Excess pressure as an analogue of blood flow velocity

Matthew K. Armstrong[a], Martin G. Schultz[a], Alun D. Hughes[b], Dean S. Picone[a], J. Andrew Black[c], Nathan Dwyer[c], Philip Roberts-Thomson[c], James E. Sharman[a]

[a]*Menzies Institute for Medical Research, University of Tasmania, Australia*

[b]*Institute of Cardiovascular Science, University College London, London, United Kingdom*

[c]*Department of Cardiology, Royal Hobart Hospital, Australia*

Sources of support:

MKA is supported by an International Postgraduate Research Scholarship from the Menzies Institute for Medical Research. MGS is supported by a National Health and Medical Research Council Early Research Career Fellowship (reference 1104731). ADH receives support from the British Heart Foundation (CS/13/1/30327, PG/13/6/29934, PG/15/75/31748, CS/15/6/31468, PG/17/90/33415, IG/18/5/33958), the National Institute for Health Research University College London Hospitals Biomedical Research Centre, the UK Medical Research Council (MR/P023444/1) and works in a unit that receives support from the UK Medical Research Council (MC_UU_12019/1). DSP is supported by a Menzies Community Postdoctoral Fellowship.

Conflict of interest:

None declared.

Corresponding author:

James E. Sharman

Menzies Institute for Medical Research, University of Tasmania

Private Bag 23, Hobart, 7000, AUSTRALIA.

Phone: +61 3 6226 4709 Fax: +61 3 6226 7704

Email: James.Sharman@utas.edu.au

Word count: 3027 **Tables:** 3 **Figures:** 3

Abstract

Introduction: Derivation of blood flow velocity from a blood pressure waveform is a novel technique which could have potential clinical importance. Excess pressure, calculated from the blood pressure waveform via the reservoir-excess pressure model, is purported to be an analogue of blood flow velocity, but this has never been examined in detail, which was the aim of this study.

Methods: Intra-arterial blood pressure was measured sequentially at the brachial and radial arteries via fluid filled catheter simultaneously with blood flow velocity waveforms recorded via Doppler ultrasound on the contralateral arm (n=98, aged 61±10, 72% male). Excess pressure was derived from intra-arterial blood pressure waveforms using pressure-only reservoir-excess pressure analysis.

Results: Brachial and radial blood flow velocity waveform morphology were closely approximated by excess pressure derived from their respective sites of measurement (median cross-correlation coefficient r=0.96 and r=0.95 for brachial and radial comparisons respectively). In frequency analyses, coherence between blood flow velocity and excess pressure was similar for brachial and radial artery comparisons (brachial and radial median coherence=0.93 and 0.92 respectively). Brachial and radial blood flow velocity pulse heights were correlated with their respective excess pressure pulse heights ($r = 0.53$, $p < 0.001$ and $r = 0.43$, $p < 0.001$ respectively).

Conclusion: Excess pressure is an analogue of blood flow velocity, thus affording the opportunity to derive potentially important information related to arterial blood flow using only the blood pressure waveform.

Key words: Hemodynamics, Pulse wave analysis, Invasive

Introduction

Continuous non-invasive recording of blood pressure (BP) and flow is valuable in the settings of anaesthesiology, cardiology and emergency care for the hemodynamic assessment and management of the critically ill. Several methods exist for recording continuous non-invasive BP, many of which are straightforward to apply and nondemanding for the operator [1]. Continuous non-invasive measures of blood flow velocity and volumetric flow are also possible via Doppler ultrasound. However, Doppler-capable devices can be prohibitively expensive and require the presence of a skilled operator to hold the transducer at a fixed angle over the artery. Given the interdependence of BP and blood flow, methods have been proposed whereby volumetric blood flow may be estimated via analysis of the BP waveform (e.g. pulse contour analysis), thus circumventing the challenges posed by conventional blood flow assessment [2–5]. Yet, methods utilising pulse contour analysis have been shown to be inaccurate during hemodynamic instability [6].

The reservoir-excess pressure model is a heuristic model of arterial hemodynamics that separates the measured BP waveform into reservoir pressure and excess pressure components. [7,8] These components can be derived from peripheral arterial BP waveforms recorded invasively or non-invasively [9,10]. In their original study outlining the reservoir-excess pressure model, Wang et al. [7] demonstrated striking similarities between the shape of the excess pressure and volumetric flow waveforms in the dog aorta. More recently, excess pressure derived from non-invasively acquired carotid artery waveforms closely approximated aortic volumetric flow in humans. [11] Thus, excess-pressure represents a potential opportunity to measure clinically relevant information related to both BP and flow from only the arterial BP waveform and without the requirement for specialised flow-monitoring equipment. However, the equivalency of excess pressure to blood flow velocity has never been simultaneously compared using invasive BP and direct measurement of blood flow velocity in humans, which was the aim of this study.

Methods

Participants. A total of 146 individuals were approached for inclusion in the study at the Royal Hobart Hospital (Hobart, Australia) prior to elective coronary angiography. Study exclusion criteria included inter-arm cuff systolic and/or diastolic BP difference >5 mmHg (n=5), the presence of aortic stenosis or arrhythmias (n=8), arterial access only available via the femoral artery (n=7) and technical or medical issues arising that prevented the measurement of study variables (n=13). Additionally, data capture was unsuccessful at the brachial and radial arteries

in 5 and 9 individuals respectively, and 6 individuals declined study participation. Reservoir-excess pressure model analysis failed to meet pre-specified quality control (P∞ > 0 and <diastolic BP) in 14 individuals (brachial n=5, radial n=9), so complete data were available for 97 brachial and 89 radial comparisons of flow velocity with excess pressure. Participants' clinical history (hypertension, smoking and hyperlipidaemia status) and anthropometric measurements were obtained from coronary angiography pre-assessment documentation. Clinical information was collected from the hospital digital health records. All participants gave written informed consent and ethical approval was granted by the University of Tasmania Human Research Ethics Committee.

