Associations of reservoir-excess pressure parameters derived from central and peripheral arteries with kidney function

Reservoir pressure parameters and kidney function

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BACKGROUND: Central artery reservoir-excess pressure parameters are clinically important but impractical to record directly. However, diastolic waveform morphology is consistent across central and peripheral arteries. Therefore, peripheral artery reservoir-excess pressure parameters related to diastolic waveform morphology may be representative of central parameters and share clinically important associations with end-organ damage. This has never been determined and was the aim of this study. METHODS: Intra-arterial blood pressure waveforms were measured sequentially at the aorta, brachial and radial arteries among 220 individuals (aged 61±10 years, 68% male). Customised software was used to derive reservoir-excess pressure parameters at each arterial site (reservoir and excess pressure, systolic and diastolic rate constants) and clinical relevance was determined by association with estimated glomerular filtration rate (eGFR). RESULTS: Between the aorta and brachial artery, the mean difference in the diastolic rate constant and reservoir pressure integral was -0.162S^{-1} (P=0.08) and -0.772 mmHg.s (P=0.23) respectively. The diastolic rate constant had the strongest and most consistent associations with eGFR across aortic and brachial sites (β=-0.20, P=0.02; β=-0.20, P=0.03 respectively; adjusted for traditional cardiovascular risk factors). Aortic, but not brachial peak reservoir pressure was associated with eGFR in adjusted models (aortic β=-0.48, P=0.02). CONCLUSIONS: The diastolic rate constant is the most consistent reservoir-excess pressure parameter, in both its absolute values and associations with kidney dysfunction, when derived from the aorta and brachial artery. Thus, the diastolic rate constant could be utilized in the clinical setting to improve BP risk stratification.

Keywords: Hemodynamics, Physiology, Vascular Stiffness, Hypertension

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Introduction

High blood pressure (BP) is the leading risk factor for cardiovascular disease (CVD) but does not account for all the CVD risk associated with BP [1]. Additional information on CVD risk may be provided by detailed analysis of arterial BP waveform morphology using the reservoir-excess pressure model [2]. This model deconstructs the BP waveform into a reservoir and excess pressure and systolic and diastolic rate constant [3]. The reservoir pressure is analogous to the instantaneous volume of blood stored in the vessel. Furthermore, the systolic and diastolic rate constants relate to the rate of filling and discharge of the reservoir pressure respectively [4]. The excess pressure is what remains once the reservoir pressure has been subtracted from the total pressure. The reservoir pressure and diastolic rate constant are predominantly components of the diastolic phase while the excess pressure and systolic rate constant occur during the systolic phase. Previous studies have shown central reservoir-excess pressure parameters predict adverse CVD outcomes independent of conventional risk factors, including BP [5–8]. However, direct measurement of central reservoir-excess pressure parameters is impractical in routine clinical practice and derivation of these parameters is limited to peripheral arterial sites.

Central (aortic) BP rather than peripheral (brachial or radial) BP represent the hemodynamic load experienced by the end organs (e.g. brain, kidneys and heart) and may provide superior CVD risk prediction over peripheral BP waveform parameters [9]. However, pulsatile components of BP waveform morphology are amplified from central to peripheral arteries [10–12]. Consequently, some reservoir-excess pressure parameters undergo amplification from central to peripheral arteries and are not representative of central parameters [13]. Conversely, diastolic BP waveform morphology is relatively stable between central and peripheral arteries [13]. This raises the possibility that peripheral diastolic reservoir-excess pressure parameters may provide a better representation of the central hemodynamic load experienced by the end organs and share clinically important associations with sub-clinical markers of end-organ damage such as impaired kidney function. Extending on this hypothesis, the aim of this study was to determine which reservoir-excess pressure parameters were

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the most consistent, and whether they were similarly associated with estimated glomerular filtration rate (eGFR) across central and peripheral arteries.

Methods

Participants. Individuals scheduled for elective coronary angiography at the Royal Hobart Hospital (Hobart, Australia) were approached for inclusion in the study. As required for the clinical procedure participants were requested to arrive at the coronary angiography laboratory in a post absorptive state, having avoided exercise, alcohol, caffeine and food for eight hours. Exclusion criteria comprised technical or medical issues that arose during the study, inter-arm cuff systolic and/or diastolic BP difference >5 mmHg, the presence of arrhythmia or aortic stenosis and if intra-arterial access via the right radial artery was unsuccessful. Additionally, participants were excluded on issues pertaining to the derivation of reservoir-excess pressure parameters (more detail is provided below). Complete data were available for analysis on 243 participants. The study was granted ethical approval by the University of Tasmania Human Research Ethics Committee and all participants gave written informed consent. For more detail regarding study protocol and exclusions, see supplemental material.

