Physiological and clinical insights from reservoir-excess pressure analysis

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Abstract

There is a growing body of evidence indicating that reservoir-excess pressure model parameters provide physiological and clinical insights above and beyond standard blood pressure (BP) and pulse waveform analysis. This information has never been collectively examined and was the aim of this review. Cardiovascular disease is the leading cause of mortality worldwide, with BP as the greatest cardiovascular disease risk factor. However, brachial systolic and diastolic BP provide limited information on the underlying BP waveform, missing important BP related cardiovascular risk. A comprehensive analysis of the BP waveform is provided by parameters derived via the reservoir-excess pressure model, which include reservoir pressure, excess pressure, and systolic and diastolic rate constants and Pinfinity. These parameters, derived from the arterial BP waveform, provide information on the underlying arterial physiology and ventricular-arterial interactions otherwise missed by conventional BP and waveform indices. Application of the reservoir-excess pressure model in the clinical setting may facilitate a better understanding and earlier identification of cardiovascular dysfunction associated with disease. Indeed, reservoir-excess pressure parameters have been associated with sub-clinical markers of end-organ damage, cardiac and vascular dysfunction, and future cardiovascular events and mortality beyond conventional risk factors. In the future, greater understanding is needed on how the underlying physiology of the reservoir-excess pressure parameters informs cardiovascular disease risk prediction over conventional BP and waveform indices. Additional consideration should be given to the application of the reservoir-excess pressure model in clinical practice using new technologies embedded into conventional BP assessment methods.

Keywords: hemodynamics, blood flow, modelling, windkessel, waves

The burden of cardiovascular disease and hypertension

Cardiovascular disease (CVD) remains the leading cause of mortality globally, despite improvements in the management and prevention of CVD over the last 15 years.[1,2] More recently, the rate of decline in CVD mortality has abated in several high-income countries, highlighting a need for concerted efforts to improve CVD prevention and management.[2,3] One potential area for improvement is in the assessment and control of blood pressure (BP).[4] High BP (hypertension) is the leading risk factor for CVD, afflicting 1.1 billion individuals globally.[5,6] A 25% reduction in the prevalence of hypertension could prevent 1.7 million deaths per year.[7] Thus, BP measurement is one of the most important clinical tests, and accurate assessment of BP associated CVD risk is critical for improving clinical outcomes.

BP is conventionally measured using an inflatable cuff at the upper arm, from which the systolic and diastolic BP are estimated. Automated oscillometric devices use algorithms applied to data from the digitally recorded arterial pressure waveform during cuff deflation. This oscillometric method of BP assessment increasingly supersedes the auscultatory technique that was first popularised in the 1896 paper by Scipione Riva-Rocci.[8,9] Despite its age, non-invasive cuff measured BP remains the clinical standard for the diagnosis and management of hypertension worldwide. However, even when BP is measured and managed appropriately (according to guidelines), there remains a portion of BP related CVD risk not attributable to systolic and diastolic BP alone.[10] This suggests that conventionally measured systolic and diastolic BP does not provide a comprehensive picture of the harm caused by raised BP. Indeed, systolic and diastolic BP represent only the peak and nadir of an otherwise complex and featured BP waveform (Figure 1). Therefore, there may be clinically important information embedded within the BP waveform that is missed by systolic and diastolic BP alone.[11] This review will discuss the reservoir-excess pressure model, a novel method of BP

waveform analysis, and the extent to which model parameters provide important insights into arterial physiology and BP related risk.

The arterial pulse

Knowledge of the relationship between the arterial pulse (the physical manifestation of the BP waveform) and disease dates back to the Ancient Egyptians in 1550 BC.[12] In 1863 Marey provided the first continuous non-invasive recordings of the BP waveform using the sphygmograph, a mechanical device that amplified the applanated pulse through a system of levers.[13] More recently, high-fidelity non-invasive transducers that digitally record the BP waveform from superficial arteries has facilitated the use of pulse-wave analysis as a tool for CVD risk assessment.[14] In its most basic form, pulse-wave analysis derives indices from morphological features defined by inflection points on the BP waveform, as well as area under the curve analysis (Figure 2). However, data relating these conventional pulse-wave analysis indices to hard clinical outcomes are inconsistent.[14–17] Equally problematic is the lack of consensus regarding the physiological interpretation of pulse-wave analysis indices. For example, augmentation index is widely purported to be indicative of wave reflection or vascular stiffness. Yet, consensus documentation recommends against the use of augmentation index as a marker of arterial stiffness and the notion of aortic augmentation index arising from discrete wave reflections has been debunked.[18–21] Likewise, the textbook notion that dP/dt max (a parameter derived from pulse-wave analysis) represents cardiac contractility has also been discredited using invasive data in humans.[22] Furthermore, evidence suggests a more comprehensive understanding of the risk posed by BP may be achieved through assessment of central (aortic) BP as opposed to conventional brachial BP measures.[14] In this regard, pulse-wave analysis has been used to estimate aortic systolic and diastolic BP via a generalised transfer function or proprietary algorithm.[23–28] Accurate assessment of aortic BP would likely provide incremental clinical value to standard brachial cuff BP risk

stratification. Still, assessment of aortic systolic and diastolic BP alone has similar shortcomings as conventional brachial cuff BP measures by providing little detail of the underlying BP waveform beyond its extremes. On the other hand, parameters derived from the reservoir-excess pressure model have shown promise in providing additional physiological and clinical insights relating to the underlying BP waveform beyond standard systolic and diastolic BP or pulse-wave analysis techniques. Therefore, the reservoir-excess pressure model represents a potential opportunity to improve the information obtained from BP measurement, including offering the potential for earlier and more accurate identification of BP-related CVD risk.