Blood flow velocity and intra-arterial blood pressure acquisition. Methods relating to the recording of intra-arterial BP have previously been published. [12] Intra-arterial BP was recorded using a fluid filled catheter with intra-arterial access via the right radial artery. Blood flow velocity was recorded using two-dimensional pulsed Doppler ultrasound with 12 MHz linear-array transducer (Vivid i, GE Healthcare, Chicago, IL, USA; Figure 1). Pulsed wave Doppler flow velocities were recorded at a transmission frequency of 12 MHz, with a fixed angle of insonation of 60 degrees and sample volume encompassing the lumen cross-section. The envelope of peak instantaneous blood flow velocity was derived offline using EchoPAC software (GE Healthcare, Chicago, IL, USA; Figure 1) and converted to text format for analysis using automated line tracing software. Immediately following completion of the coronary angiography procedure, the catheter was positioned in the right mid-brachial artery and continuous intra-arterial BP was recorded. Simultaneously with intra-arterial brachial BP recordings, blood flow velocity was recorded from the mid-brachial artery on the contralateral arm. Following successful data capture at the brachial artery, the intra-arterial catheter was pulled back to the radial artery and intra-arterial radial BP was recorded simultaneously with radial blood flow velocity recorded on the contralateral arm. Intra-arterial BP was recorded at a sampling frequency of 1000 Hz. Continuous intra-arterial BP and blood flow velocity waveforms were then ensemble averaged using up to 7 cardiac cycles (no less than 4) and the ensembled waveforms were cropped to the shortest cardiac cycle. The ensemble averaged waveforms were used for analysis.

Derivation of excess pressure waveform. Analysis of the ensemble averaged BP waveforms was performed using custom-written scripts in MATLAB (The MathWorks Inc, USA). Reservoir pressure (P_{res}) was estimated from:

$$\frac{dP_{res}}{dt} = ks(P - P_{res}) - kd(P_{res} - P_{\infty}) \quad (1)$$

where P is the total measured pressure, ks is the systolic rate constant, kd is the diastolic rate constant and P_{∞} is the arterial asymptotic pressure. This first-order linear differential equation was solved as:

$$P_{res} = e^{-(ks+kd)t} \int_0^t P(t')e^{(ks+kd)t'}dt' + \frac{kd}{ks+kd} \times (1 - e^{-(ks+kd)t})P_{\infty} \quad (2)$$

The diastolic parameters, kd and P_{∞} were estimated by fitting an exponential curve to P during diastole, and ks was estimated by minimizing the sum of squares of error between P and P_{res} obtained over diastole. To calculate the excess pressure, P_{res} was subtracted from P. Derivation of P_{res}, excess pressure, ks and kd from the BP waveform can be seen in Figure 1.

Additional processing. Excess pressure and flow velocity waveforms were zero normalised and temporally aligned by cross-correlation. Prior to normalising, the pulse height of blood flow velocity and excess pressure waveform was calculated by subtracting the minimum value from the maximum value (e.g. maximum flow velocity – minimum flow velocity).

Statistical analysis. Unless stated otherwise, data are expressed as mean ± SD or n (%). All statistical analyses were performed in R, version 3.5.3 for Windows (R Foundation for Statistical Computing, Vienna, Austria). Cross-correlation (via the *ccf* function) and magnitude-squared coherence (via the *spec.pgram* function) were used to compare agreement between excess pressure waveforms and blood flow velocity waveforms in the time and frequency domain respectively. In time domain analyses, values of coherence were quantified between 0 and 1 and interpreted in a similar manner to the Pearson's R coefficient. Specifically, a coherence value of 0 indicates no causal relationship between excess pressure and flow, whereas a coherence value of 1 indicates a linear frequency response between excess pressure and flow. To reduce the influence of noise (from high frequencies), the mean of coherence values up to 10Hz were calculated. Zou's confidence interval was used to determine differences in cross-correlation coefficients between groups [13,14]. Linear regression and Pearson's r were used to examine associations of continuous variables after the assumption of linearity was confirmed by examination of residuals. Read re-read reliability of flow velocity and BP

measures was determined by two-way mixed model analysis and summarized by the intraclass correlation.

Results

Clinical characteristics. Clinical characteristics of study participants are presented in Table 1. Participants were middle to older age and consisting of mostly males and often with coronary artery disease defined by mild to severe narrowing in at least one coronary vessel. Hemodynamic variables of study participants are presented in Table 2.

