saline were compared concordant CI increase or decrease was observed in 69.5% of all measurements (Fig. 3). In six instances (18%), there was an increase in TG-CI with fluid challenge, but a decrease or no change with invasive PICCO-CI. In eight measurements (24%), PICCO-CI increased with fluid administration as opposed to a decrease when CI was determined with TG. Comparison of CI changes tracked by TG and reference method is visualized by 4-quadrant plot (Fig. 3).

Discussion

Our results show that noninvasive oscillometric brachial artery pulse wave acquisition with TG is feasible in haemodynamically unstable ICU patients. TG pulse wave analysis derived SV and CO, though, are clinically relevantly lower when compared to reference thermodilution measurements with the PICCO system.

Different methods of pulse wave analysis can be used to calculate SV from the arterial pressure curve, depending on the underlying model of the circulation and the mathematical transformations performed[10,11]. Systolic pulse contour analysis as used with TG is based on the Windkessel model, according to which SV is proportional to the area under the systolic portion of the pressure curve[12]. As with all other pulse wave analysis methods, individual aortic impedance has to be taken into account to calculate absolute SV and thus CO values based on this relationship. As opposed to calibrated pulse wave analysis methods, TG uses mathematical transformations only to determine aortic impedance[1,7]. When compared with calibrated pulse wave analysis, uncalibrated techniques have generally been shown to be less reliable and to underestimate CO especially in haemodynamically unstable patients with constantly changing vascular tone[3,13–15]. This was recently confirmed in a meta-analysis of uncalibrated noninvasive CO monitoring devices used perioperatively[16].

With established uncalibrated CO determination devices, the pulse wave is usually obtained from a distal arterial site such as the radial artery or the finger[3]. Blood pressure measurements from peripheral arterial sites have been shown to systematically underestimate central arterial pressure during haemodynamic instability, which in turn influences accuracy and precision of pulse wave derived CO[13,14,17]. Reliable blood pressure determination has been shown to be possible with TG in haemodynamically stable ambulatory patients when compared to sphygmomanometric auscultatory blood pressure readings, and oscillometric brachial blood pressure determination is routinely used both in the ICU and the operating theatre even though reliability has not been proven for adult patients in systematic precision and accuracy studies[8,18–20]. Our data show that despite the more proximal arterial site systolic blood pressure is also underestimated with TG in haemodynamically compromised patients when compared to invasive femoral arterial pressure measurement. Diastolic blood pressure, on the other hand, is overestimated, yielding a deformed pulse wave with diminished pulse pressure used to calculate SV and CO.

To our knowledge, there are only two other studies evaluating the performance of oscillometry-based SV and CO calculation. Liu and coworkers compared oscillometrically derived SV with echocardiographic measurements in 55 haemodynamically stable patients undergoing routine cardiac disease diagnosis[21]. Using a different pulse contour analysis algorithm, the authors found a strong correlation and only minor differences between oscillometry-based and echocardiography-derived SV. Oscillometric SV calculation was evaluated in ten ICU patients in the other study and compared to pulmonary artery thermodilution measurements[7]. Precision and accuracy were reported to be 0.25 ± 12.5 ml (as compared to 21.2 ± 25.1 ml in our study, data not shown), but it was not stated whether TG-SV was higher or lower than thermodilution SV, and only limited data was provided concerning the haemodynamic status of the study subjects. Both studies reported better accuracy of the oscillometric devices that we could show. A possible explanation could be an amount of haemodynamic instability in our patients, which can decrease the sensitivity of peripheral sensors. Thus, final CO/SV calculation can become erroneous.

Bland-Altman analysis of SV and CO data in our study revealed that there was a linear correlation between the dimension of SV and CO, respectively, and the magnitude of underestimation by TG: The higher SV and CO were, the larger the difference between TG and PICCO measurements became. A similar phenomenon had been found in an earlier study performed at our institution comparing applanation tonometry-derived CO and

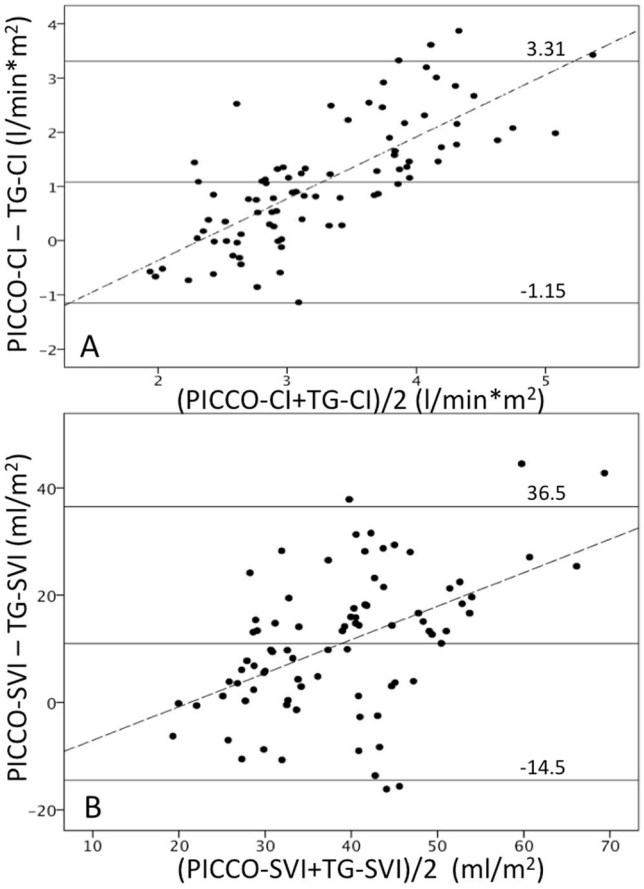

Figure 1. (**A**) Agreement between invasive PICCO measured cardiac index (PICCO-CI) and noninvasive TEL-O-GRAPH derived cardiac index (TG-CI): bias 1.08 l/min/m^2, limits of agreement −1.15 to 3.31 l/min/m^2 (percentage error 68.3%), dashed line represents the linear correlation between absolute CI level and PICCO- and TG-CI differences (Pearson's r = 0.75); (**B**) Agreement between invasive PICCO measured stroke volume index (PICCO-SVI) and noninvasive TEL-O-GRAPH derived stroke volume index (TG-SVI):bias 11 ml/m^2, limits of agreement −14.5 to 36.5 ml/m^2 (percentage error 65.7%), dashed line represents the linear correlation between absolute SVI level and PICCO- and TG-SVI differences (Pearson's r = 0.49).

pulmonary artery thermodilution measurements[14]. Because of the linearity of this error it might be possible to develop a correction factor that could be implemented in the TG-CO calculation algorithm allowing for a more precise CO estimation with TG in patients with higher CO levels.

Clinically more important than single absolute CO values often are relative CO changes in response to a therapeutic intervention[22,23]. CO trending abilities can be assessed using different methods, of which visualization with a 4-quadrant plot and reporting of concordance rates is a method frequently used[24]. We evaluated CO changes with a fluid challenge and found that TG failed to reliably trend CO changes with a concordance rate of 69.5% between TG- and PICCO-ΔCI, which was below an acceptable level of 90–95%[25]. In consistence with the low concordance, 4-quadrant plot visualized low trending ability with a relevant rate of discordant measurements, poor correlation index (r = 0.15) and wide distribution of data points around the 45° diagonal, which represents equal numerical values revealed by TG and PICCO. To our knowledge, there are no other studies assessing the ability of non-invasive oscillometric devices to track CO changes. Several studies addressed this issue for other techniques such as arterial pulse contour cardiac output monitoring systems[11,26–29], transtracheal Doppler[30], thoracic electric bioimpedance monitoring[31], transesophageal Doppler[25,32,33] with different findings. In general, arterial pulse contour based CO analysis was shown to track CO changes with poor reliability comparable to our results. For other devices, studies showed a better performance. Authors of the published studies used different statistical methods to assess the ability of devices to track CO changes, which makes comparisons between these studies more complicated. Of note, the 4-quadrant plot used in the majority of the published studies as well as in our study, is an excellent tool to visualize the trending ability between the test and reference device. However, it lacks the clearly defined numeric values, which could be used for comparisons between studies, and for the definition of good, acceptable, and poor agreement.

We showed clinically relevant differences in absolute CO values calculated with TG compared to thermodilution measurements. This could be an important factor explaining the poor ability to track CO changes by the

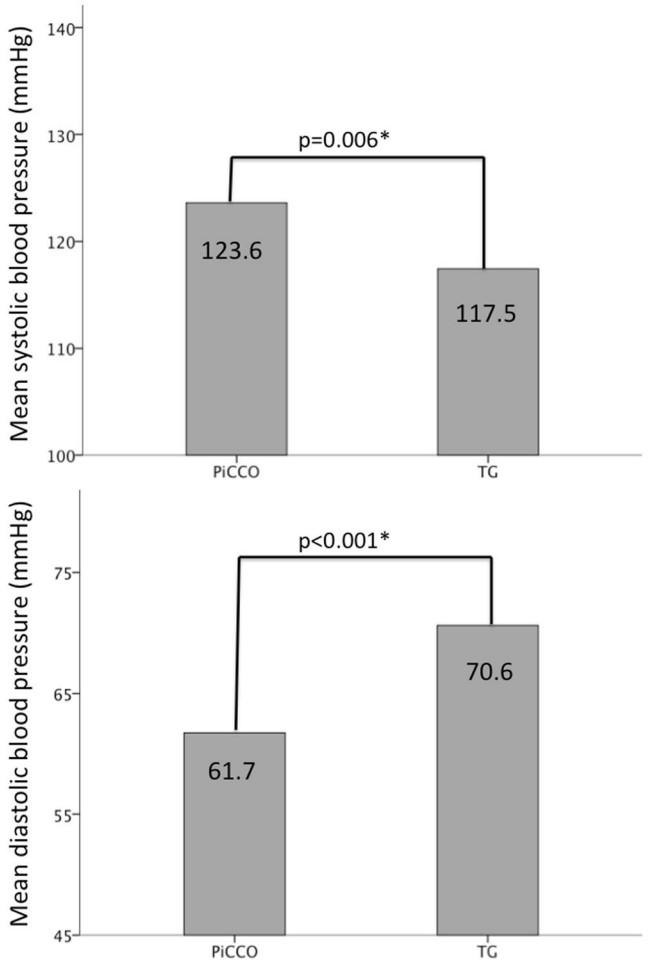

Figure 2. Comparison of mean systolic blood pressure (**A**) and diastolic blood pressure (**B**) measured with the PICCO-system (PICCO) and TEL-O-GRAPH (TG); *-Wilcoxon matched pairs test.