Key reservoir-excess pressure model parameters

The reservoir-excess pressure model provides a heuristic approach to the analysis of the arterial BP waveform, interpreting it as a composite of reservoir pressure and excess pressure.[29,30] Key parameters derived from this model include reservoir pressure and excess pressure (quantified either as integrals, peaks or amplitudes, where the amplitude is the peak minus diastolic BP), systolic and diastolic rate constants, and Pinfinity, the asymptotic minimum of the diastolic decay in pressure (Figure 3). Though still in its infancy, there is a growing body of work detailing the physiological and clinical insights provided by the reservoir-excess pressure model (see Table 1), yet these data have never been brought together and discussed collectively. In the following pages, we outline the data relating to the physiological representation of each of the reservoir-excess pressure parameters (***physiological studies***) and how this underlying physiology may relate to the clinical value of each reservoir-excess pressure parameter (***clinical studies***). Previous findings highlighting the clinical value of the reservoir-excess pressure parameters have been summarised in Table 1, eTable 1, and eFigure 1 and 2.

Reservoir-excess pressure parameters, physiological and clinical data

Reservoir pressure

Physiological studies. During systole, blood flow into the aorta exceeds outflow resulting in increased aortic volume. The large elastic arteries (particularly the proximal aorta) act as a dynamic capacitor for blood volume to which a pressure can be ascribed. This pressure, attributable to changes in arterial blood volume, was termed the Windkessel pressure by Frank.[31] In the reservoir-excess pressure model, the windkessel pressure assumes the name of reservoir pressure; though they are similar in concept, there are nuanced differences between the windkessel and reservoir pressure that necessitate the notational distinction.[32,33] In particular this distinction emphasizes that reservoir pressure arises from waves and propagates along the arterial tree at a finite speed, whereas the Windkessel pressure is assumed to have a non-physiological infinite wave speed.

Upon first outlining their reservoir-excess pressure model, Wang et al.[29] showed that the mathematically derived reservoir pressure was proportional to cyclic variations in aortic volume over the cardiac cycle in the dog aorta. More recently, the equivalency of reservoir pressure to changes in aortic volume has been observed in man (Figure 4).[34] The capacity of the large elastic arteries to expand and buffer the rapid influx of blood volume from the heart during systole theoretically protects distal vessels from potentially damaging pulsatile hemodynamics.[35,36] In this regard, reservoir pressure may be considered a composite marker dependent on multiple factors, including left ventricular output, global arterial compliance, systemic arterial resistance, and aortic characteristic impedance.

Increased aortic stiffness (i.e., reduced large artery compliance) is an established independent risk factor for CVD and all-cause mortality and may, at least partly, underlie the association of reservoir pressure and CVD risk, where a high reservoir pressure indicates higher arterial

stiffness and worse CVD outcomes.[37] Furthermore, several numerical works have explored the theoretical basis of the reservoir pressure.[38–40] Parker et al.[38] showed that the reservoir pressure represents the theoretical minimum hydraulic work performed by the left ventricle to generate a stroke volume. Consequently, a higher reservoir pressure would suggest that greater work would be needed to be performed by the heart in order to eject a given stroke volume. This hypothesis helps explain previously observed associations between reservoir pressure and left ventricular mass index (LVMI).[41,42]

Moreover, the reservoir pressure is associated with systolic BP and pulse pressure but is relatively uniform throughout the arterial tree.[43,44] Therefore, the CVD risk predictive value of reservoir pressure derived from central artery BP waveforms may apply to reservoir pressure measured from peripheral artery locations as well. This is a potentially important concept as it provides a rationale for facilitating the accurate estimation of central artery reservoir-excess pressure indices from peripheral artery waveform recordings. Altogether, the reservoir pressure may provide useful information relating, not only to global arterial properties, but also to the hemodynamic load experienced by the heart and ventricular-arterial coupling.

Clinical studies. In prospective studies, the peak, amplitude, and integral of reservoir pressure derived from central artery BP waveforms are associated with CVD events and mortality independently of conventional CVD risk factors.[45–47] In 674 individuals with an indication for a coronary angiography procedure, Hametner et al.[45] found a higher reservoir pressure amplitude was associated with all-cause mortality and CVD events (myocardial infarction, stroke, and revascularization). Notably, model parameters were derived from non-invasively recorded BP waveforms and adjustment for confounders in multivariable models was comprehensive, bar the omission of systolic BP.

In a separate study comprising 1272 individuals with untreated hypertension and normotensive individuals, higher values for both the peak and amplitude of reservoir pressure were associated with CVD mortality.[46] In this study, adjustment for traditional CVD risk factors was wide-ranging, but models were not adjusted for heart rate. Yet, in the same study, neither the peak nor amplitude of reservoir pressure remained significantly associated with CVD mortality in an independent community-based cohort free of CVD (n=2211).[46]

In 2539 individuals from a community-based Framingham Heart Study cohort, the amplitude of reservoir pressure was positively associated with CVD events, including myocardial infarction, coronary insufficiency, heart failure, and stroke. Importantly, these relationships remained after adjustment for traditional CVD risk factors, including systolic BP and heart rate, providing arguably the most robust evidence for the CVD risk predictive value of the reservoir pressure to date.[47] In a sub-study of the Anglo-Scandinavian Cardiac Outcome trial, reservoir pressure (peak and integral) derived from untransformed peripheral artery waveforms was not associated with increased risk of CVD events; whether this difference relates to the sample studied or the use of peripheral rather than central estimates of reservoir pressure is unknown.[41] It should also be noted that, among patients with end stage renal disease, an inverse relationship between the reservoir pressure integral and all-cause mortality has previously been reported.[48] Finally, in two cross-sectional studies, reservoir pressure derived from radial artery BP waveforms was positively associated with LVMI, consistent with the notion that, physiologically, reservoir pressure provides useful information on ventricular-arterial coupling.[41,42]