Comparison of excess pressure with blood flow velocity. Comparisons of blood flow velocity and excess pressure waveforms can be seen in Figure 2. Brachial artery blood flow velocity was highly cross-correlated with excess pressure derived from brachial BP waveforms (Table 3, cross-correlation coefficient range = 0.72 to 0.99). Similarly, radial artery blood flow velocity was highly cross-correlated with excess pressure derived from radial artery BP waveforms (Table 3, cross-correlation coefficient range = 0.81 to 0.99). In frequency analyses, coherence between blood flow velocity and excess pressure was similar for brachial and radial artery comparisons (brachial median coherence = 0.93 and radial median coherence = 0.92). 32% of brachial artery excess pressure and flow comparisons had coherence values $\geqslant$0.95 and 73% had coherence $\geqslant$0.90. 27% of radial artery comparisons had coherence values $\geqslant$0.95 and 70% had coherence values $\geqslant$0.90. Mean square error was 0.09 ± 0.07 for brachial waveform comparisons and 0.11 ± 0.09 for radial waveform comparisons. Root mean square difference for blood flow velocity and excess pressure were 0.29 ± 0.11 and 0.32 ± 13 for brachial and radial artery comparisons respectively. Brachial blood flow velocity pulse height was linearly associated with excess pressure pulse height ($r = 0.52$, $p < 0.001$). Similarly, radial blood flow velocity pulse height was associated with excess pressure pulse height ($r = 0.43$, $p < 0.001$). Comparisons of wave intensity patterns using measured flow velocity and excess pressure are provided in the supplemental material.

Differences in cross-correlation coefficient between groups. There was no difference in brachial cross-correlation coefficient between individuals stratified by sex (95% confidence interval[CI] = -0.047, 0.062), hypertension status (95%CI = -0.035, 0.078), presence of coronary artery disease (95%CI = -0.053, 0.049), hyperlipidaemia (95%CI = -0.026, 0.086), smoking status (95%CI = -0.050, 0.058) or type 2 diabetes status (95%CI = -0.0650, 0.0158). Similarly, there were no differences in radial cross-correlation coefficients between groups.

Read re-read analysis. Intraclass correlation coefficient for peak blood flow velocity was 0.99 (95%CI = 0.99 to 0.99). Intraclass correlation coefficient for peak excess pressure was 0.99 (95%CI = 0.99 to 1).

Discussion

The aim of the present study was to determine the relationship of excess pressure to blood flow velocity derived from brachial and radial artery waveforms. Our main finding was that the envelope of excess pressure derived from either brachial or radial artery waveforms corresponded closely to the measured blood flow velocity envelope at each arterial site. These findings highlight that important information about the blood flow waveform may be derived from assessment of the BP waveform alone, which may be adapted for use in the clinical setting. We envision our findings may provide useful information for continuous hemodynamic monitoring and may facilitate more detailed BP waveform analysis which require measured flow, such as wave intensity and wave separation analyses. Nevertheless, future studies are needed to determine the usefulness of our findings for these purposes.

A continuous, non-invasive and operator independent method for accurate assessment of stroke volume is highly sought after for improving clinical decisions in the critical care setting. Pulse contour analysis is a method whereby stroke volume is estimated from the BP waveform and has been the focus of numerous investigations [15]. Several techniques employing pulse contour analysis have attempted to exploit the relationship between the windkessel-related BP and blood flow to estimate stroke volume. [15,16] However, these methods require individual patient calibration with a reference standard to achieve accurate absolute values of stroke volume. In this regard, calibration is often performed via transpulmonary thermodilution which necessitates intra-arterial access to the pulmonary artery. Additionally, calibration methods assume fixed arterial properties, but these change over time, ultimately resulting in inaccurate estimates and a requirement for frequent re-calibration. [17,18] Interestingly, Kamoi et al. [19] used a porcine model to show that the estimation of stroke volume may be optimised via the application of the reservoir-excess pressure model by reducing the number of fixed assumptions in the derivation of the windkessel pressure. They went on to show that the excess-pressure model in combination with pulse-wave velocity measures may facilitate more precise estimates of vessel dimensions and further improve estimates of stroke volume from the BP waveform alone. [20] Furthermore, a quantitative estimate of flow velocity may be achieved by scaling the peak of the excess pressure waveform to 1m/s, which, based on recent large population studies in Norway and Korea, seems a

reasonable estimate for an assumed peak velocity. [21–23] This may facilitate the estimation of parameters such as stroke distance (analogous to stroke index) and minute distance (analogous to cardiac index). Yet, this method provides only an approximate estimation of a quantitative flow velocity waveform and as a result, its clinical value will be greatly restricted.

As a result of the inverse relationship between the absolute magnitude of flow and characteristic impedance, surrogate flow waveforms for use in wave separation analysis do not require calibration. [3,24] Thus, previous investigators have employed a triangular flow approximation method for pressure only wave separation analysis, where flow in the aorta is assumed to be triangular in shape. [2,3] However, a more physiologically representative blood flow waveform, such as we have examined in this current study for excess pressure, may provide better results for the purpose of wave separation analysis. [24–26] Furthermore, in a recent study it was shown that aortic wave intensity analysis performed using excess pressure as a surrogate flow velocity waveform provides reasonable estimates of wave intensity parameters. The concordance between excess pressure and flow velocity observed in the present study indicate that excess pressure derived from peripheral artery BP waveforms may also prove useful for wave intensity analysis. Yet, among some individuals the concordance between excess pressure and flow velocity was poor and the implications of this for wave separation and wave intensity analyses need to be determined. Future work should aim to identify appropriate cut-off values for what constitutes good agreement between excess pressure and flow velocity. As it stands, excess pressure may provide a reasonable surrogate waveform for wave separation and intensity analysis, in most, but not all, individuals. [21,24]

In the aorta, wave intensity is dominated by a forward traveling compression wave in early systole followed by a forward travelling decompression wave immediately preceding diastole. Waves (forward and backward traveling) are present throughout the entire cardiac cycle but the intensity of backward traveling waves in the aorta during diastole is minimal. [27–29] Under these conditions, the excess pressure waveform is analogous to the blood flow velocity waveform being related to it through the characteristic impedance of the aorta. [30] However, in the peripheral arteries the contribution of backward traveling waves to the measured BP waveform is larger due to proximity to sites of impedance mismatch. [31,32] Indeed, reflected waves explain at least in part why the contribution of excess pressure to the BP waveform increases moving distally from the aorta. [10] In this regard, the concordance of excess pressure (wave related pressure) with directly measured flow velocity measured from peripheral artery waveforms, may deviate due to the contribution of backward traveling waves.