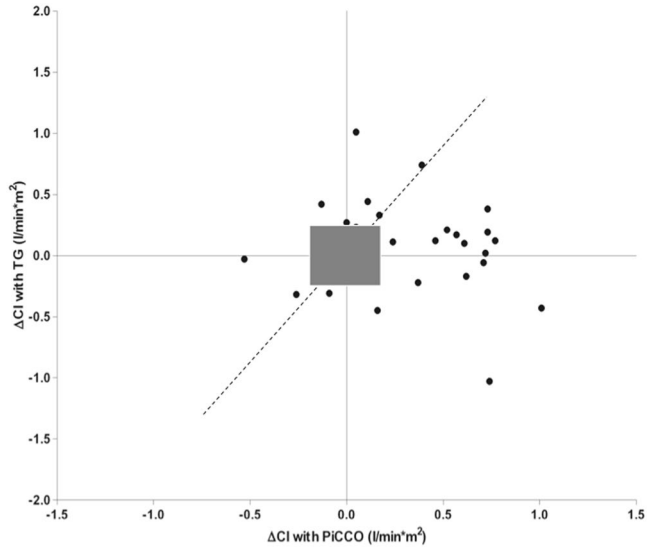

Figure 3. 4-quadrant plot of TEL-O-GRAPH (TG) derived cardiac index change (ΔCI) after a fluid challenge of 100 ml normal saline intravenously compared with PICCO measured ΔCI (concordance rate = 69.5%). Points with equal numerical values are located on the 45° diagonal within the quadrant (the dotted line). Exclusion zone is marked by grey rectangle.

tested device. Future studies should be able to show whether improvement in agreement of CO assessment would also improve the ability to track CO changes.

We acknowledge several limitations of our study. Our study group was relatively small, and in most patients more than one measurement was performed and analyzed. Most, but not all patients were on vasopressor support during study measurements. As with all studies comparing two physiologic methods, bias does not necessarily only arise on the part of the method evaluated, but can also be due to inaccuracies of the reference method[34]. Transpulmonary thermodilution CO measurement has been shown to be a reliable method in numerous studies, but the clinical gold standard it was compared with–pulmonary artery thermodilution–likewise has inherent inaccuracies and limitations[35–38]. The character of our study was observational, and apart from the standardized fluid challenge performed when clinically indicated, no intervention was carried out for study purposes. Confounding factors such as positive end-expiratory pressure on mechanical ventilation were therefore not controlled, and the study population was rather heterogeneous. Our study is a method-comparison study of non-invasive CO assessment vs. invasive thermodilution CO measurement as a clinical "gold standard". Invasive CO monitoring was performed because of the critical illness of our patients. Thus, the findings obtained in our study are limited to this group of critically ill and haemodynamically unstable patients and cannot readily be transferred to other less ill patient collectives.

Despite these limitations, we were able to show that noninvasive oscillometric CO determination is feasible in the ICU. TG does not require specialized equipment as with applanation tonometry or finger blood pressure measurement, and the pulse wave is derived more proximally than with those techniques[39,40]. With TG, CO can be determined at the same time as the blood pressure is taken, and blood pressure measurement is performed with a method well established in patient monitoring. Future studies will have to show if modifications in the calculation algorithm like the introduction of a correction factor for increasing CO values can improve the performance of oscillometric pulse wave analysis and CO determination.

In conclusion, our study shows that oscillometry-based CO determination is generally possible in haemodynamically unstable ICU patients. Even though precision and accuracy of CO estimation with TG were not sufficient, we were able to demonstrate a linear correlation between the dimension of CO and its underestimation with TG pulse wave analysis. A correction of this systematic error could increase CO determination accuracy significantly, so that oscillometry-derived CO estimation could potentially become an alternative to other more complex noninvasive CO determination methods in the ICU.

Methods

The study was approved by the Charité Universitätsmedizin Berlin regional research ethics committee (ref: EA1/184/15). All methods were performed in accordance with the relevant guidelines and regulations. Informed consent was obtained from the patient or their legal representative, respectively, before enrollment in the study.

A total of 38 patients treated in the medical ICU of the Charité Campus Benjamin Franklin university hospital in Berlin, Germany between June 2015 and June 2016 and monitored with a PICCO system (Pulsion Medical Systems, Feldkirchen, Germany) as part of their clinical treatment were prospectively enrolled in the study. Exclusion criteria were age below 18 years, pregnancy, known aortic valve, aortic arch, axillary or brachial artery stenosis, as well as cardiac arrhythmias precluding noninvasive calculation of haemodynamic parameters by the TG blood pressure monitoring device. Patients were categorized as haemodynamically unstable if mean arterial pressure (MAP) was <65 mmHg or vasopressor therapy was necessary to maintain MAP ≥ 65 mmHg.

The TG device used in the study was kindly provided by I.E.M., Stolberg, Germany. With TG brachial blood pressure is determined oscillometrically with a conventional brachial blood pressure cuff, and the arterial pulse wave is derived using a high fidelity pressure sensor with the cuff inflated at the diastolic blood pressure level for ten seconds. Estimation of left ventricular stroke volume (SV) and CO is achieved by a series of mathematical transformations of the brachial pulse wave described in detail elsewhere[7]. Briefly, the aortic pressure waveform is calculated using generalized transfer functions (Fourier analysis and de-compensation into wave harmonics), and the aortic flow curve by the means of an adopted, multidimensional Windkessel model. SV is then derived from the time lag between pressure and flow curves, generally referred to as the "characteristic impedance (Zc)". CO is calculated by multiplying SV with the heart rate also derived from the arterial pulse wave.

With the PICCO system, CO was determined using transpulmonary themodilution. A bolus of 20 mL of cold (0–6 °C) normal saline solution was manually injected (injection time ≤10 seconds) into the distal lumen of a central venous catheter and detected in the systemic circulation by a thermistor-tipped femoral artery catheter (Pulsiocath PV2015L20, Pulsion Medical Systems, Feldkirchen, Germany). CO was calculated as the mean value of three consecutive measurements. To obtain SV, CO was divided by the heart rate determined with electrocardiography (ECG) monitoring.

Noninvasive SV (TG-SV) and CO (TG-CO) were determined at the time of invasive PiCCO CO (PICCO-CO) and SV (PICCO-SV) measurements. For TG measurements, blood pressure cuff size was chosen according to the manufacturer's specifications (cuff sizes for arm circumferences of 24–34 cm and 32–42 cm, respectively – for arm circumference between 32 and 34 cm the smaller cuff was used). If possible, measurements were performed on both the left and the right arm, and TG-SV and TG-CO calculated as the mean of three (unilateral) or six (bilateral) measurements, respectively.

CO and SV results were indexed to body surface area, and are referred to as cardiac index (CI) and stroke volume index (SVI), respectively. At the time of measurements, blood pressures determined both noninvasively with TG at the brachial artery and invasively with the PICCO system in the external iliac artery were recorded as well as heart rate determined with TG and ICU ECG monitoring, respectively. Patient population characteristics and severity of illness scores (simplified acute physiology score, SAPS, and sepsis-related organ failure assessment score, SOFA) were also registered.

Data were analyzed using Graph-Pad Prism 5 (GraphPad Software, La Jolla, CA, USA) and SPSS Statistics 23.0 (IBM, New York, NY, USA). Results are expressed as mean ± standard deviation. Statistical differences between paired measurements were assessed using nonparametric Wilcoxon testing, and a two-sided p value of <0.05 was considered statistically significant. For agreement between invasive PICCO-CI / PICCO-SVI and noninvasive TG-CI /TG-SVI determinations, Bland-Altman analysis was performed calculating bias as the mean difference between paired measurements, and the 95% confidence interval as limits of agreement. Percentage error was then calculated as suggested by Critchley and Critchley[34]. Linear regression analysis was used to evaluate the progressive deviation between PICCO-CI and TG-CI observed with rising CI levels. To compare CI-changes (ΔCI) induced by a fluid challenge and registered with PICCO and TG, respectively, a 4-quadrant plot was generated and the concordance rate determined[41]. For CO, the recommended margin for the exclusion zone in a 4-quadrant plot is 0.5 l/min[24]. To compare CI changes, the exclusion zone was defined by dividing 0.5 l/min by mean body surface area.

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Author Contributions

A.R.: conception and design of the article, drafting the article; final approval of the version to be published; accountable for all aspects of the work. F.C.: analysis and interpretation of data, drafting the article; final approval of the version to be published; accountable for all aspects of the work. A.S.: acquisition of data, drafting the article; final approval of the version to be published; accountable for all aspects of the work. M.T.: analysis and interpretation of data, revising the article for important intellectual content; final approval of the version to be published; accountable for all aspects of the work. W.Z.: analysis and interpretation of data, revising the article for important intellectual content; final approval of the version to be published; accountable for all aspects of the work. M.G.: analysis and interpretation of data, revising the article for important intellectual content; final approval of the version to be published; accountable for all aspects of the work.

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ORIGINAL RESEARCH
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Non-invasive Oscillometry-Based Estimation of Cardiac Output – Can We Use It in Clinical Practice?