Excess pressure

Physiological studies. Excess pressure is calculated as the difference between total measured BP and reservoir pressure and has been proposed to represent additional or 'unnecessary' work performed by the heart in ejecting the stroke volume.[38] Consequently, elevated excess

pressure may be indicative of an inefficient interaction between the ventricular and vascular systems, and representative of superfluous hemodynamic load on the heart. Assuming an average heart rate of 70 beats per minute, the heart beats ≈100 thousand times per day, it is not hard to imagine that even small inefficiencies compound over time, leading to structural adaptations in the heart and adverse cardiovascular-related outcomes (consistent with previously observed associations of excess pressure with LVMI and CVD events).[42,49]

When derived from aortic or carotid BP waveforms, excess pressure is proportional to aortic blood flow.[29,50] Viewing the circulatory system as 3-element Windkessel (Westkessel), the equivalency of excess pressure to flow arises due to the constant of proportionality between excess pressure and aortic flow which should be related to the characteristic impedance of the aorta.[33] Outside the aorta, the relationship between peripheral artery excess pressure and blood flow velocity was recently confirmed in the brachial and radial arteries.[51] The relationship of excess pressure to aortic blood flow may partly explain associations between excess pressure and markers of CVD, such as carotid intima-media thickening, reductions in brain grey matter volume, and reduced renal function.[41,52,53] For these reasons, excess pressure may be indicative of local hemodynamic forces linked to endothelial dysfunction and site-specific predilection for atherosclerotic disease.

Clinical studies. In a longitudinal study among 2069 individuals participating in a randomized clinical trial of antihypertensive therapy, Davies et al.[41] showed that the integral of excess pressure was positively associated with adverse CVD events independent of traditional CVD risk factors, including systolic BP, but not heart rate. A notable feature of this study was the use of the un-transformed radial artery BP waveform for the derivation of excess pressure. Because non-invasive recording of radial artery BP waveforms is somewhat

uncomplicated, excess pressure may represent a suitable candidate for translation into the clinical setting.

Similar findings from other prospective studies have shown that the excess pressure integral and amplitude is associated with CVD events and mortality, and all-cause mortality among individuals with heart failure, acute coronary syndrome or end stage renal disease.[48,54,55] Furthermore, among healthy individuals, the integral of excess pressure is positively associated with declining renal function, but this was observed in a small sample with limited adjustment for confounders (age, sex, body mass index, systolic BP and heart rate).[53]

New data from a Framingham Heart Study community-based cohort with a 15 year follow up observed that the excess pressure amplitude but not excess pressure integral estimated from carotid artery tonometry using a pressure-dependent rate constants was positively associated with future CVD events after adjustment for age and sex, but this association was attenuated after further adjustment for conventional CVD risk factors.[47] It is uncertain whether differences between this finding and previous studies reflect differences in the study sample (the Framingham Heart Study cohort was free of overt CVD), or the use of carotid as opposed to peripheral waveforms. Notably, excess pressure derived from carotid artery BP waveforms was not significantly associated with CVD outcomes in the Second Australian National Blood Pressure Study cohort.[56] It is possible that the value of excess pressure as a marker of CVD risk may be most applicable among individuals with higher baseline CVD risk. Indeed, excess pressure in the Framingham Heart Study cohort was lower (median 5.3 mmHg.s; interquartile range 4, 7.1 mmHg.s) and had fewer individuals with high excess pressure compared to values previously reported by Davies et al. [41] among individuals with hypertension (median 6 mmHg.s; interquartile range 1.8, 17.0 mmHg.s).

Lastly, cross-sectional associations of excess pressure include LVMI (positive association), carotid intima-media thickness (positive association), and brain grey matter volume (negative association).[41,52] Consistent with excess pressure representing the superfluous work performed by the heart, high excess pressure has been positively correlated with LVMI.[41] Associations with carotid intima-media thickness and loss of brain grey matter volume may owe to high excess pressure representing the transmission of damaging pulsatile wave energy into the peripheral vasculature. Thus, high excess pressure may be a useful marker denoting early identification of both cardiac and vascular dysfunction. Notably, cross-sectional associations of excess pressure have only been reported among clinical populations (individuals with hypertension or type 2 diabetes). Still, these data help understand previous associations between excess pressure and CVD events and mortality and all-cause mortality.

Diastolic rate constant

Physiological studies. The diastolic rate constant is a parameter derived from the reservoir pressure curve. Therefore, much of the discussion regarding the physiology of the reservoir pressure is relevant to the diastolic rate constant as well. During systole, the large elastic arteries expand to accommodate blood volume ejected from the heart. During diastole, the aortic valve is closed, flow into the aorta stops and the large arteries recoil, buffering the pressure as it falls to diastolic BP.