[33] There was some evidence for this in our wave intensity analyses using measured flow velocity (supplemental material, Figure S1). In the 75th percentile example (i.e. good concordance), there was minimal backward wave activity. Whereas, in the 25th percentile example (i.e. poor concordance) there was noticeably greater backward wave activity. The overall importance of this in practice remains to be comprehensively determined, certainly we still observed strong relationships on average between excess pressure and blood flow velocity at peripheral arterial sites. In this regard, when using excess pressure as a flow surrogate for wave intensity analyses, we observed that the forward compression wave was somewhat comparable to that obtained by wave intensity analyses using the measured flow velocity. Nevertheless, we also observed that backward wave activity was not reproducible when using excess pressure as a flow surrogate, as evidenced by the median and 25th percentile examples in Figure S1. Therefore, caution should be exercised before employing peripheral artery excess pressure for the purposes of wave intensity analysis and more detailed studies are needed to confirm the usefulness of our findings for these envisioned applications.

Previous studies have shown that excess pressure derived from peripheral artery BP waveforms is associated with cardiovascular events and impaired kidney function independent of conventional risk factors. [9,34,35] A numerical analysis of the reservoir-excess pressure model posits that excess pressure represents the additional work performed by the heart above the minimum required work. [36] This suggests that excess pressure may be a marker of circulatory inefficiency. This current study extends previous findings of the equivalency of aortic blood flow velocity with excess pressure to brachial and radial arteries. In this regard, excess pressure may facilitate more detailed BP waveform analyses, such as wave intensity analysis, which could provide useful clinical information for deeper BP phenotyping and risk stratification beyond excess pressure alone. [37] Altogether, when derived from peripheral artery BP waveforms, excess pressure may be considered a cardiovascular risk marker encompassing information on cardiovascular efficiency and local blood flow dynamics.

Limitations

Due to the nature of the clinical setting and procedure from which the data were collected, it was not possible to acquire simultaneous intra-arterial BP and blood flow velocity in the same arm. Thus, it is assumed that hemodynamics between arms are comparable, an assumption that may not be true for all individuals. However, inter-arm cuff systolic BP differences >5 mmHg was a study exclusion criterion and may have lessened the potential influence of inter-arm hemodynamic variability. Additionally, our study sample included mostly older people who

were undergoing coronary angiography and is not representative of young, healthy individuals nor critical care patients for whom comprehensive hemodynamic monitoring is most valuable. Future studies should determine if the findings of the present study are generalisable to young, healthy individuals and patients in the surgical or intensive care settings. Finally, we provide some hypothesis generating discussion on the potential usefulness of our findings and though there was good agreement between excess pressure and flow velocity among many individuals, in others there are clear differences, which may have important implications for the envisioned applications of our findings. In future studies it would be valuable to identify potential predictors of poor concordance between excess pressure and flow to help refine this method.

Conclusion

Excess pressure derived via the pressure only reservoir-excess pressure model may represent a useful method for assessment of arterial hemodynamics and circulatory function. Previous studies have shown that aortic excess pressure is proportional to aortic volumetric flow. In the present study, excess pressure derived from peripheral artery BP waveforms corresponded closely to the measured flow velocity waveform. This is of potential clinical importance as continuous non-invasive recording of peripheral artery BP waveforms is easy to perform and thus, removes barriers associated with conventional methods of blood flow assessment. Indeed, many non-invasive continuous hemodynamic monitoring systems seek to estimate hemodynamic indices from the peripheral artery BP waveform, including finger, radial and brachial BP waveforms. [38] Therefore, our findings could have implications for the clinical assessment of hemodynamic parameters and may provide important information for improving continuous, non-invasive and operator independent hemodynamic monitoring.

References

1 Stenglova A, Benes J. Continuous Non-Invasive Arterial Pressure Assessment during Surgery to Improve Outcome. *Front Med* 2017; 4:1–8.

2 Qasem A, Avolio A. Determination of Aortic Pulse Wave Velocity From Waveform Decomposition of the Central Aortic Pressure Pulse. *Hypertension* 2008; 51:188–195.

3 Westerhof BE, Guelen I, Westerhof N, Karemaker JM, Avolio A. Quantification of Wave Reflection in the Human Aorta From Pressure Alone. *Hypertension* 2006; 48:595–601.

4 Harms MPM, Wesseling KH, Pott F, Jenstrup M, Van Goudoever J, Secher NH, *et al.* Continuous stroke volume monitoring by modelling flow from non-invasive measurement of arterial pressure in humans under orthostatic stress. *Clin Sci* 1999; 97:291–301.

5 Wesseling KH, Jansen JRC, Settels JJ, Schreuder JJ. Computation of aortic flow from pressure in humans using a nonlinear, three-element model. *J Appl Physiol* 1993; 74:2566–2573.