Intra-arterial blood pressure acquisition. During all intra-arterial BP recordings participants refrained from moving and talking and were free of substances that may have caused acute hemodynamic changes (such as vasoactive medication and contrast dye), as per guideline recommendations [14]. Intra-arterial access was made via the right radial artery (as per routine clinical procedures) and BP waveforms were recorded using a 6Fr (47% of cases) or 5Fr (53% of cases) fluid filled catheter. All BP waveform recordings were made following completion of the coronary angiography procedure. Firstly, aortic BP waveforms were recorded from the proximal ascending aorta. Following this, the catheter was pulled back to the brachial artery (mid humerus) and brachial BP waveforms were recorded. Lastly, the catheter was pulled back to the radial artery and the sheath used to gain radial access was partially removed to allow for the most distal measurement of radial BP waveforms. At each arterial location the position of the catheter was confirmed by fluoroscopy and the catheter was flushed before any waveform recordings were made. A minimum of 20 seconds of

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stable BP waveform recordings were collected at each arterial site, encompassing at least 2 respiratory cycles. The continuous intra-arterial BP waveform recordings were then ensemble averaged into a single beat which was used for analysis. Each study took approximately 3 to 4 minutes to complete. Pop tests were performed to confirm appropriate dynamic response of the fluid filled system as outlined by Gardner [15]. Raw continuous intra-arterial BP waveform data were recorded using an analogue to digital converter at a frequency of 1000Hz (LabChart 7, AD Instruments, Bella Vista, Australia).

Derivation of reservoir-excess pressure parameters. Units for continuous BP waveform recordings were converted from volts to mmHg using 2-point calibration method. Custom-written scripts were used to derive reservoir-excess pressure parameters from the ensembled BP waveform. Reservoir pressure was calculated from:

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

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. Aortic, brachial and radial BP waveforms were excluded from the final analysis based on non-physiological reservoir-excess pressure parameters identified by a P∞ greater than diastolic BP or less than 0 and a negative diastolic rate constant (n = 23 excluded).

Assessment of kidney function. Kidney function was determined by eGFR calculated using the Cockcroft-Gault equation with additional adjustment for weight extremes as previously recommended [16,17]. The Cockcroft-Gault equation was chosen for its improved CVD risk mortality prediction among populations with elevated cardiovascular risk [18].

Statistical analysis. Data are expressed as mean ± SD or (n%). All statistical analyses were performed in R, version 3.5.1 for Windows (R Foundation for Statistical Computing, Vienna, Austria). Pearson correlations were used to assess associations of reservoir-excess pressure

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parameters derived from waveforms measured at the aorta, brachial and radial artery with eGFR. Multivariable linear regression was performed to test the independent association of reservoir-excess pressure parameters with eGFR adjusting for known CVD risk factors (age, systolic BP, body mass index, sex, type 2 diabetes mellitus, hyperlipidaemia, family history of cardiovascular disease, heart rate and antihypertensive medication use). All data were normally distributed and linear models met the assumption of normally distributed residuals. Differences in reservoir-excess pressure parameters between arterial sites were assessed by percentage change and one-way analysis of variance with Tukey's Honest Significant Difference Test for post hoc comparisons. Logistic regression was performed to determine the odds of diastolic rate constant for predicting the presence of an estimated glomerular filtration rate ≤59 mL/min (results presented in supplementary material). A P value <0.05 was considered significant.

Results

Participant characteristics. Participants' clinical characteristics are presented in Table 1. Participants were mostly middle-to-older age, overweight and male. There was a wide range of eGFR values (28.0 to 181.5 mL/min) and on average participants had moderately impaired kidney function according to eGFR. In this regard, 25% of participants had an eGFR ≤59 mL/min, 45% had an eGFR between 60 and 89 mL/min and the remaining 30% of participants had an eGFR ≥90 mL/min. 8% of participants included in the present study had physician diagnosed renal disease. Most participants had coronary artery disease, defined as mild to severe coronary artery stenosis in at least one coronary artery. Furthermore, half of all participants had physician diagnosed hypertension, however BP was on average well controlled.