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While invasive thermodilution techniques remain the reference methods for cardiac output (CO) measurement, there is a currently unmet need for non-invasive techniques to simplify CO determination, reduce complications related to invasive procedures required for indicator dilution CO measurement, and expand the application field toward emergency room, non-intensive care, or outpatient settings. We evaluated the performance of a non-invasive oscillometry-based CO estimation method compared to transpulmonary thermodilution. To assess agreement between the devices, we used Bland–Altman analysis. Four-quadrant plot analysis was used to visualize the ability of Mobil-O-Graph (MG) to track CO changes after a fluid challenge. Trending analysis of CO trajectories was used to compare MG and PiCCO^{QR} calibrated pulse wave analysis over time (6 h). We included 40 patients from the medical intensive care unit at the Charité – Universitätsmedizin Berlin, Campus Benjamin Franklin between November 2019 and June 2020. The median age was 73 years. Forty percent of the study population was male; 98% was ventilator-dependent and 75% vasopressor-dependent at study entry. The mean of the observed differences for the cardiac output index (COI) was 0.7 $l*min^{-1}*m^{-2}$ and the lower, and upper 95% limits of agreement (LOA) were -1.9 and 3.3 $l*min^{-1}*m^{-2}$, respectively. The 95% confidence interval for the LOA was ± 0.26 $l*min^{-1}*m^{-2}$, the percentage error 83.6%. We observed concordant changes in CO with MG and PiCCO^{QR} in 50% of the measurements after a fluid challenge and over the course of 6 h. Cardiac output calculation with a novel oscillometry-based pulse wave analysis method is feasible and replicable in critically ill patients. However, we did not find clinically applicable agreement between MG and thermodilution or calibrated pulse wave analysis, respectively, assessed with established evaluation routine using the Bland–Altman approach and with trending analysis methods. In summary, we do not recommend the use of this method in critically ill patients at this time. As the basic approach is promising and the CO determination with MG very simple to perform, further studies should be undertaken both in hemodynamically stable patients, and in the critical care setting to allow additional adjustments of the underlying algorithm for CO estimation with MG.

Keywords: non-invasive, cardiac output measurement, thermodilution, oscillometric, pulse wave analysis

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INTRODUCTION

Cardiac output (CO) is a key determinant of oxygen delivery and thus an important parameter to assess the hemodynamic situation of critically ill patients, guide perioperative goal-directed therapy, and monitor response to therapeutic interventions (Cecconi et al., 2014). CO can be measured or estimated using invasive, minimally invasive, and non-invasive techniques as well (Sakka et al., 1999; Saugel et al., 2021). While invasive indicator dilution techniques such as pulmonary arterial or transpulmonary thermodilution remain the clinical gold standard and reference methods for CO measurement, and minimally invasive CO determination methods are also available for use in the intensive care unit (ICU), there is a currently unmet need for non-invasive techniques to further simplify CO estimation, reduce complications related to invasive techniques such as pulmonary artery catheterization, and to facilitate use in non-intensive care settings, e.g., for rapid hemodynamic assessment in the emergency room or even in outpatient settings. In this study, we evaluated a non-invasive oscillometry-based pulse wave analysis CO estimation technique for use in critically ill patients.

MATERIALS AND METHODS

Eligible patients treated in the medical ICU of the Charité – Universitätsmedizin Berlin, Campus Benjamin Franklin were enrolled between November 2019 and June 2020. The Charité – Universitätsmedizin Berlin regional research ethics committee approved the study (ref: EA1/184/15). All methods were performed following the relevant guidelines and regulations.

Only patients monitored hemodynamically with the invasive CO determination PiCCO^{QR} device (Pulsion Medical Systems, Feldkirchen, Germany) as part of their ICU treatment were included in the study. Exclusion criteria were age below 18 years, pregnancy, known severe aortic valve, aortic arch, axillary, or brachial artery stenosis, as well as cardiac arrhythmias precluding non-invasive calculation of haemodynamic parameters. Patients were considered haemodynamically unstable if mean arterial pressure (MAP) was <65 mmHg or vasopressor therapy was necessary to maintain MAP ≥ 65 mmHg.

The test device for non-invasive CO estimation was the Mobil-O-Graph (MG)^{QR} (MG; I.E.M., Stolberg, Germany) blood pressure monitoring device equipped with an improved CO calculation algorithm (Hypertension Management Software Client 5.2, 2018). With MG, CO is estimated from the arterial pulse wave derived with a high fidelity pressure sensor integrated into the blood pressure cuff while being inflated at diastolic blood pressure level for 10 s. Cuff size was chosen according to manufacturer instructions: regular size for arm circumferences of 24–34 cm, large size for arm circumference 32–42 cm. The measurement site was left or right upper arm. The construction of the aortic pressure waveform was made using generalized transfer functions (Fourier analysis and decompensation into wave harmonics) and transformation from aortic pressure to aortic flow waveform was performed with an adopted, and multidimensional Windkessel model. Basic principle used is derivation of stroke volume (SV) from pulse contour analysis (PCA) determined with oscillometry. SV is proportional to the area of the flow curve during systole. The computation of the aortic flow from pressure was based on the 3-element windkessel model determined by aortic characteristic impedance, aortic compliance and peripheral resistance. These parameters were identified using Levenberg–Marquardt algorithm. SV was derived from the time lag between aortic pressure and flow curve (characteristic impedance, Zc). Finally, CO was calculated by multiplying SV with the heart rate. Detailed underlying mathematical principles related to CO estimation with MG are described elsewhere (Wassertheurer et al., 2008). For comparison with reference CO, the mean value of two consecutive CO determinations performed with MG was used in each patient. CO was corrected for body surface area and expressed as cardiac output index (COI).

Reference CO was measured using transpulmonary thermodilution with the PiCCO^{QR} system: A bolus of 20 mL of cold (0–6°C) 5% glucose solution was manually injected (injection time ≤10 s) into the distal lumen of a central venous catheter while the patient was in a supine position and then detected in the systemic circulation by a thermistor-tipped femoral artery catheter (Pulsiocath PV2015L20, Pulsion Medical Systems, Feldkirchen, Germany). As with MG CO estimation, two consecutive CO measurements were performed, a mean was calculated for inclusion in the final analysis and COI calculated.

We performed CO measurements with the test (MG) and reference (thermodilution with PiCCO^{QR}) devices before, and after a fluid challenge with 150 mL of crystalloid solution. In addition, we performed trend analyses with MG and PiCCO^{QR} -calibrated pulse wave analysis over a maximum of 6 h (Laight and Levin, 2015). Furthermore, invasively and non-invasively measured blood pressure and heart rate were obtained from routine hemodynamic monitoring and included in the comparison analysis. Demographic and specific clinical patient characteristics were obtained from the hospital patient data management systems.

Statistics

Data were analyzed using Graph-Pad Prism 5 (GraphPad Software, La Jolla, CA, United States) and SPSS Statistics 25.0 (IBM, New York, NY, United States). Continuous variables are presented as median with quartiles. Categorical variables are presented as absolute numbers with percentages. Statistical differences between paired measurements were assessed using a nonparametric Wilcoxon test, and a two-sided p-value of <0.05 was regarded as statistically significant. Bland–Altman analysis was used to assess agreement between test and reference device where the mean of the observed differences was calculated as a measure for accuracy and the 95% LOA as a measure for precision including their 95% confidence intervals (Bland and Altman, 2007; Lu et al., 2016). Furthermore, we calculated the percentage error of agreement, which was computed from the one-sided width of the LOA divided by the average of CO. For trending analysis after the fluid challenge, the 4-quadrant plot technique was used. We expressed CO change

after fluid challenge as relative change according to the following equation:

$$\frac{CO\ after\ fluid\ challenge - CO\ before\ fluid\ challenge}{CO\ bevore\ fluid\ challenge} * 100\%$$

For the purpose of the study, we defined an exclusion zone of 15% (Saugel et al., 2015). To compare long-term trends in CO, slopes of the trajectories for each method were calculated as shown in the **Supplementary Figures 1, 2**. Within-subject method reliability was assessed with intraclass correlation coefficient calculated with the two-way mixed model.

RESULTS

We included 45 participants in the study. Five patients had incomplete measurement data sets due to technical problems so that 40 patients were included in the final analysis. The median age was 73 years, 40% of the study population was male, 98% was ventilator-dependent, and 75% vasopressor-dependent at study entry. Clinical and demographic parameters are presented in **Table 1**. Concerning hemodynamic data, there were significant differences not only between CO determinations with MG and PiCCO^{QR}, respectively, but also between non-invasive and invasive blood pressure measurements: Both diastolic and MAPs were significantly higher with MG than measured invasively in the femoral artery (70 vs. 55 mmHg, $p < 0{,}001$, and 90 vs. 80 mmHg, $p < 0{,}001$, respectively). Conversely, systolic blood pressure was lower with MG than with invasive measurement (118 vs. 123 mmHg), even though this difference was not statistically significant. Both CO and COI were significantly lower with MG as compared with PiCCO^{QR} (4.9 vs. 6.1 l*min^{-1} and 2.6 vs. 3.2 l*min^{-1}*m^{-2}, respectively). Obtained CO values ranged from 3.2 to 10.7 l*min^{-1} for MG and from 2.9 to 17.8 l*min^{-1} for PiCCO^{QR}. Further details concerning hemodynamic parameters are depicted in **Table 2**.

Cardiac output and COI obtained with MG significantly correlated with CO and COI obtained with reference device (Pearson's $r = 0.40$; $p < 0.0001$). Findings for COI are presented in **Figure 1**. Using explorative data analysis, we identified four values as "outliers." We performed addition correlation analysis with Pearson's $r = 0.28$ ($p = 0.02$), which is shown in **Supplementary Figure 2**.

The mean of the observed differences for the CO was 1.3 l*min^{-1} and the lower, and upper 95% LOA were -3.5 and

TABLE 1 | Baseline patient characteristics.

Age, years	73 (62;82)
Male	16 (40%)
Height, cm	170 (165;180)
Weight, kg	74 (65;89)
Body surface area, m^2	1,90 (1,68;2,09)
Body mass index, kg/m^2	25,5 (22,5;27,8)
SAPS II$^{\#}$-Score at study entry	66 (51;77)
SOFA*-Score at study entry	11 (8;13)
Vasopressor therapy at study entry, n (%)	30 (75%)
Ventilation	
On intensive care unit admission	29 (73%)
At study entry	39 (98%)
Duration of intensive care unit stay, days	22 (11;32)
Mortality	
28-days mortality	18 (45%)
3 months mortality	24 (60%)
Chronic illness	36 (90%)
Coronary heart disease	14 (35%)
Prior myocardial infarction	9 (23%)
Chronic heart failure	9 (23%)
Arterial hypertension	30 (75%)
Smoker	10 (25%)
Dyslipidemia	11 (28%)
Diabetes mellitus	19 (48%)
Peripheral arterial disease	5 (13%)
Prior stroke	11 (28%)
Acute kidney injury	24 (60%)
Dialysis dependent kidney injury	17 (43%)
Chronic kidney disease	9 (23%)
Sinus rhythm at study entry	27 (68%)

Continuous parameters presented as median (quartiles), categorical variables presented as number of subjects (%).