6 Bein B, Meybohm P, Cavus E, Renner J, Tonner PH, Steinfath M, *et al.* The Reliability of Pulse Contour-Derived Cardiac Output During Hemorrhage and After Vasopressor Administration. *Anesth Analg* 2007; 105:107–113.

7 Wang J-J, O'Brien AB, Shrive NG, Parker KH, Tyberg J V. Time-domain representation of ventricular-arterial coupling as a windkessel and wave system. *Am J Physiol Heart Circ Physiol* 2003; 284:H1358-68.

8 Aguado-Sierra J, Alastruey J, Wang J-J, Hadjiloizou N, Davies J, Parker KH. Separation of the reservoir and wave pressure and velocity from measurements at an arbitrary location in arteries. *Proc Inst Mech Eng Part H J Eng Med* 2008; 222:403–416.

9 Davies JE, Lacy P, Tillin T, Collier D, Cruickshank JK, Francis DP, *et al.* Excess Pressure Integral Predicts Cardiovascular Events Independent of Other Risk Factors in the Conduit Artery Functional Evaluation Substudy of Anglo-Scandinavian Cardiac Outcomes Trial. *Hypertension* 2014; 64:60–68.

10 Peng X, Schultz MG, Picone DS, Black JA, Dwyer N, Roberts-Thomson P, *et al.* Arterial reservoir characteristics and central-To-peripheral blood pressure amplification in the human upper limb. *J Hypertens* 2017; 35:1825–1831.

11 Michail M, Narayan O, Parker KH, Cameron JD. Relationship of aortic excess pressure obtained using pressure-only reservoir pressure analysis to directly measured aortic flow in humans. *Physiol Meas* 2018; 39. doi:10.1088/1361-6579/aaca87

12 Armstrong MK, Schultz MG, Picone DS, Black JA, Dwyer N, Roberts-Thomson P, *et al.* Brachial and Radial Systolic Blood Pressure Are Not the Same. *Hypertension* 2019; 73:1036–1041.

13 Zou GY. Toward Using Confidence Intervals to Compare Correlations. *Psychol Methods* 2007; 12:399–413.

14 Diedenhofen B, Musch J. Cocor: A comprehensive solution for the statistical comparison of correlations. *PLoS One* 2015; 10:e0121945.

15 Jansen JRC, van den Berg PCM. Cardiac Output by Thermodilution and Arterial Pulse Contour Techniques. In: *Functional Hemodynamic Monitoring*.Springer, Berlin, Heidelberg; 2005. pp. 135–152.

16 Wang J-J, de Vries G, Tyberg J V. Estimation of left ventricular stroke volume by impedance cardiography: its relation to the aortic reservoir. *Exp Physiol* 2013; 98:1213–24.

17 Bendjelid K. When to recalibrate the PiCCO ™ ? From a physiological point of view,

the answer is simple. *Acta Anaesthesiol Scand* 2009; 53:689–690.
18 Alhashemi JA, Cecconi M, Hofer CK. Cardiac output monitoring: an integrative perspective. *Crit Care* 2011; 15:214.
19 Kamoi S, Pretty C, Docherty P, Squire D, Revie J, Chiew YS, *et al.* Continuous Stroke Volume Estimation from Aortic Pressure Using Zero Dimensional Cardiovascular Model: Proof of Concept Study from Porcine Experiments. *PLoS One* 2014; 9:e102476.
20 Kamoi S, Pretty C, Balmer J, Davidson S, Pironet A, Desaive T, *et al.* Improved pressure contour analysis for estimating cardiac stroke volume using pulse wave velocity measurement. *Biomed Eng Online* 2017; 16:51.
21 Hughes AD, Park C, Ramakrishnan A, Mayet J, Chaturvedi N, Parker KH. Feasibility of Estimation of Aortic Wave Intensity Using Non-invasive Pressure Recordings in the Absence of Flow Velocity in Man. *Front Physiol* 2020; 11:1–9.
22 Dalen H, Thorstensen A, Vatten LJ, Aase SA, Stoylen A. Reference values and distribution of conventional echocardiographic Doppler measures and longitudinal tissue Doppler velocities in a population free from cardiovascular disease. *Circ Cardiovasc Imaging* 2010; 3:614–622.
23 Choi JO, Shin MS, Kim MJ, Jung HO, Park JR, Sohn IS, *et al.* Normal echocardiographic measurements in a Korean population study: Part I. cardiac chamber and great artery evaluation. *J Cardiovasc Ultrasound* 2015; 23:158–172.
24 Hametner B, Wassertheurer S, Kropf J, Mayer C, Holzinger A, Eber B, *et al.* Wave reflection quantification based on pressure waveforms alone-methods, comparison, and clinical covariates. *Comput Methods Programs Biomed* 2013; 109:250–259.
25 Kips JG, Rietzschel ER, De Buyzere ML, Westerhof BE, Gillebert TC, Van Bortel LM, *et al.* Evaluation of Noninvasive Methods to Assess Wave Reflection and Pulse Transit Time From the Pressure Waveform Alone. *Hypertension* 2009; 53:142–149.
26 Hametner B, Weber T, Mayer C, Kropf J, Wassertheurer S. Effects of Different Blood Flow Models on the Determination of Arterial Characteristic Impedance. *IFAC Proc Vol* 2012; 45:918–923.
27 Baksi AJ, Treibel TA, Davies JE, Hadjiloizou N, Foale RA, Parker KH, *et al.* A Meta-Analysis of the Mechanism of Blood Pressure Change With Aging. *J Am Coll Cardiol* 2009; 54:2087–2092.
28 Baksi AJ, Davies JE, Hadjiloizou N, Baruah R, Unsworth B, Foale RA, *et al.* Attenuation of reflected waves in man during retrograde propagation from femoral artery to proximal aorta. *Int J Cardiol* 2016; 202:441–5.
29 Hughes AD, Parker KH. The modified arterial reservoir: An update with consideration of asymptotic pressure (P ∞) and zero-flow pressure (P zf). *J Eng Med* 2020; 44. doi:10.1177/0954411920917557
30 Westerhof N, Westerhof BE. Waves and Windkessels reviewed. *Artery Res* 2017; 18:102–111.
31 Hope SA, Tay DB, Meredith IT, Cameron JD. Waveform dispersion, not reflection, may be the major determinant of aortic pressure wave morphology. *Am J Physiol Circ Physiol* 2005; 289:H2497–H2502.
32 Zambanini A, Cunningham SL, Parker KH, Khir AW, McG. Thom SA, Hughes AD. Wave-energy patterns in carotid, brachial, and radial arteries: a noninvasive approach using wave-intensity analysis. *Am J Physiol Circ Physiol* 2005; 289:H270–H276.
33 Davies JE, Hadjiloizou N, Leibovich D, Malaweera A, Alastruey-Arimon J, Whinnett ZI, *et al.* Importance of the aortic reservoir in determining the shape of the arterial pressure waveform - The forgotten lessons of Frank. *Artery Res* 2007; 1:40–45.
34 Climie RED, Picone DS, Sharman JE. Longitudinal changes in excess pressure