Consistency of reservoir-excess pressure parameters across central and peripheral arteries. The mean difference in the diastolic rate constant between the aorta and brachial artery was -0.162 S^{-1} (2.396 ± 0.797 and 2.234 ± 0.742 S^{-1} respectively, P = 0.08) and the mean difference between the brachial and radial arteries was -0.039 S^{-1} (2.234 ± 0.742 and 2.196 ± 0.787 S^{-1} respectively, P = 0.86). Between the aorta and radial artery, the mean difference in the diastolic rate constant was -

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0.201 S^{-1} (P = 0.02). The mean difference in the reservoir pressure integral between the aorta and brachial artery was -0.772 mmHg.s (18.724 ± 4.972 and 17.952 ± 4.694 mmHg.s respectively, P = 0.23) and the mean difference between the brachial and radial arteries was -0.206 mmHg.s (17.952 ± 4.694 and 17.746 ± 4.593 mmHg.s respectively, P = 0.90). Between the aorta and radial artery, the mean difference in the reservoir pressure integral was -0.979 mmHg.s (P=0.10). These differences accounted for an 8.3% and 4.1% decrease in the diastolic rate constant and reservoir pressure integral respectively from the aorta to radial artery. The mean difference in the systolic rate constant between the aorta and radial artery was -5.289 S^{-1} (14.912 ± 5.129 and 9.622 ± 6.554 S^{-1} respectively, P <0.001). The mean difference in the excess pressure integral between the aorta and radial artery was 2.603 mmHg.s (5.389 ± 2.458 and 7.992 ± 3.460 mmHg.s respectively, P <0.001). Overall, from the aorta to radial artery, changes in the systolic rate constant and excess pressure integral represented a 35.5% decrease and a 48.3% increase respectively.

Associations of reservoir excess pressure parameters derived from central and peripheral arteries with kidney function. Bivariate associations of reservoir-excess pressure parameters with eGFR are presented in Table 2. Diastolic rate constants derived from aortic, brachial and radial BP waveforms were associated with eGFR (Figure 1). There was no difference in the strength of correlation of diastolic rate constants derived from aortic, brachial or radial waveforms with eGFR (z <1.9, P >0.05 for all). Moreover, associations of diastolic rate constants with eGFR at aortic and brachial artery locations remained in multivariable analyses (Table 3). Associations of diastolic rate constants derived from radial BP waveforms did not persist after multiple adjustment (β = -0.043, P = 0.598). Additional multivariable analyses were performed with further adjustment for diastolic BP, pulse pressure or mean arterial pressure, but the principal findings were unchanged (data not shown). Furthermore, diastolic rate constants derived from aortic and brachial artery waveforms were associated to a similar extent with eGFR among participants with an eGFR ≤59 mL/min (aortic r = -0.34, P = 0.009 and brachial r = -0.34, P = 0.012) and participants with an eGFR ≥60 mL/min (aortic r = -0.33, P <0.001 and brachial r = -0.31, P <0.001). However, only the aortic diastolic rate constant

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was associated with eGFR among participants with an eGFR ≥60 in multivariable analyses (β = -6.98, p = 0.01). Peak reservoir pressure derived from aortic and brachial BP waveforms were associated with eGFR but not from radial BP waveforms (Table 2). Only peak aortic reservoir pressure remained associated with eGFR in multivariable models adjusted for all confounders bar age (β = -0.479, 95% confidence interval (CI) = -0.201, -0.159). Aortic, brachial and radial excess pressure integrals were associated with eGFR (Table 2) but these associations did not persist in multivariable models (P >0.25 for all).

Discussion

The aim of this study was to determine which of the reservoir-excess pressure parameters were most consistent across central and peripheral arteries and if they were similarly associated with eGFR. The principal findings were, of the reservoir-excess pressure parameters, the brachial diastolic rate constant, brachial reservoir pressure and radial reservoir pressure were most consistent with their aortic equivalents. However, the diastolic rate constant had the strongest and most consistent associations with eGFR when derived from the aorta and brachial artery. These findings suggest that the diastolic rate constant could provide clinically meaningful CVD risk information above and beyond conventional cuff measured BP.

BP has been measured using conventional cuff methods for over 100 years. However, cuff measured BP only provides information on the extremes of BP (systolic and diastolic BP) and gives no information on the underlying BP waveform. The reservoir-excess pressure model is a novel method for deriving additional clinical information from BP waveform morphology [2]. In this regard, reservoir-excess pressure parameters derived via tonometry-based methods have been shown to have clinical value [20]. Furthermore, it has been shown to be feasible to derive reservoir-excess pressure parameters from BP waveforms recorded via cuff-based BP devices, but more work is required to refine the accuracy of this method [19]. In the present study, using intra-arterial BP data, the diastolic rate constant and reservoir pressure were the most consistent of the reservoir pressure parameters across the aorta to brachial artery segment. The consistency of both these parameters is not surprising