TABLE 2 | Hemodynamic parameters with Mobil-O-Graph^{QR} and PiCCO^{QR}.

	Mobil-O-Graph^{QR}	PiCCO^{QR}	*p*-Value*
Systolic blood pressure, mmHg	118 (109;131)	123 (111;137)	0.658
Diastolic blood pressure, mmHg	70 (63;78)	55 (50;64)	<0.001
Mean arterial pressure, mmHg	90 (84;102)	80 (70;87)	<0.001
Heart rate, 1/min	89 (73;99)	87 (74;99)	0.6
Cardiac output, l*min^{-1}	4.9 (4.2;5.8)	6.1 (5.0;7.5)	<0.001
Cardiac output index, l*min^{-1}*m^{-2}	2.6 (2.2;3.3)	3.2 (2.7;4.0)	<0.001

Parameters presented as median (quartiles).
**Wilcoxon–Test for related samples.*

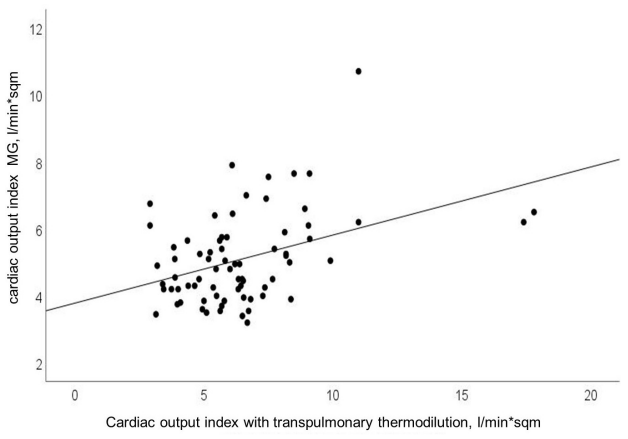

FIGURE 1 | Relationship between cardiac output index (CO-Index) measured with transpulmonary thermodilution and Mobil-O-Graph (MG); Pearson's $r = 0.40$; $p < 0.0001$.

6.1 l*min^{-1}, respectively. 95% confidence interval for the LOA was ±0.49 l*min^{-1}. The mean of the observed differences for the COI was 0.7 l*min^{-1}*m^{-2} and the lower, and upper 95% limit of agreement is -1.9 and 3.3 l*min^{-1}*m^{-2}, respectively. 95% confidence interval for the LOA was ± 0.26 l*min^{-1}*m^{-2} (**Figure 2**). The percentage error was 83.6%.

The intraclass correlation coefficient for PiCCO^{QR} was 0.97 and for MG 0.89.

Bland–Altman plots for systolic, mean, diastolic BP are shown in **Figure 3**.

We observed concordant changes in COI after fluid challenge in 50 percent of all measurements. **Figure 4** shows relative CO change (per cent) after fluid challenge for the test and reference device.

In the trending analysis of calculated CO with MG and PiCCO^{QR} over 6 h, we observed concordant increases or decreases in the CO slope in 50 percent of measurements as a correlate for the trend of changes.

DISCUSSION

In the present study, we evaluated the performance of a non-invasive oscillometry-based method for CO determination (MG) under static conditions and its ability to trend the changes in CO after fluid challenge and over a course of several hours in critically ill patients. We found a moderate correlation between CO estimation with MG and reference PiCCO^{QR} measurements and an acceptable mean bias between test and reference device with wide margins in LOA and a high percentage error. Since we performed repeated measurements per subject, high LOA and percentage error may be partly caused by the imprecision of either method (Saugel et al., 2020). We, thus, performed reliability analysis for the test and reference methods, respectively, and observed excellent intraclass correlation coefficients indicating low within-subject variance and high reliability of both methods. The algorithm used in MG relies on the precise derivation of the arterial pressure curve. Indeed, the exact determination of the arterial pressure curve with MG is a challenging process as data acquisition is realized using an occlusive cuff applied to the upper arm recording a wide range of oscillometric amplitudes (Wassertheurer et al., 2008). In our study cohort consisting of critically ill and vasopressor-dependent patients, the arterial pressure waveform signal in the brachial artery can be disturbed or differ significantly from that in the femoral artery (Teboul et al., 2016). Usually, diastolic and mean blood pressure are similar in peripheral and central arteries, and systolic blood pressure is higher in the femoral compared to brachial artery due to wave reflection (Kroeker and Wood, 1955). However, we observed clinically relevant lower systolic and clinically relevant higher diastolic and MAP with even statistical significance for diastolic and MAP between MG and PiCCO^{QR}, which is a common finding when blood pressure levels between peripheral (non-invasive), and central (invasive) measurements have been compared in critically ill patients. Imprecise estimation of central arterial pressure during hemodynamic instability can influence the accuracy of derived CO (Compton et al., 2008; Compton and Schafer, 2009).

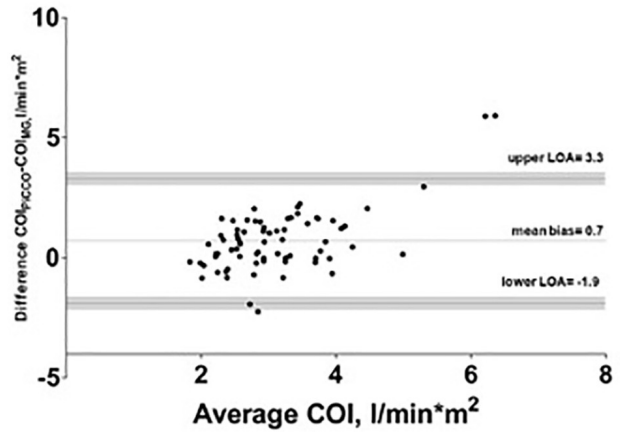

FIGURE 2 | Bland–Altman analysis of cardiac output index (COI) with test (Mobil-O-Graph-MG) and reference method (PiCCO^{QR} thermodilution). Gray shaded area represents 95% confidence interval of limits of agreement (LOA).

Plenty of non-invasive CO monitoring devices, which rely on non-invasive pulse wave analysis, pulse wave transit time, or thoracic bioimpedance as a basic principle for CO calculation, have been described in the literature (Papaioannou et al., 2020). Acknowledging that direct comparison with other non-invasive CO determination methods based only on published literature has its limitations due to different reference methods used and different study populations, our data ranged within the margins of published evidence. However, a very recent review on currently available technologies for CO determination using pulse wave analysis does not mention oscillometry as a potential method (Saugel et al., 2021), even though it has some very practical advantages like easiness, and rapidity of measurements as well as no requirement for any specific operator training.

Algorithmic refinements had been made by the manufacturer in 2018. Compared to a previous study with the older software we observed a lower mean bias with comparable LOA and higher percentage error in this study (Reshetnik et al., 2017). A recent study by Papaioannou et al. (2020) showed a comparable mean bias in a smaller cohort in the ICU. According to the cut-off of 30 percent for the percentage error, proposed by Critchley and Critchley (1999) the percentage error found in our study points to precision in need for improvement. As visualized in **Figures 1**, **2**, we observed some extreme values, which can be considered as outliers. Additional correlation analysis without outliers showed same finding of poor correlation between test and reference device.

In the clinical setting tracking CO changes with therapy or overtime is usually more important than the determination of single absolute CO values. Our study is one of the few, in which not only CO response to a singular fluid challenge was considered, but also the ability to track CO changes over a longer period. We observed concordant changes in CO with MG and PiCCO^{QR} in 50 percent of the measurements after volume change and over several hours, which points to a weak concordance.

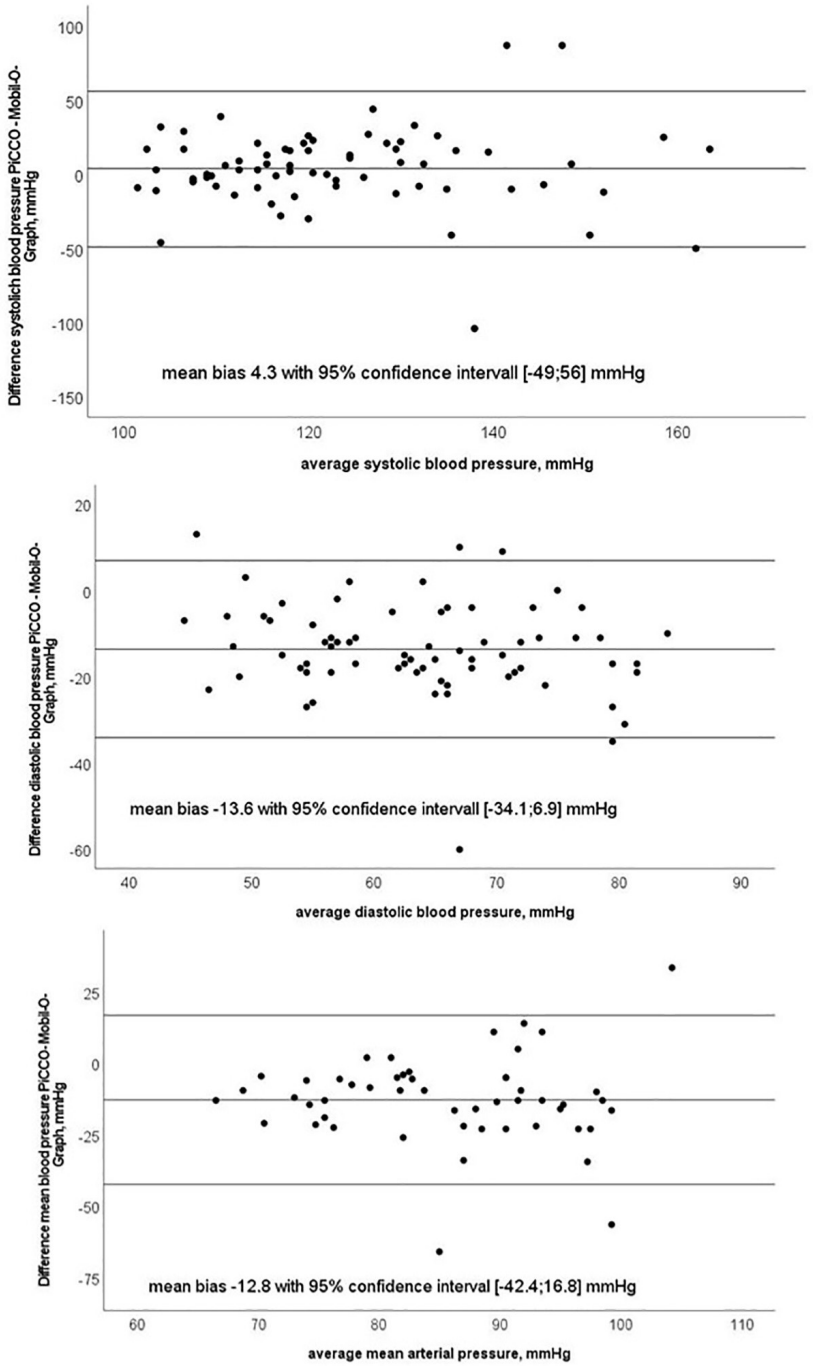

FIGURE 3 | Bland–Altman plots of systolic, diastolic and mean blood pressure with test (Mobil-O-Graph-MG) and reference method (PiCCO^{QR} thermodilution).