independently predict declining renal function among healthy individuals-a pilot study. *Am J Hypertens* 2017; 30:772–775.
35 Armstrong MK, Schultz MG, Picone DS, Black JA, Dwyer N, Roberts-Thomson P, *et al.* Associations of Reservoir-Excess Pressure Parameters Derived From Central and Peripheral Arteries With Kidney Function. *Am J Hypertens* 2020; 33:325–330.
36 Parker KH, Alastruey J, Stan G-B. Arterial reservoir-excess pressure and ventricular work. *Med Biol Eng Comput* 2012; 50:419–24.
37 Chiesa ST, Masi S, Shipley MJ, Ellins EA, Fraser AG, Hughes AD, *et al.* Carotid artery wave intensity in mid- to late-life predicts cognitive decline: the Whitehall II study. *Eur Heart J* 2019; 40:2300–2309.
38 Truijen J, van Lieshout JJ, Wesselink WA, Westerhof BE. Noninvasive continuous hemodynamic monitoring. *J Clin Monit Comput* 2012; 26:267–278.

TABLE 1. Clinical characteristics of study participants

Variable	Mean ± SD or n (%)
Age (years)	61.1 ± 10.4
Sex (male)	70 (72)
Height (cm)	170.1 ± 10.8
Weight (kg)	87.4 ± 16.5
BMI (kg/m2)	30.2 ± 4.5
Family history of CVD	55 (60)
Hypertension	37 (41)
Current smoker	18 (19)
Hyperlipidaemia	65 (70)
Type 2 diabetes mellitus	28 (30)
Coronary artery disease	71 (76)

n = 97. CVD, cardiovascular disease; SD, standard deviation.

TABLE 2. Hemodynamic variables of study participants

Variable	Mean ± SD
Brachial	
Invasive SBP (mmHg)	135.7 ± 23.5
Invasive DBP (mmHg)	66.5 ± 10.5
Invasive mean arterial pressure (mmHg)	94.3 ± 13.0
Peak flow velocity (cm/s)	68.1 ± 18.6
Mean flow velocity (cm/s)	9.1 ± 4.3
Heart rate (bpm)	62.8 ± 10.9
Peak excess pressure (mmHg)	41.4 ± 13.5
Excess pressure integral (mmHg)	
Radial	
Invasive SBP (mmHg)	141.8 ± 24.7
Invasive DBP (mmHg)	66.8 ± 10.6
Invasive mean arterial pressure (mmHg)	94.2 ± 13.2
Peak flow velocity (cm/s)	50.6 ± 16.3
Mean flow velocity (cm/s)	8.5 ± 5.4
Heart rate (bpm)	61.9 ± 10.7
Peak excess pressure (mmHg)	48.5 ± 14.7
Excess pressure integral (mmHg)	8.05 ± 3.5

n = 97. BP, blood pressure; SD, standard deviation.

TABLE 3. Cross-correlation coefficients (r value) of flow velocity with excess pressure derived from brachial and radial arteries

Arterial site	25th percentile	Median	75th percentile
Brachial	0.94	0.96	0.97
Radial	0.92	0.95	0.96

Figure legends

Figure 1. Example of reservoir-excess pressure parameters derived from an ensemble averaged brachial blood pressure waveform (left panel). Measurement of brachial artery Doppler ultrasound flow velocity (right panel).

Figure 2. Comparisons of flow velocity (solid line) with excess pressure (dashed line) and respective blood flow velocity-excess pressure loop. Xcor is the cross-correlation coefficient. Figures represent typical examples of excess pressure and flow velocity comparisons in 75th percentile, median and 25th percentile of cross-correlation value. Coherence was 0.98 (minimum = 97) for the 75th percentile example, 0.94 (minimum = 89) for the median example, and 0.86 (minimum = 71) for the 25th percentile example.

Figure 3. Radial blood flow velocity and excess pressure (A) with associated first derivatives (B) and frequency coherence (C). Complex blood flow velocity waveform morphology was well matched by excess pressure and maximum coherence occurred at a frequency of 0.7 Hz.