The rate at which reservoir pressure decays during diastole (diastolic rate constant) depends on the compliance of the systemic arteries that comprise the reservoir and the resistance to outflow via the microcirculation (Figure 3). The diastolic rate constant is simply the inverse of the time constant (tau) of the diastolic decay, which for a simple 2-element Windkessel (assuming constant compliance and resistance with a zero asymptotic pressure) is proportional to the product of systemic arterial resistance and compliance.[57] With reductions in both systemic vascular resistance and arterial compliance, discharge of the reservoir

pressure occurs faster, and the rate of diastolic decay is increased. A higher diastolic rate constant could lead to greater transmission of detrimental pulsatile forces into the peripheral vasculature potentially causing end-organ damage. This may be one mechanism underpinning previously observed associations between the diastolic rate constant and CVD events and mortality.

Zero-flow pressure (Pzf) represents the pressure at which flow through the microcirculation stops, often termed critical closing pressure. The Pzf has a substantial influence on estimates of tau[58] and there is extensive evidence that it is not zero; detailed discussion can be found in the recent studies by Hughes et al.[33] and Behnam et al.[47] Originally, Pzf was thought to equal venous pressure but evidence (summarised in[33]) suggests that Pzf is higher than mean systemic filling pressure and is typically ~23 to 30mmHg.[33] Pinfinity is the pressure asymptote of the diastolic decay (Figure 3) and is assumed to be equal to Pzf. Traditionally, Pinfinity is taken as a free parameter estimated from fitting a mono-exponential function with a constant to the diastolic pressure decay. However, this may result in an over estimation of Pzf, particularly when the diastolic decay exhibits high concavity.[47] Highlighting the effect of Pinfinity on tau, Behnam et al.[47] observed values of tau 50% lower when Pinfinity was fixed (at 20 mmHg) compared to when Pinfinity was taken as a free parameter. Consequently, estimates of compliance will also be 50% lower when using the fixed versus free Pinfinity; however the amplitudes of reservoir pressure and excess pressure were similar between the two approaches (fixed verses free).[47] Overall, when interpreting tau, and therefore the diastolic rate constant, consideration should be given to the method of waveform fitting, and particularly the calculation of Pinfinity.

Clinical studies. There is a relative dearth of studies reporting associations between the diastolic rate constant and CVD risk. In one study reporting data from two independent cohorts, one healthy community-based and one consisting of normotensive and untreated hypertensive individuals, Cheng et al.[46] observed a higher diastolic rate constant was associated with greater CVD mortality after adjusting for multiple traditional CVD risk factors (including age, sex, systolic BP, body mass index, fasting glucose, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, smoking, and alcohol). Similarly, among the healthy community-based Framingham Heart Study cohort, the diastolic time constant was associated with CVD events in models adjusted for traditional CVD risk factors (including age, sex, total cholesterol, high-density lipoprotein cholesterol, smoking, antihypertensive medication, and diabetes mellites).[47] However, the relationship between the diastolic time constant and CVD risk was attenuated after additional adjustment for systolic BP and heart rate.

Conversely, among 838 elderly hypertensive individuals, the diastolic rate constant was not significantly associated with incident CVD events.[56] A potential limitation of this study was that the primary end point (fatal and nonfatal stroke and myocardial infraction) was only observed in 43 patients, thus, limiting the power of the study and increasing the possibility of a false negative result. In patients with end-stage renal disease, the diastolic rate constant was positively associated with all-cause and CVD mortality, but this association was attenuated to the null in multivariable models adjusted for heart rate, age, sex, comorbidities, type of dialysis, dialysis vintage and carotid-to-femoral pulse-wave velocity.[48]

In general, the diastolic rate constant seems to exhibit stronger associations with CVD risk in studies conducted among healthy individuals and thus, may be a more sensitive marker of CVD risk in these populations. This may partly explain previously observed the non-significant findings among individuals with end stage renal disease and elderly individuals

with hypertension.[48,56] Whereas significant associations were observed among, for the most part, healthy community based cohorts.[46,47] However, previous studies reporting associations between the diastolic rate constant and CVD risk have also employed different methods to calibrate non-invasively recorded BP waveforms (systolic and diastolic BP or mean and diastolic BP calibration).[48,56] Yet, the influence of the calibration method is not evident in these previous studies and two of the studies discussed above present data for both calibration methods with no difference to the principal results.[46,48]

Finally, in a cross-sectional study, using invasive BP waveform data, a higher diastolic rate constant was associated with lower estimated glomerular filtration rate.[59] Interestingly, the authors showed that the inverse association between the diastolic rate constant and estimated glomerular filtration rate was similar when derived from aortic or brachial artery BP waveforms.[59] These observations are unsurprising given the physiological dependence of the diastolic rate constant on systemic arterial compliance, and it would be valuable to determine associations of the diastolic rate constant with other markers of target organ damage.

Systolic rate constant

Physiological studies. The systolic rate constant, like the diastolic rate constant, is derived from the reservoir pressure curve and is therefore also intimately related to it. The physiology underpinning the reservoir pressure is discussed in detail above. Pertaining to the systolic rate constant, as blood volume is ejected from the heart during systole, the arterial reservoir increases; the rate at which the reservoir pressure increases is quantified by the systolic rate constant. As such, the systolic rate constant will show some inverse relationship with the aortic characteristic impedance and systemic arterial compliance, which may account for associations with CVD risk reported in some studies.[46,47,56] Aortic stiffness increases with age and forms part of the pathology of CVD, leading to higher pulse pressure and increased transmission of pulsatile forces into the peripheral vasculature,[37] or adverse effects on left

ventricular structure and function. Furthermore, aortic characteristic impedance is also influenced by aortic diameter. Aortic diameter has previously been implicated as a potential mechanism in the progression of pulse pressure increases among individuals with hypertension.[60,61] Altogether, the systolic rate constant likely represents a marker comprising information related to ventricular-arterial interaction, ventricular load, and large artery stiffness, where a higher systolic rate constant might be expected to be associated with greater CVD risk.