Of note, in 67% of cases with non-concordant CO changes recordings were performed while the patients received high-dose vasopressor therapy. Similar findings were reported for other CO calculation methods (Monnet et al., 2010). Indeed, there is evidence that pulse wave analysis devices may struggle to adapt to changes in vascular tone induced by vasopressors (Meng et al., 2011).

We acknowledge several limitations of the study. The number of enrolled subjects was relatively small. We did not use pulmonary artery catheter as the reference method. The vasopressor doses possibly contributing to significant variation in calculated CO varied between the subjects. Arterial compliance has a major influence on CO estimation derived from pulse wave analysis. Rapid changes in vasomotor tone, in particular

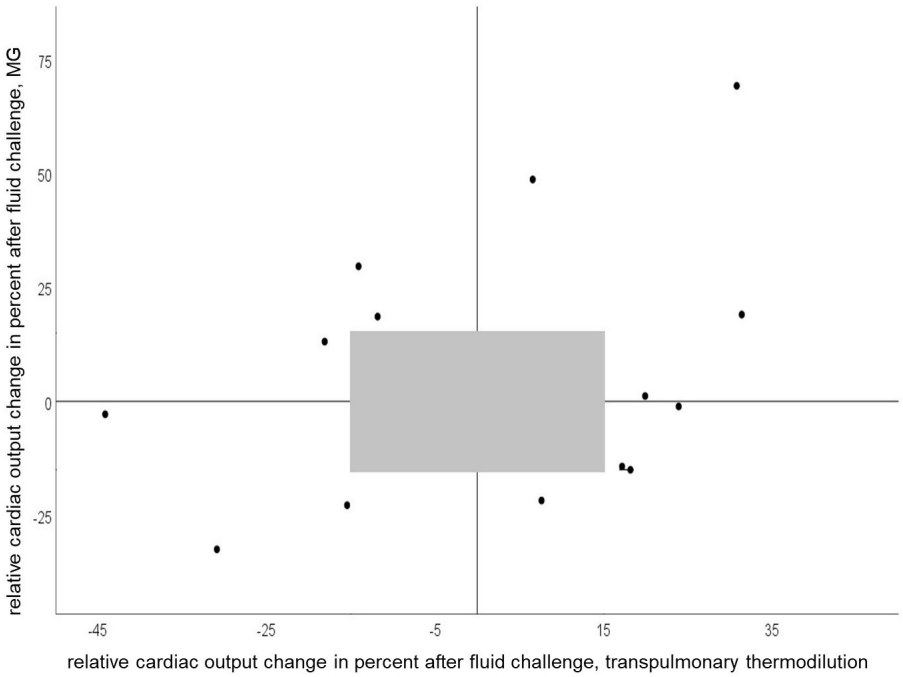

FIGURE 4 | Four-quadrant plot of relative cardiac output change after a fluid challenge of 150 ml with Mobil-O-Graph and PiCCO^{QR} (concordance rate = 50%). Gray shaded area represents exclusion zone of 15%.

with higher vasopressor dose, can have an impact on arterial compliance and consequently impair the CO estimation. Due to the non-randomized study design, we cannot account for all possible confounding factors, which may influence the CO. We did not compare BP values between both arms prior to the validation.

CONCLUSION

To conclude that CO calculation with a novel oscillometry-based pulse wave analysis method is feasible and replicable in critically ill patients. However, a clinically applicable agreement between MG and thermodilution used as a reference method in critically ill patients was not observed using the Bland–Altman approach and with trending analysis methods. In summary, we do not recommend using this method in critically ill patients at this time. As the basic approach is promising and the CO calculation with MG very simple, further studies should be performed in hemodynamic stable patients and critical care setting to gain additional data to be able to further adjust the underlying algorithm for CO determination in this device.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Charité Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AR: conception of design, analysis and interpretation of the data, drafting the article, and final approval of the version to be published. JG: conception of design, analysis and interpretation of the data, and drafting the article. MG: conception of design and providing intellectual content of critical importance. FC: interpretation of the data, revising the article, and final approval of the version to be published. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphys.2021.704425/full#supplementary-material

Supplementary Figure 1 | Cardiac output change in a patient over the time course registered with Mobil-O-Graph^{QR} and PiCCO^{QR} pulse contour analysis.

Supplementary Figure 2 | Relationship between cardiac output index (CO-Index) measured with transpulmonary thermodilution and Mobil-O-Graph (MG) after exclusion of outliers; Pearson's $r = 0.28$; $p = 0.02$.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

5 Diskussion

5.1 Stellenwert der PWV im Allgemeinen

Basierend auf den einleitend dargestellten Veränderungen der arteriellen Gefäßstruktur, geht die fortschreitende Arteriosklerose mit der Erhöhung der Gefäßsteifigkeit einher. Daher kann deren Einbezug in die Gesamtbeurteilung des kardiovaskulären Risikos die Prognosegenauigkeit verbessern. Es ist inzwischen in zahlreichen Studien gezeigt worden, dass die erhöhte Gefäßsteifigkeit der großen arteriellen Gefäße einen unabhängigen Risikofaktor darstellt, welcher mit kardiovaskulären Erkrankungen assoziiert ist. [34-36]

Von den verfügbaren Methoden der nicht-invasiven Bestimmung der Gefäßsteifigkeit hat sich die Messung der aortalen PWV aus folgenden Gründen in den klinischen Studien durchgesetzt:

a) die Aorta weist die höchste Elastizität auf und spielt somit im einleitend beschriebenen Windkesselmodel eine entscheidende Rolle;[37]

b) die Veränderungen der aortalen Struktur haben direkten Einfluss auf die Änderung der Hämodynamik am Herzen, in den Nieren und im Gehirn und sind somit direkt mit pathophysiologischen Effekten der erhöhten Gefäßsteifigkeit assoziiert. Diese steigt physiologisch entlang der Aorta von zentral nach peripher, so dass die aortale PWV als regionale Messung die Effekte auf alle kardiovaskulär relevanten Organe berücksichtigen würde.[37]

Die verfügbaren Methoden sind zwar in der Lage eine präzise lokale PWV zu erfassen, allerdings ist das Ausmaß des arteriellen Gefäßschadens in unterschiedlichen arteriellen Gefäßabschnitten verschieden bzw. ist das dadurch entstehende kardiovaskuläre Risiko variabel. Beispielsweise weist die Aorta lokal eine höhere Steifigkeit als die

lokal gemessene Steifigkeit der A. carotis in Kollektiven der Diabetiker:innen und Patient:innen mit arteriellem Hypertonus auf.[38] Die Bestimmung der regionalen PWV, wie z.B. cfPWV, erfasst die Gesamt-PWV des Abschnitts zwischen den Messstellen. Diese hat sich im Laufe der letzten zwei Jahrzehnte als Goldstandard der nicht-invasiven Beurteilung der arteriellen Gefäßsteifigkeit etabliert: einerseits, weil die Erfassung der Druckkurven an der A. carotis und A. femoralis vergleichsweise einfach nicht-invasiv gelingt und andererseits, weil die gesamte Aorta damit in die Bestimmung der PWV einbezogen wird. 2013 wurde die cfPWV deshalb als Standardmethode für die Beurteilung der subklinischen Organschädigung in die Leitlinie der europäischen kardiologischen und hypertensiologischen Gesellschaften aufgenommen.[36] Am häufigsten verwendete, in der Literatur beschriebene Methoden sind die Mechanotransduktion mit dem Complior®-System und die Tonometrie mit dem Sphygmocor®-System.[39,40] Die so gemessene cfPWV wird als Standardmethode betrachtet, dennoch sind die genannten Methoden mit relevanten Einschränkungen insbesondere in Hinblick auf die Anwendung in der klinischen Routine behaftet: Die Berechnung der PWV ist von der möglichst exakten Bestimmung sowohl der Distanz zwischen den Messpunkten als auch der Transitzeit abhängig. Die Schätzung der wahren Distanz wird bei diesen Methoden basierend auf der oberflächlichen Distanzmessung zwischen den anatomischen Messpunkten vorgenommen. Diese Schätzung ist abhängig von Messmethode, Körperoberfläche und Adipositas mit einer nicht zu unterschätzenden Ungenauigkeit verbunden.[15,16] Auch die Bestimmung der Pulswellen-Transitzeit bedingt abhängig vom verwendeten Algorithmus 5-15% Schwankungen der PWV-Werte.[41] Im Gegensatz zu der Bemessung der Distanz, welche entsprechend dem Expertenkonsens als Abstand Carotis-Femoralis*0,8 erfasst wird, existiert kein Standardprotokoll zur Mes-

sung der Pulswellen-Transitzeit.[39,42] Zudem sind die Methoden zeitaufwendig und bedürfen speziell geschulten Personals, was die Anwendung außerhalb klinischer Studien sehr erschwert.