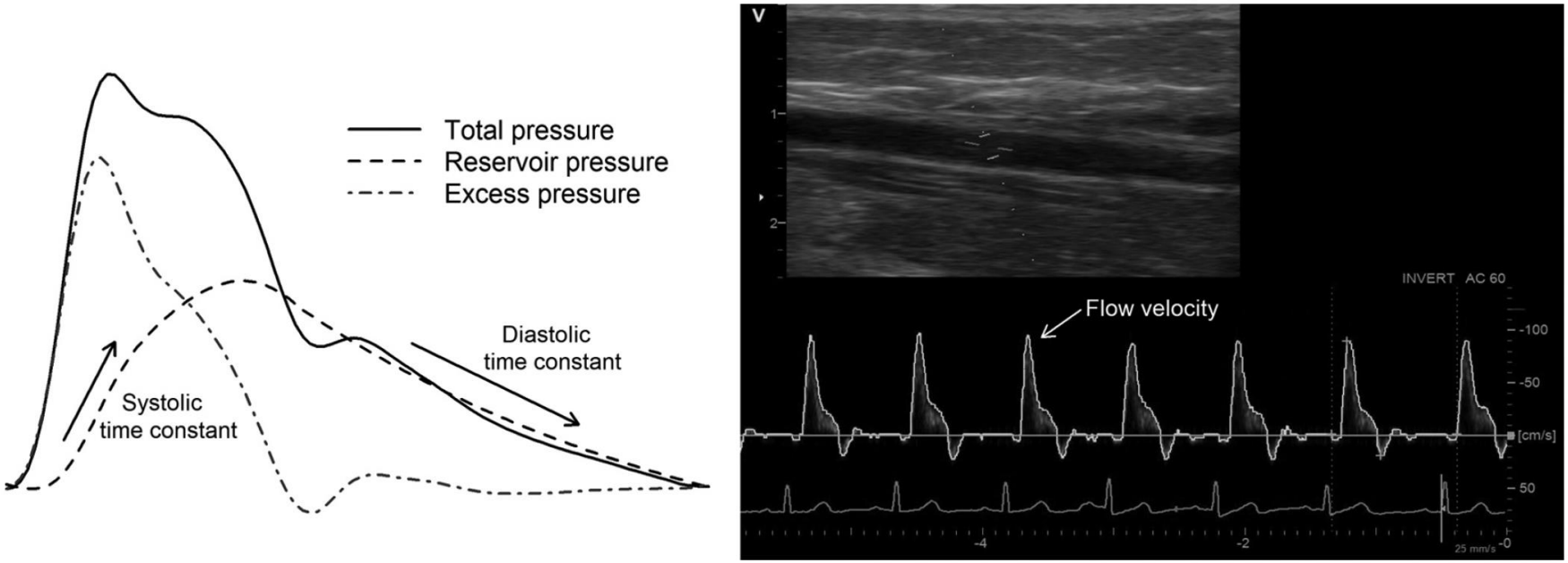
Total pressure
Reservoir pressure
Excess pressure
Systolic
time constant
Diastolic
time constant
Flow velocity
INVERT AC 60
[cm/s]
25 mm/s

Figure 1

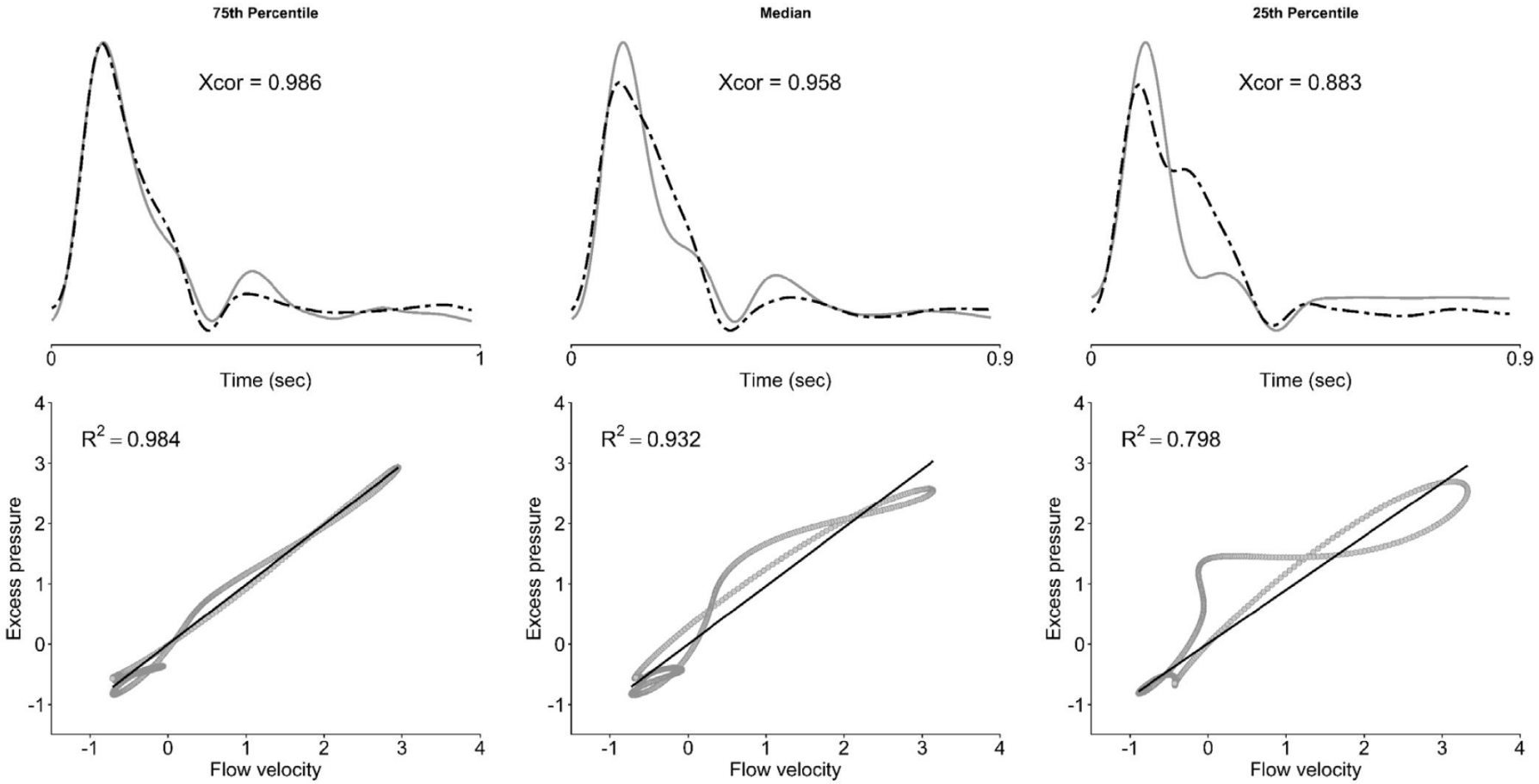
75th Percentile
Xcor = 0.986
0
1
Time (sec)
R2 = 0.984
Excess pressure
Flow velocity
Median
Xcor = 0.958
0
0.9
Time (sec)
R2 = 0.932
Excess pressure
Flow velocity
25th Percentile
Xcor = 0.883
0
0.9
Time (sec)
R2 = 0.798
Excess pressure
Flow velocity