Clinical studies. In healthy community-based cohorts and cohorts with disease, the systolic rate constant is associated with CVD events and mortality.[46–48,56] However, the direction of associations between the systolic rate constant and adverse outcomes across these previous studies are inconsistent. Firstly, in 3483 healthy and untreated hypertensive individuals across two prospective cohorts, a higher systolic rate constant was associated with higher CVD mortality and performed better than conventional pulse-wave analysis indices, including augmentation index and augmentation pressure and conventional brachial pulse pressure (adjusted hazards ratio = 1.18).[46] Similarly, among individuals free of overt CVD, results from the Framingham Heart Study analysis have shown that a higher systolic time constant (the inverse of the systolic rate constant) was associated with lower risk of CVD events (adjusted hazards ratio = 0.92).[47] Among individuals with hypertension, a higher systolic time constant (lower systolic rate constant) was associated with fewer future CVD events (adjusted hazards ratio for primary end point = 0.33, eTable 1 and eFigure 1).[56] Conversely, in a patient population with end-stage renal disease, the systolic rate constant derived from carotid, but not radial artery BP waveforms, was inversely associated with all-cause mortality (adjusted hazards ratio = 0.81) and CVD mortality (adjusted hazards ratio = 0.81).[48] It may be possible that differences between healthy and patient populations contribute to these divergent findings, but more work is needed to explain these differing associations. There are no studies

that have reported on cross-sectional associations between markers of target organ damage and the systolic rate constant.

Future directions: improving BP risk stratification

Conventional pulse-wave analysis was developed with a view to derive more information from the underlying arterial BP waveform than could be derived from standard systolic and diastolic BP alone. This field has provided significant new information but has fallen short of definitively explaining cardiovascular physiology or offering impetus to change clinical practice. Evidence from studies using the reservoir-excess pressure model offers additional information on CVD risk beyond conventional pulse-wave analysis indices across distinct populations. However, the understanding of the reservoir-excess pressure model is still in its relative infancy and more research is needed. Indeed, in traditional calculations of reservoir-excess pressure parameters, the diastolic rate constant is the product of compliance and resistance which are assumed to be constant. Whereas, the recent analysis from the Framingham Heart study attempts to account for pressure-dependent non-linearities in compliance and resistance in the calculation of the rate constants.[47] This new calculation represents an adjustment to the traditional reservoir-excess pressure calculation but makes some assumptions about the nature of the pressure dependence of the diastolic time constant (tau) and the value of the asymptotic pressure. Interestingly, in a community-based sample, model parameters derived with both the new modified calculation and the traditional calculation were significantly associated with CVD events after adjusting for age and sex. Yet, after additional adjustment for conventional CVD risk factors, only parameters derived via the new modified calculation remained significant.[47] Ultimately, the usefulness of any hemodynamic model is decided by its associations with clinical outcomes but also with arterial physiological phenomena.

The evidence base outlining physiological and clinical insights provided by the reservoir-excess pressure parameters continues to grow, but deficiencies remain. The systolic and diastolic rate constants have shown some promise for the prediction of CVD events and mortality, but data is still lacking. Results pertaining to the systolic rate constant in particular are inconsistent in their direction of association with risk, and additional work on the underlying cause of these discrepancies is warranted. Moreover, there is little to no data assessing associations of the rate constants with markers of target organ damage, and these studies are needed. Furthermore, the clinical value of each model parameter, when derived from different arterial locations, has not been fully determined. A greater understanding of the relationship of model parameters derived from different arterial locations with markers of CVD risk would be beneficial for identifying the most clinically useful combination of arterial location and model parameter.

The recording of non-invasive arterial BP waveforms by tonometry, though uncomplicated to perform, is operator dependent, which remains a barrier to the broader uptake of arterial waveform analysis for the assessment of CVD risk in clinical practice. Recently, new technologies have afforded the opportunity to measure the arterial BP waveform non-invasively using cuff-based BP devices.[62] Incorporation of reservoir-excess pressure parameters into conventional BP measurement methods should remove barriers to its clinical use, but a refinement of the methods is needed.[62] Nevertheless, even perfectly accurate measures of cuff-based reservoir-excess pressure parameters are not helpful without also showing clear and consistent associations with clinical outcomes independent of CVD risk factors already available in clinical practice. In this review we have highlighted a number of studies that have observed independent associations between reservoir-excess pressure parameters and CVD risk. That said, there is a lack of consistency in the strength and direction of these associations across studies, most of which have been observed in different

patient populations and with reservoir-excess pressure parameters derived from different arterial locations. In this regard, more work is needed to understand the association between reservoir-excess pressure parameters and clinical outcomes among healthy/community-based populations. It also remains to be seen which of the reservoir-excess pressure parameters is most clinically useful. Additionally, new cuffless biometric wearable devices are emerging that measure BP and record the BP waveform from the underlying hemodynamics at various arterial sites including, but not limited to, the wrist, ears and fingers. However, amplification of systolic BP from central to peripheral arteries may hinder the accurate assessment of a clinically important BP (i.e., central, or brachial BP). By taking advantage of the reservoir-excess pressure model it may be possible to derive indices measured from peripheral artery BP waveforms that are representative of central parameters but also are associated with CVD risk when derived from the radial BP, without the need of direct knowledge the central BP.