Neben der PWV sind weitere hämodynamische Parameter wie der zentrale Blutdruck, zentrale Pulsdruck und der Augmentationsindex in der Literatur mit Arteriosklerose assoziiert. Allerdings sind diese Parameter auch von der Herzfrequenz (hier insbesondere der Augmentationsindex) und von der ventrikulären Kontraktilität abhängig und spiegeln somit nicht alleine die arterielle Gefäßsteifigkeit wider.[43] In der Framingham-Studie zeigte sich die prädiktive Kraft der aortalen Gefäßsteifigkeit (beschrieben als cfPWV) höher als die der brachialen Gefäßsteifigkeit (beschrieben mit Carotis-Radialis PWV), des Augmentationsindexes und des zentralen Pulsdruckes.[44] Die Berechnung des zentralen Blutdruckes erfolgt anhand der peripheren Pulskurvenanalyse. Um den absoluten nummerischen Wert zu bestimmen ist ein Skalierungsparameter notwendig. Als solcher fungiert der mittlere arterielle Druck (MAD), der theoretisch zwar relativ präzise in jungen Patient: innen mit elastischen Gefäßen erfasst werden kann. In der Praxis jedoch ist es gerade mit steigendem Alter zunehmend schwieriger den MAD exakt oszillometrisch zu bestimmen. Die oszillometrische Messung hat sich in der täglichen Praxis der peripheren Blutdruckmessung bewährt. So haben wir zeigen können (Manuskript 1), dass die verwendeten Geräte eine klinische adäquate Präzision in der Messung der peripheren Blutdrücke aufweisen. Schleicht sich schon ein geringer Fehler in die Bestimmung des MAD ein, so potenziert sich dieser bei dem peripheren systolischen und dadurch auch bei dem zentral systolischen Blutdruck, der algorithmusbedingt sehr stark mit dem peripheren systolischen Blutdruck korreliert.[45] Die Ungenauigkeit in der MAD-Bestimmung sowie die algorithmus-bedingte enge Korrelation zwischen dem peripheren und zentralen Blutdruck sähen Zweifel am zentralen Blutdruck als zusätzlichem unabhängigen kardiovaskulären Marker bzw. als bedeutendem

hämodynamischem Parameter.[46] Obwohl meine Arbeitsgruppe sich auch mit dem zentralen Blutdruck beschäftigte[47], entschieden wir uns aus oben genannten Gründen diesen nicht mehr intensiv zu verfolgen.

5.2 Beurteilung der oszillometrischen PWV-Kalkulation unter besonderer Berücksichtigung der Anforderungen der klinischen Praxis

Die in der Einleitung dargestellten grundlegenden physikalischen Prinzipien erlauben es die hämodynamischen Zustände im arteriellen Kreislaufsystem zu beschreiben. Eine optimale Beurteilung der Hämodynamik im arteriellen System gelingt, wenn man in der Lage ist den Blutfluss zu charakterisieren. Die direkte Flussmessung mit nicht-invasiven Verfahren ist sehr schwierig, so dass üblicherweise die arterielle Druckkurve nicht-invasiv erfasst wird und basierend darauf der Fluss kalkuliert wird.

2008 veröffentlichte die Arbeitsgruppe von Siegfried Wassertheurer einen speziellen Algorithmus (ARC-Solver). Dieser analysiert oszillierende Amplituden der Pulswelle an der okklusiven Manschette um die A. brachialis am Oberarm. Auf diese Weise können a) die periphere Pulskurve generiert; b) diese mit Hilfe der mathematischen Modelle in eine aortale Druckkurve transferiert; c) der Blutfluss modelliert und d) die PWV und das HZV kalkuliert werden.[21]

In ihrer Erstveröffentlichung zum ARCSolver-Algorithmus merkten die Autoren an, dass trotz der Applikation der hierzu passenden physikalischen Theorien die zusätzliche Anwendung eines neuronalen Netzwerkes erforderlich ist.[21] Somit beruht der Algorithmus nicht nur auf allgemeingültigen mathematischen Formeln und physikalischen Prinzipien, sondern auch auf empirischen Daten aus einem per se begrenzten Patientenkollektiv. Die Validität der Ergebnisse wurde seitdem mehrfach für verschiedene hämodynamische Parameter überprüft. 2010 zeigten Wassertheurer et al. in einem Kollektiv von 302 kardiologischen und hypertensiologischen Patient: innen, dass

der oszillometrisch geschätzte zentrale systolische Blutdruck und Augmentationsindex den mit tonometrischer Methode gemessenen Werten sehr ähnelt.[48] Im Manuskript 2 gezeigte Daten weisen auch auf eine gute Korrelation zwischen den oszillometrisch kalkulierten PWV-Werten und tonometrisch gemessener PWV hin. Im Studiendesign wählten wir bewusst die Tonometrie als nicht-invasive Referenzmethode, obwohl in der Leitlinie eine invasive Messung als Goldstandard vorgeschlagen wird.[25] Ergänzend zu den unter 5.1 dargestellten Überlegungen ist Folgendes zu vermerken: Nahezu alle klinischen Studien verwendeten die tonometrische Methode zur PWV-Bestimmung, da diese nicht-invasiv und im Vergleich zu MRT- oder ultraschallbasierten Methoden weniger zeit- und ressourcen-intensiv ist. Die Mehrheit der prospektiven klinischen Studien verwendeten cfPWV als Surrogatparameter der arteriellen Steifigkeit in ihren Analysen und konnten ihren prädiktiven Wert in Bezug auf kardiovaskuläre Ereignisse in unterschiedlichen Populationen zeigen.[18,39,49-53] Somit gibt es gute Evidenz der Assoziation zwischen cfPWV und kardiovaskulärer Morbidität und Mortalität. Daher ist es sinnvoll die oszillometrische Methode mit der cfPWV als Referenz zu verwenden.

Unsere Daten zeigen, dass die einzelnen cfPWV-Werte eine stärkere Variabilität als die oszillometrisch ermittelte PWV aufweisen. Auch in anderen Studien ist eine höhere Variabilität der gemessenen cfPWV-Einzelwerte beschrieben, was in der Konsequenz bedeutet, dass mehrfache Einzelmessungen notwendig sind um den tatsächlichen Wert besser einzuschätzen.[54] Unsere Ergebnisse hingegen zeigen, dass die oszillometrisch ermittelten PWV-Einzelwerte – auch unabhängig von der Lage der Patient:innen und Erfahrung der bedienenden Person – sehr robust sind. Somit erscheint die oszillometrische PWV-Bestimmung für den Einsatz in der klinischen Routine aus folgenden Gründen der cfPWV als Goldstandard überlegen: a) die Untersuchung ist einfach und schnell da nur eine Einzelwertbestimmung pro Messdurchgang notwendig ist und lediglich an einem anatomischen Punkt gemessen wird; b) die Ergebnisse sind

untersucher- und situations-unabhängig robust; c) multiple Messungen im zeitlichen Verlauf sind sehr einfach möglich.

5.3 Spezifika der Oszillometrie und Vergleich mit anderen Methoden, die auf dem Windkesselmodel beruhen

Im Allgemeinen basiert die oszillometrische Bestimmung der arteriellen Gefäßsteifigkeit in der Analogie zur Elektrizitätslehre auf Modellen, die Kapazität und Widerstand in Serie kombinieren. Einer direkten Messung eines peripher erfassten Parameters folgt eine Reihe von mathematischen und physikalischen Annahmen, welche zur Berechnung der aortalen PWV verwendet werden. Dieses Vorgehen an sich verleiht der Methode im Vergleich zur direkten Messung Limitationen. So sind die berechneten Werte nicht immer direkt vergleichbar mit den nominalen Werten der invasiven Messung oder tonometrischen nicht-invasiven Messung. Dieser Umstand ist auch bei den anderen Methoden, welche auf theoretischen mathematischen Modellen wie dem Windkesselmodel beruhen, bekannt.[55] Einer der wichtigen Diskussionspunkte bei algorithmus-basierten Kalkulationsmethoden ist wie ausgeprägt der Einfluss der einzelnen unabhängigen Variablen auf die Zielvariable ist. So ist rezent für den ARCSolver-Algorithmus beschrieben, dass die Assoziation mit Alter und Blutdruck in der Berechnung der aortalen PWV gerade bei gesunden Proband: innen stark ist.[56] Als Konklusion äußerten die Autoren Zweifel am zusätzlichen Nutzen der aortalen PWV abseits vom Einfluss des Blutdruckes und Alters. In der Tat konnten Schwartz et al. eine sehr enge Korrelation zwischen der aortalen PWV und dem Alter (Korrelationsindex R^2=0,998) sehen.[56] Eine ähnlich hohe Korrelation zwischen oszillometrisch gemessener aortaler PWV und dem arteriellen Blutdruck konnten wir auch in unseren Untersuchungen beobachten. Die Studie wurde in einem Kollektiv Gesunder durchgeführt. Möglicherweise

ist hier zur Schätzung der Gefäßsteifigkeit eine alleinige Berechnung anhand von Parametern wie Alter und arteriellem Blutdruck ausreichend.[57] Allerdings zeigt die anhand des Blutdruckes und Alters berechnete PWV im Gegensatz zur cfPWV keinen zusätzlichen prädiktiven Wert bezüglich der kardiovaskulärer Ereignisse in Kollektiven mit hohem kardiovaskulären Risiko (z.B. Patient:innen mit Hypertonus, Lipidstoffwechselstörung, chronischer Niereninsuffizienz, Diabetes mellitus, etc.).[57] Erste Daten weisen darauf hin, dass die oszillometrische PWV einen unabhängigen kardiovaskulären prädiktiven Effekt in Patient:innen mit hohem basalen kardiovaskulären Risiko zeigt. So beobachteten beispielsweise Sarafidis et al. in Hämodialyse-Patient: innen, dass die oszillometrisch gemessene aortale PWV als einziger Parameter mit erhöhter kardiovaskulärer Mortalität und höherer Rate kardiovaskulärer Ereignisse korreliert, während keine statistisch signifikante Korrelation sowohl für den Blutdruck als auch fürs Alter bestand.[58]

Derzeit gibt es keine andere Methode zum Vergleich, die ausschließlich anhand der oszillometrisch-basierten Pulskurvenanalyse, des Alters und des gemessenen peripheren Blutdruckes die aortale PWV berechnet. In der Literatur sind zwei weitere Methoden – Arteriograph (TensioMed, Budapest, Ungarn) und Vasotens (BPLab, Smolensk, Russland) – beschrieben, die oszillometrisch die Pulskurve erfassen. Anhand der Pulskurve wird jedoch lediglich die Transitzeit ermittelt. Im Falle des Arteriographs wie in der Abbildung 6 gezeigt, wird die Transitzeit als Intervall zwischen dem Beginn der Vorwärtswelle und dem Beginn der Reflektionswelle angenommen.[59] Bei Vasotens-Algorithmus wird die Transitzeit als Intervall zwischen dem Druckmaximum der Vorwärtswelle und dem Druckmaximum der Reflektionswelle angenommen.[60,61] Zur Berechnung der PWV ist die Distanzmessung notwendig, welche auf dem Abstand zwischen Jugulum und Symphyse basiert. Die Notwendigkeit die Distanz zu messen verlängert die Untersuchungsdauer und bringt die damit verbundenen Messfehler ein.