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as both the diastolic rate constant and reservoir pressure are mathematically aligned with mid-to-late diastolic waveform morphology [4]. Therefore, it could be expected that because the diastolic rate constant and reservoir pressure derived from brachial artery waveforms are similar to central artery parameters, they represent the true hemodynamic load experienced by the end organs. However, only the diastolic rate constant was associated with kidney function to a similar extent at the aorta and brachial artery suggesting that the diastolic rate constant may be a more clinically viable reservoir-excess pressure parameter, at least for the relationship with kidney function. Moreover, use of antihypertensive medication has been shown to influence the morphology of the BP waveform and may have influenced our results [21]. Reassuringly, adjustment for antihypertensive medication use did not alter the principal findings of the present study but its effect should not be discounted.

One of the strengths of the reservoir-excess pressure model over other hemodynamic constructs is that its parameters resemble physiological phenomena [4]. Aortic inflow during systole is received by the large arteries which expand to accommodate increased blood volume and is analogous to the reservoir pressure. During diastole, BP steadily declines and the large arteries recoil, which facilitates continuous blood flow even when aortic input is zero [22]. In a stiffened arterial system, the buffering function of the large arteries is diminished, and arterial recoil occurs faster [23], thus leading to the rate of discharge of the reservoir pressure being greater and the diastolic rate constant being higher. As such, the diastolic rate constant is dependent not only on forces opposing the discharge of the reservoir pressure (i.e. resistance to outflow distal to its site of measurement) but also on the total arterial compliance. Arterial compliance (the inverse of arterial stiffness) is itself an independent risk factor for end-organ damage and may in part explain the association of diastolic rate constant with impaired kidney function in the present study [24]. Stiffening of the large arteries and subsequent attenuation of their buffering capacity results in excessive pulsatile forces penetrating further into the micro vasculature. This has deleterious consequences for highly perfused organs such as the brain, heart and kidneys and may lead to target organ damage [25].

The reservoir-excess pressure model may only be valid in the aorta since this is likely the only location where the assumption of ‘zero flow’ could be met, since there are numerous flow

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oscillations (forward and reflected) that occur in periphery [26]. An interesting finding of the present study was that aortic, but not brachial or radial peak reservoir pressure was associated with impaired kidney function. This indicates that the derivation of reservoir pressure, at least in regard to its clinical utility, may be most useful when derived from aortic BP waveforms. Conversely, excess pressure was associated with impaired kidney function when derived from aortic, brachial and radial arteries (albeit with much less strength and consistency than for the associations with the diastolic rate constant). These findings are consistent with data from independent investigators showing excess pressure derived from the radial artery independently predicts target organ damage and cardiovascular events [20]. Our observed lack of consistency in associations of excess pressure with impaired kidney function across central and peripheral arteries is probably due to individual variability in the amplification of excess pressure from central to peripheral arteries [13]. This site-specific variability suggests that central excess pressure may be more difficult to measure in a clinical setting at peripheral arterial locations.

A strength of the present study was the use of intra-arterial BP waveforms, which allowed for the accurate derivation of central and peripheral reservoir-excess pressure parameters. On the other hand, if handled incorrectly the use of fluid filled system for intra-arterial BP waveform recordings is a potential limitation. However, rigorous quality control procedures were employed, appropriate dynamic responses were confirmed via pop-tests and all measurements were performed in accordance with guideline recommendations [14]. A limitation of our study is the use of eGFR for the assessment of kidney function. It would have been beneficial to determine associations of the diastolic rate constant with additional bio-markers such as albuminuria or proteinuria. Finally, our participants were mostly middle to older age male patients with an indication for coronary angiography and therefore may not be representative of the general population, or other patient cohorts.

In conclusion, we have shown that of the reservoir-excess pressure parameters the diastolic rate constant and reservoir pressure were most consistent across the aorta to brachial artery segment. However, only the diastolic rate constant had consistent associations with impaired kidney function when derived from the aorta and brachial artery. In this regard, the diastolic rate constant could be

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utilized in the clinical setting to provide additive information related to BP waveform morphology to help improve BP risk stratification.

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Figure legends

Figure 1. Associations of diastolic rate constants derived from aortic, brachial and radial intra-arterial BP waveforms with estimated glomerular filtration rate (eGFR).

Table 1. Clinical characteristics of study participants (n=220).