Concluding comment

Reservoir-excess pressure parameters provide insights into arterial physiology and are associated with CVD risk independent of conventional CVD risk factors. Utilization of model parameters in routine clinical practice may be feasible but is still some way off. In the clinical setting, the mathematical detail underpinning the model parameters is not necessary. This review provides a high-level overview of the physiological and clinical value of the reservoir-excess pressure parameters, helping close the gap between research and clinical translation.

Author contributions:

MA - Conception, data interpretation and manuscript preparation and revision.

MS - Data interpretation and critical manuscript revision.

AH - Data interpretation and critical manuscript revision.

DP - Data interpretation and critical manuscript revision.

JS - Conception, data interpretation and critical manuscript revision.

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Figure legends:

Figure 1. Conventional blood pressure (BP) assessment methods employ the oscillometric or manual auscultatory method to derive values for systolic and diastolic BP and provide little information on the underlying arterial BP waveform. Systolic BP is the peak of the arterial BP waveform and diastolic BP the nadir. Pulse pressure is the difference between systolic and diastolic BP.

Figure 2. Intra-arterial aortic blood pressure measured continuously over one cardiac cycle and overlaid with parameters derived via conventional pulse-wave analysis. dP/dt max is the point at which the rate of increase in pressure is highest. P1 is the anacrotic notch or first systolic inflection point and P2 is the systolic blood pressure. Augmentation pressure (AP) is the difference between P1 and P2 and is used, along with pulse pressure (PP), to calculate augmentation index (AIx), a common pulse-wave analysis index (AIx = AP/PP). Incisura, or the dicrotic notch, marks the end of systole and closure of the aortic valve. Tr is the time to P1 and systolic and diastolic duration is the length of time spent in cardiac contraction and relaxation, respectively.

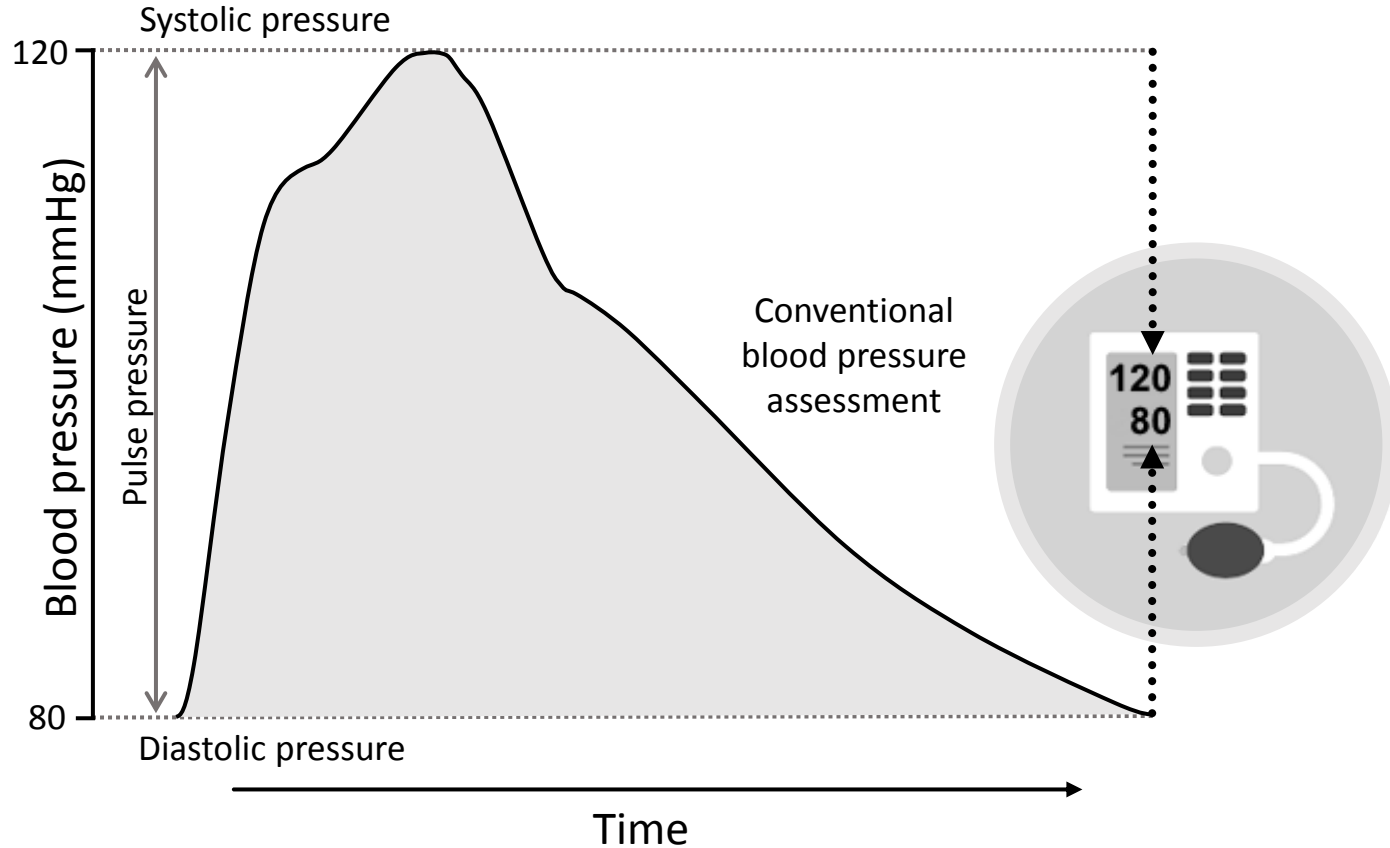
Figure 3. Parameters derived from an ensemble averaged intra-arterial aortic blood pressure waveform via reservoir excess pressure analysis. Parameters may be measured as peak or integral (area under the curve) values of the reservoir and excess pressure curves. Shaded areas represent model parameters derived by the integration of the reservoir and excess pressure curve. The systolic and diastolic rate constants represent the rate of increase and decrease of the reservoir pressure, respectively. Pinfinity ($P\infty$) is the asymptote of the diastolic BP decay and is assumed to represent the BP at which flow through the microcirculation stops.