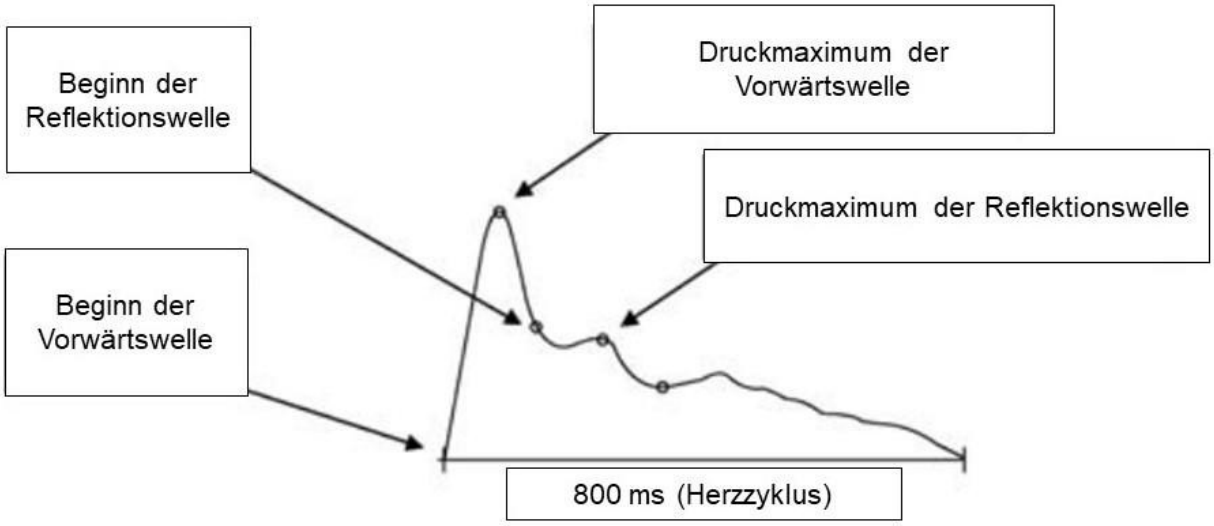

Abbildung 6: Mit Arteriograph oszillometrisch generierte Pulswelle. Verwendung mit freundlicher Genehmigung des Wolther Kluwer Health, in Anlehnung an Baulmann et al.[59]

Im Gegensatz zu cfPWV, für die es einen Konsens gibt, dass die Werte ≥ 10 m/s als pathologisch erhöht gelten, fehlt derzeit eine offizielle Empfehlung für den Grenzwert oszillometrisch gemessener PWV, obwohl bereits die ersten Beschreibungen der Referenzwerte in einer gesunden Population publiziert sind.[39,62,63] Kritisch anzumerken ist jedoch, dass die pauschale Empfehlung von einem Grenzwert von 10 m/s für die cfPWV unabhängig von dem dazugehörigen Blutdruckwert (hierzu ausführliche Diskussion unter Punkt 5.4) und dem Alter bzw. Alterskategorien gemacht wurde. Ob der für die cfPWV etablierte Grenzwert von 10 m/s ohne weiteres auf die oszillometrische Methode übertragen werden kann, ist derzeit noch nicht geklärt. Erste Daten weisen darauf hin, dass die Verwendung desselben Grenzwertes auch für die oszillometrisch erfasste aortale PWV prädiktiv für die erhöhte Gesamtmortalität ist.[64] Unabhängig von bestimmten Grenzwerten, ist eine grundsätzliche Assoziation der oszillometrisch ermittelten aortalen PWV mit einem Endorganschaden und kardiovaskulären Ereignissen in unterschiedlichen Populationen und mit unterschiedlichen oszillometrischen Methoden beschrieben.[65-69]

Immer wieder wird der Stellenwert der PWV als Marker der Arteriosklerose und Steuerungsparameter für die Therapie in Frage gestellt. Der Grund sind bislang fehlende etablierte therapeutische Optionen, die direkt die Arteriosklerose und PWV adressieren. Wir sehen dennoch den Vorteil der PWV als einen Parameter der nicht-invasiven Hämodynamik, der uns erlaubt den strukturellen und funktionellen Zustand des arteriellen Systems besser zu beschreiben und nachweislich eine unabhängige Assoziation mit kardiovaskulären Ereignissen hat. Einen interessanten Ansatz die PWV als therapeutischen Zielparameter zu verwenden, wählten Laurent et al. in ihrer rezenten Studie, in der sie die Steuerung der Blutdruckeinstellung anhand der cfPWV (Ziel<10 m/s) mit der konventionellen Blutdruckeinstellung verglichen. Der primäre Endpunkt (Kombination aus Schlaganfall und akutem Koronarsyndrom) unterschied sich zwar nicht statistisch signifikant zwischen den Gruppen, allerdings konnte eine bessere Blutdruckeinstellung in der Interventionsgruppe und eine Verzögerung der Arteriosklerose, beurteilt anhand der cfPWV-Trends über die Zeit, erreicht werden.[70]

5.4 Blutdruckunabhängige Darstellung der PWV als notwendige Voraussetzung zur Einschätzung des wahren arteriellen Gefäßschadens

Ein physiologischer Zusammenhang zwischen dem im Gefäß vorherrschenden Blutdruck und der PWV ist lange bekannt.[27] In den klinischen Studien wurden unterschiedliche Methoden verwendet um dieser Tatsache Rechnung zu tragen: Eine Idee ist die PWV in eine blutdruckunabhängige dimensionslose Variable zu überführen. Ein solches Vorgehen wurde bei dem so genannten *cardiac ankle vascular Index* (CAVI) gewählt und die ermittelte PWV in eine komplexe Gleichung mit dem systolischen, diastolischen Blutdruck und der Blutdichte eingegeben.[71] Bei der Verwendung des CAVI ist zu bedenken, dass nicht nur die aortale PWV, sondern auch die periphere PWV

und somit die Gefäßsteifigkeit der peripheren Gefäße ins Endergebnis eingehen. Die Assoziation von CAVI mit den kardiovaskulären Endpunkten ist fraglich, obwohl es Daten gibt, die auf eine Assoziation zwischen CAVI und kardiovaskulären Ereignissen hinweisen.[72]

Am häufigsten wurde eine allgemeine statistische Adjustierung mit „Blutdruck“ als Einflussvariable vorgenommen.[73] Dieses ist zwar auf der Populationsebene anwendbar, bildet jedoch nicht die individuelle Assoziation zwischen der PWV und dem Blutdruck ab.

Unser Ziel war es deshalb einen Parameter zu entwickeln, welcher eine individuelle Assoziation zwischen dem Blutdruck und der PWV abbildet. Wie im Manuskript 3 gezeigt, gelang uns das, indem eine mathematische Kalkulation der blutdruckunabhängigen PWV, basierend auf einer Punktewolke aus der seriellen PWV und einer 24-Stunden-Langzeitmessung vorgenommen wurde. So kann die Normierung auf jeden beliebigen Blutdruckwert vorgenommen werden. Wir haben uns für die Normierung auf den zentral-systolischen Blutdruckwert von 120 mmHg entschieden und so den Parameter PWV_{120} etabliert. Zu den Vorteilen der blutdrucknormierten PWV zählen die Distinktion zwischen dem individuellen blutdruck-vermittelten Effekt auf die PWV und dem arteriellen Gefäßschaden und die Möglichkeit diese bei wiederholten Messungen intraindividuell und interindividuell vergleichbar zu machen. So konnten wir zeigen, dass Schwankungen der PWV bei Dialysepatient: innen innerhalb einer Woche ein Ausdruck der physiologischen Abhängigkeit der PWV vom Blutdruck und nicht von strukturellen Gefäßwandveränderungen waren (Manuskript 4). Ähnliche PWV-Schwankungen wurden bereits 2015 bei Dialysepatient: innen durch Koutroumbas et al. für die oszillomet- rische aortale PWV beschrieben, ohne dass die Autoren auf die physiologische Ab- hängigkeit des arteriellen Blutdruckes eingehen.[74] Die tonometrische Messung der cfPWV ergab ebenfalls keine kurzfristige Änderung

intradialytisch bzw. zwischen den Dialysesitzungen, sofern die Änderung des Blutdruckes berücksichtigt wurde.[75-77]

5.5 Oszillometrie-basierte berechnete aortale PWV als neuer Marker für die verbesserte kardiovaskuläre Prognose

Die bislang als Goldstandard etablierte cfPWV war ein lange und viel in den Studien untersuchter Parameter, wenn es um die Einschätzung der arteriellen Gefäßsteifigkeit oder des kardiovaskulären Risikos ging. Die oszillometrie-basiert berechnete aortale PWV entwickelte sich als eine in der Handhabung sehr einfache Methode und hat deshalb das Potential die cfPWV abzulösen. Als neuer Marker für die verbesserte kardiovaskuläre Prognose ist es für die aortale PWV notwendig bestimmte Voraussetzungen zu erfüllen.[78] Hinsichtlich der Assoziation zwischen der aortalen PWV und der kardiovaskulären Mortalität und Morbidität gibt es derzeit gute Evidenz aus prospektiven Kohortenstudien, wobei bislang randomisierte Studien fehlen. Es gibt bislang wenige Daten zur unabhängigen prognostischen Wertigkeit der aortalen PWV, insbesondere, weil die physiologisch bedingte Korrelation mit dem arteriellen Blutdruck wenig berücksichtigt wurde. Durch meine Arbeiten konnte ich einen wichtigen Beitrag zum Verständnis der individuellen Blutdruckabhängigkeit der aortalen PWV im Besonderen, aber auch der PWV im Allgemeinen, leisten. Die entwickelte Methode der Blutdruck- adjustierung gibt die Möglichkeit einer unkomplizierten Verwendung in Studien und klinischer Routine. Auch in Bezug auf weitere Anforderungskriterien wie klinische Robustheit, Kosteneffektivität und Handhabung konnte ich durch meine Arbeiten die Evidenz für die aortale PWV erweitern und gerade diese Punkte bei der oszillometrischen Methode als sehr positiv hervorheben.