Variable	mean ± SD or n (%)
Age (years)	61.4 ± 9.8
Sex (male)	150 (68)
Height (cm)	170.4 ± 10.9
Weight (kg)	86.1 ± 16.5
Body mass index (kg/m^2)	29.6 ± 4.7
Hypertension	111 (73)
Current smoker	48 (22)
Type 2 diabetes mellitus	60 (27)
Coronary artery disease	114 (64)
eGFR (mL/min)	77.1 ± 25.7
Cuff systolic blood pressure (mmHg)	132.3 ± 17.3
Cuff diastolic blood pressure (mmHg)	76.8 ± 11.1
Heart rate (bpm)	64.0 ± 10.9

eGFR, estimated glomerular filtration rate.

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Table 2. Bivariate associations of site-specific reservoir-excess pressure parameters with estimated glomerular filtration rate.

Variable	Aortic	Brachial	Radial
Diastolic rate constant	-0.38 (<0.001)	-0.38 (<0.001)	-0.26 (<0.001)
Excess pressure integral	-0.29 (<0.001)	-0.22 (0.002)	-0.28 (<0.001)
Max excess pressure	-0.24 (<0.001)	-0.08 (0.264)	-0.28 (<0.001)
Max reservoir pressure	-0.25 (0.003)	-0.19 (0.006)	0.04 (0.548)
Systolic rate constant	0.17 (0.018)	<0.01 (0.970)	0.13 (0.066)

Data are r (p).

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Table 3. Multivariable analyses of the associations between estimated glomerular filtration rate and diastolic rate constants derived from blood pressure waveforms recorded at the aorta and brachial artery.

Arterial site	Independent variable				
Aorta		**β**	**P**	**Partial R^2**	**Adjusted R^2**
	Diastolic rate constant	-0.203	0.019	0.022	0.39
	Age	-0.430	<0.001	0.120	
	Aortic systolic BP	-0.071	0.348	0.003	
	Male sex	0.286	<0.001	0.069	
	Body mass index	-0.083	0.227	0.006	
	T2DM	0.064	0.440	0.004	
	Hypercholesterolemia	-0.081	0.213	0.006	
	Family history of hypertension	0.128	0.066	0.013	
	Heart rate	0.027	0.676	<0.001	
	Antihypertensive medication	-0.034	0.598	0.001	
Brachial					
	Diastolic rate constant	-0.199	0.027	0.031	0.36
	Age	-0.427	<0.001	0.169	
	Brachial systolic BP	0.148	0.056	0.024	
	Male sex	0.275	<0.001	0.092	
	Body mass index	-0.037	0.581	0.002	
	T2DM	0.055	0.421	0.004	
	Hypercholesterolemia	-0.051	0.438	0.004	
	Family history of hypertension	0.111	0.109	0.015	
	Heart rate	0.009	0.893	<0.001	
	Antihypertensive medication	-0.037	0.562	0.002	

BP, blood pressure; T2DM, type 2 diabetes mellitus. R^2 is ANOVA adjusted R squared.

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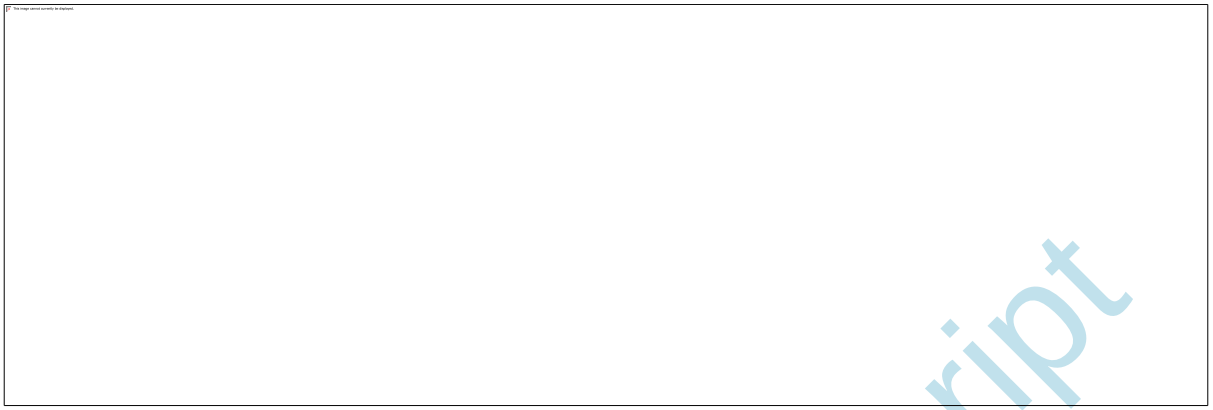
Figure 1



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