Figure 2

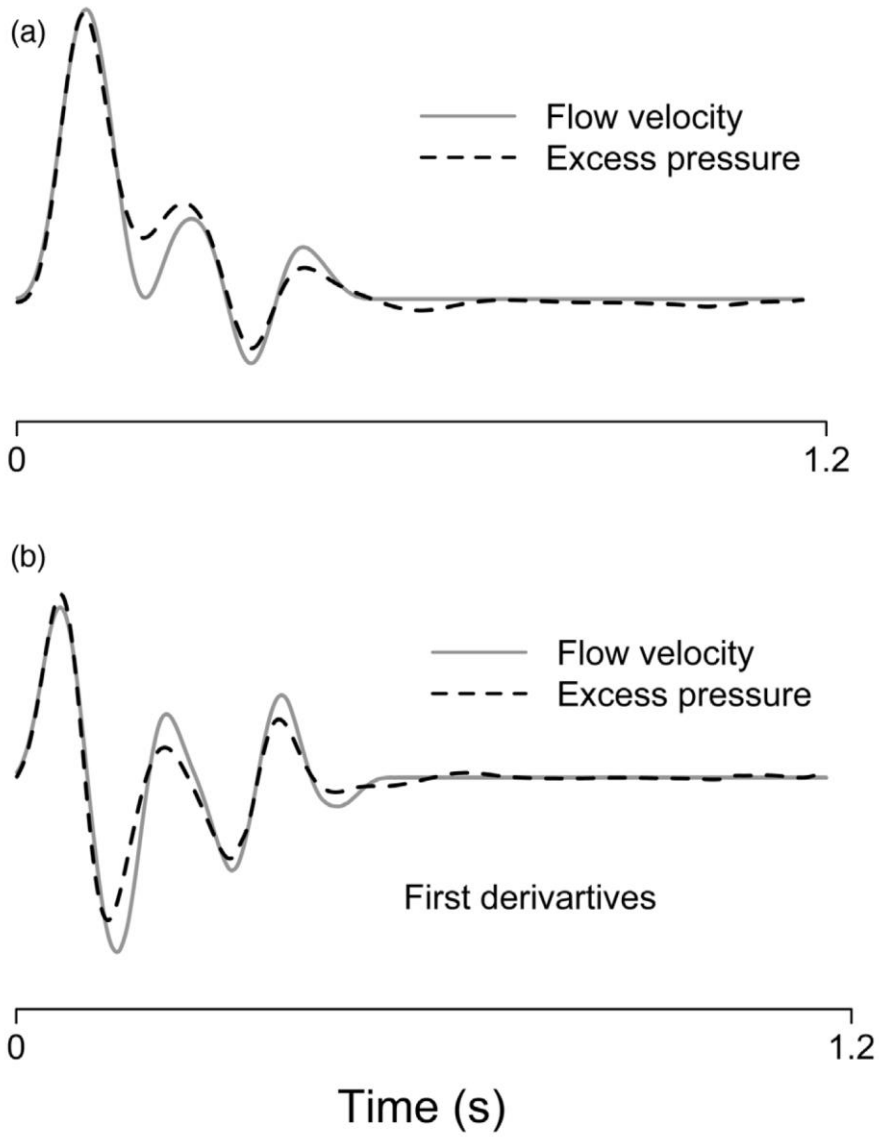
(a)
Flow velocity
Excess pressure
0
1.2
(b)
Flow velocity
Excess pressure
First derivartives
0
1.2
Time (s)

Figure 3