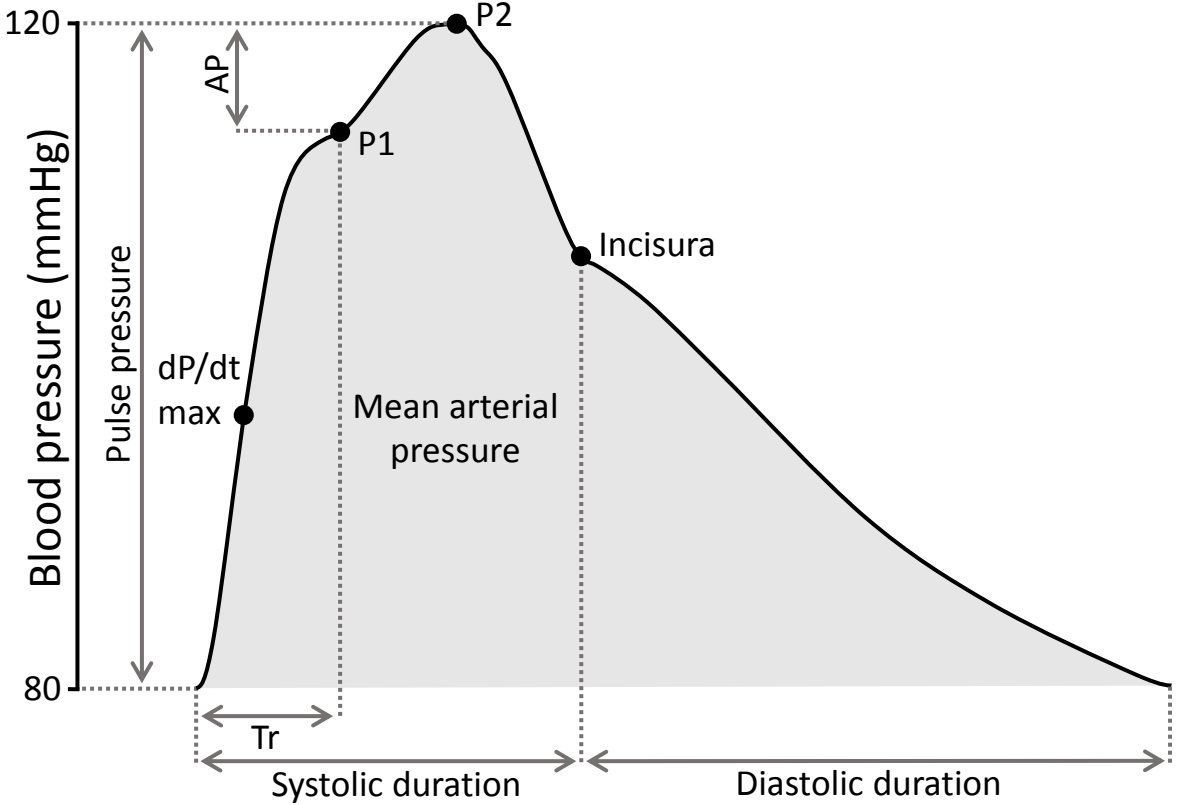
Figure 4. Relationship of reservoir pressure (dashed line) derived via the reservoir-excess pressure model and aortic volume measured via ultrasound in 9 individuals undergoing coronary artery bypass surgery (left). Aortic volume was scaled to reservoir pressure for presentation. Change in aortic volume over the cardiac cycle is well matched by reservoir pressure (right, $R^2 = 0.95$, max cross-correlation $r = 0.97$). From Schultz et al. [34]