5.6 Oszillometrische Kalkulation des HZV

Das HZV ist eine der entscheidenden Determinanten der Sauerstoffversorgung. Die Kenntnis des HZVs ist einer der wichtigsten Punkte in der hämodynamischen Überwachung der Patient: innen. Als klinischer Standard der HZV-Messung hat sich die invasive Indikator-Dilutionsmethode (Pulmonalarterieller Katheter oder transpulmonale Thermodilution) etabliert. Da die Methoden invasiv sind, beschränkt sich deren Anwendung auf nur wenige spezielle Settings wie die Intensivstation oder den kardiochirurgischen Operationssaal.

Die Kenntnis des HZVs als statische Größe aber auch seine Veränderung nach therapeutischen Maßnahmen ist auch außerhalb der oben genannten speziellen Settings sehr hilfreich. So ist beispielsweise die HZV-Veränderung bei Patient: innen mit Herzinsuffizienz unter therapeutischer Rekompensation von großem Interesse, da diese das Therapieansprechen anzeigt und ein therapeutischer Zielparameter sein kann. Neue nicht-invasive Ansätze der HZV-Kalkulation können die Anwendung des HZVs z.B. auf einer peripheren Krankenhausstation oder sogar im ambulanten Bereich möglich machen.

Einige nicht-invasive Verfahren der HZV-Messung sind untersucht worden: der suprasternale Dopplerultraschall, die Pulswellenanalyse mit modifizierter Windkesselfunktion, die Pulswellentransitzeit, die Radialarterientonometrie, die thorakale oder endotracheale Bioimpedanz, die Bioreaktanz und die CO_2-Rückatmung.[79] Die oszillometrische Schätzung des HZVs ist eine bisher kaum beachtete Methode. So wird sie in einem rezenten Review der nicht-invasiven Verfahren zur HZV-Bestimmung nicht erwähnt.[80] Genau wie die oszillometrische Methode nutzen die Finger-Cuff-Methode und die radiale Applanationstonometrie die Pulskurvenanalyse zur HZV-Bestimmung.[81,82] Im Vergleich zu den anderen Methoden, die nicht-invasive Pulskurvenanalyse verwen-

den, zeigen unsere Daten vergleichbare Ergebnisse (Manuskripte 5 und 6). Eine zuverlässige HZV-Kalkulation mittels Pulskurvenanalyse ist von mehreren Faktoren abhängig: Ähnlich wie bei der PWV-Kalkulation ist die HZV-Berechnung von der präzisen Pulskurvendarstellung abhängig. Insbesondere ist eine möglichst genaue Bestimmung des systolischen Anteils der Pulskurve essentiell, da dies bei der HZV-Berechnung relevant ist. Bedingt durch die Tatsache, dass die Referenzmethode fast immer eine invasive Indikatormethode ist, werden die Validierungsstudien solcher nicht-invasiven Methoden meist mit einem Kollektiv intensivstationärer Patient: innen durchgeführt. Diese sind häufig vasopressorabhängig und hämodynamisch instabil. Darunter ist sowohl die Blutdruckbestimmung als auch die Erfassung der Pulskurvenanalyse besonders in peripheren Arterien erschwert. Grundsätzlich wird die Pulskurve durch die nicht-invasiven Methoden automatisch generiert und nicht durch die Bedienenden überprüft, so dass sich Artefakte in der Darstellung der Pulskurve einschleichen können. Auch können rapide Veränderungen im Vasotonus die Durchführbarkeit der Pulskurvenanalyse beeinträchtigen.[83] Im Hinblick auf die bisher publizierten Daten kann für keines der derzeit verfügbaren nicht-invasiven Verfahren zur HZV-Messung eine Empfehlung ausgesprochen werden, da diese in den Studien im Vergleich zu den Referenzverfahren eine breite Ergebnisstreuung aufweisen.[79] Unsere Daten erweitern die Evidenz und untersuchen zum ersten Mal die Performance der oszillometrie-basierten HZV-Kalkulation. Im Kollektiv der hämodynamisch instabilen intensivstationären Patient:innen kann diese Methode wie andere nicht-invasive Technologien derzeit die Referenzverfahren nicht ersetzen. Allerdings gibt es erste Hinweise darauf, dass die HZV-Schätzung bei nicht kritisch-kranken und hämodynamisch stabilen Patient:innen von Vorteil sein kann. So haben Yenerçağ et al. gesehen, dass die Optimierung der kardialen Resynchronisationstherapie basierend auf der oszillometrischen nicht-invasiven HZV-Kalkulation eine verlässliche Option darstellt.[84] Godoy et al. sahen eine

gute Konkordanz des HZVs zwischen Oszillometrie und transthorakaler Echokardiographie.[85]

Gerade die oszillometrische Methode bietet durch ihre einfache Anwendbarkeit großes Potential für die breite klinische Routine, so dass einer unserer aktuellen Forschungsschwerpunkte auf der Weiterentwicklung des Algorithmus und Methodenanwendung insbesondere bei hämodynamisch stabilen Patient: innen liegt. Meine Arbeiten in diesem Bereich haben zur Erweiterung der Datenlage hinsichtlich der oszillometrischen HZV-Schätzung beigetragen und dienten als Grundlage zur Weiterentwicklung des mathematischen Algorithmus.

6 Zusammenfassung

In der komplexen Welt der Hämodynamik im arteriellen Gefäßsystem waren Blutdruck und Herzfrequenz lange Zeit die einzigen verfügbaren nicht-invasiven hämodynamischen Variablen. In den letzten Jahrzehnten wurden weitere relevante Parameter wie PWV, zentraler Blutdruck und HZV etabliert. Insbesondere die Rolle der cfPWV als Surrogatparameter des strukturellen arteriellen Gefäßschadens (Arteriosklerose) wurde in vielen klinischen Studien untersucht. Die cfPWV zeigte als unabhängiger kardiovaskulärer Risikomarker in unterschiedlichen Kollektiven die Assoziation mit kardiovaskulärer Morbidität und Mortalität.

Seit Jahren stehen uns zuverlässige invasive und nicht-invasive Messmethoden zur Verfügung. In den letzten zehn Jahren wurden sowohl die oszillometrische Technik als auch die mathematischen Algorithmen so weiterentwickelt, dass eine nicht-invasive Kalkulation der erweiterten hämodynamischen Parameter möglich wurde. Durch ihre einfache Handhabung eignet sich diese Messung sehr gut für die breite Anwendung sowohl in klinischen Studien als auch in der klinischen Routine. Meine Arbeiten zeigen, dass die Methode eine sehr zuverlässige Messung der PWV in unterschiedlichen Kollektiven und unter verschiedenen Bedingungen bei gleichzeitig sehr einfacher, robuster und schneller Messdurchführung leistet. Dies gelingt zuverlässig, obwohl selbst unter Anwendung der gängigen physikalischen Prinzipien und Applikation komplexer mathematischer Algorithmen die Abbildung der realen Situation im arteriellen Gefäßsystem nicht einfach ist. Basierend auf der oszillometrischen PWV-Bestimmung konnte ich einen Algorithmus entwickeln, der eine blutdruck-unabhängige PWV-Darstellung erlaubt. Solche Darstellung gibt eine exaktere Widerspiegelung des vorhandenen arteriellen Gefäßschadens. Damit wird im Setting der klinischen Studien und Routineun-

tersuchungen eine bessere Abschätzung des kardiovaskulären Risikos für das Individuum ermöglicht. Ich konnte zudem zeigen, dass die oszillometrische HZV-Kalkulation bei hämodynamisch-instabilen intensivstationären Patien: innen machbar ist und wichtige erste Einblicke in die Methodengenauigkeit und Methodengrenzen bekommen. Die gewonnenen Daten wurden gleichzeitig auch die Grundlage für die Weiterentwicklung des Algorithmus und sind Voraussetzung für weitere Studien.

Meine Arbeiten haben den Stellenwert der Oszillometrie in der Kalkulation der PWV und des HZVs unter verschiedenen Gesichtspunkten und in unterschiedlichen Patientenkollektiven angeschaut. Sie haben einen wichtigen Beitrag zur Verständniserweiterung der Methode geleistet und eine Grundlage zur Anwendung der blutdruckunabhängigen individuellen Abschätzung der Gefäßsteifigkeit geschaffen. Die generierten Ergebnisse ermöglichen den Einsatz der Oszillometrie in zukünftigen interventionellen Studien mit dem Ziel der Modifikation der Gefäßsteifigkeit und in der breiten klinischen Routine.

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9 Erklärung

Gemäß dem § 4 Abs. 3 (k) der HabOMed der Charité

Hiermit erkläre ich, dass - weder früher noch gleichzeitig ein Habilitationsverfahren durchgeführt oder angemeldet wurde, - die vorgelegte Habilitationsschrift ohne fremde Hilfe verfasst, die beschriebenen Ergebnisse selbst gewonnen sowie die verwendeten Hilfsmittel, die Zusammenarbeit mit anderen Wissenschaftlern/Wissenschaftlerinnen und mit technischen Hilfskräften sowie die verwendete Literatur vollständig in der Habilitationsschrift angegeben wurden, - mir die geltende Habilitationsordnung bekannt ist. Ich erkläre ferner, dass mir die Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis bekannt ist und ich mich zur Einhaltung dieser Satzung verpflichte.

19.02.2022.

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