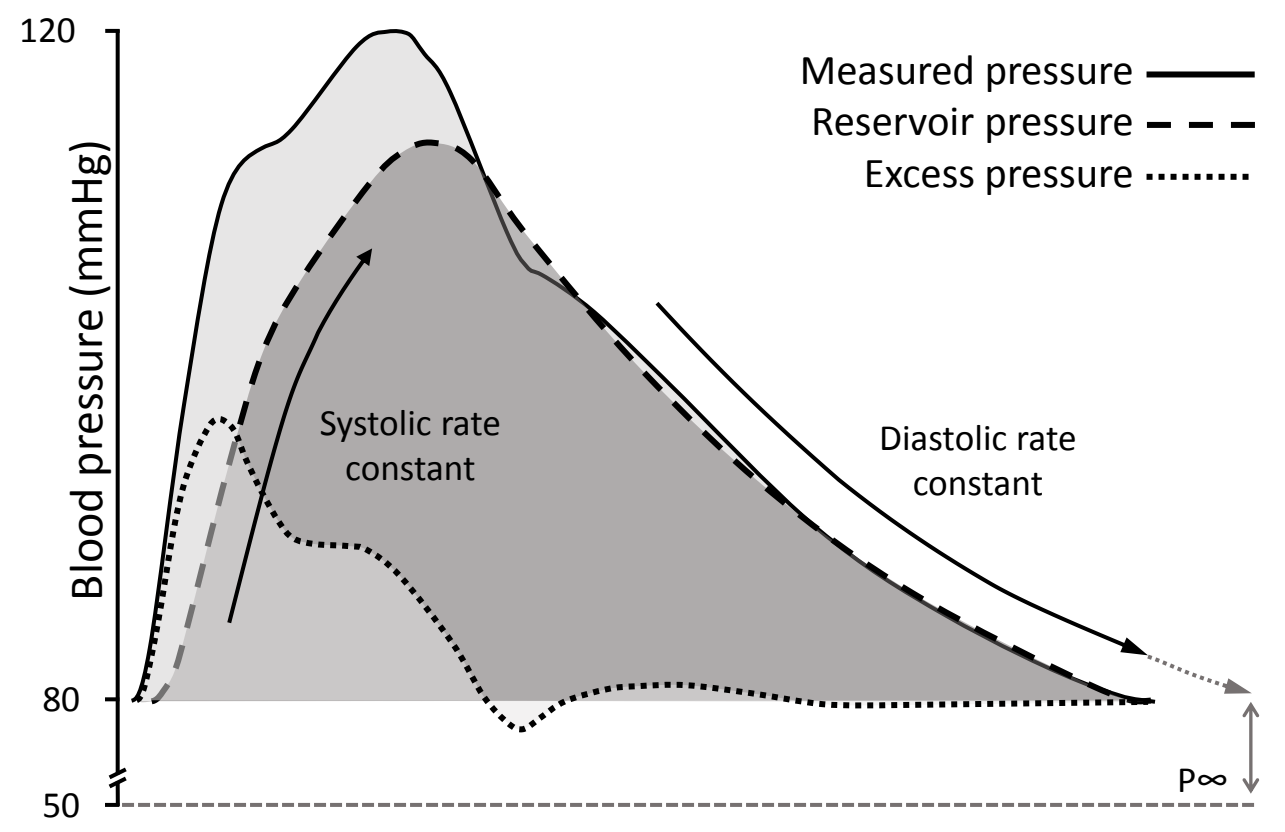
Table 1. Studies of reservoir excess pressure parameters associated with cardiovascular risk.

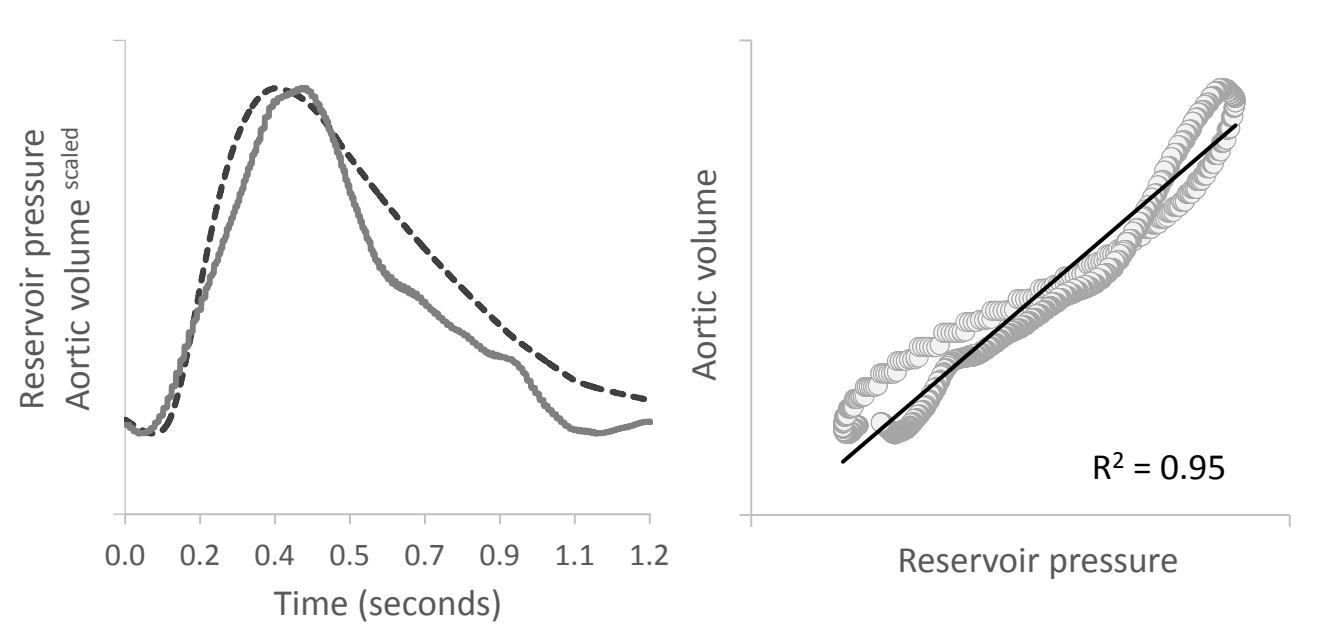
Study, year	N	Age	Male (%)	Method	Site	GTF used?	Findings
Reservoir pressure parameters and all cause and CV mortality and CV events							
Hametner[45], 2014	674	64±NA	57	Tonometry	Radial	Y	**Pr** amplitude‡ predicts CV events & mortality (3.8y FU)
Davies[41], 2014	2069	63±8	81	Tonometry	Radial	N	**Pxs** integral‡ predicts CV events (3.5y FU)
Narayan[56], 2015	838	72±0.2	46	Tonometry	Carotid	N	**Ks**‡ predicts CV events (4.4y FU)
Cheng[46], 2016	1272	52±13	54	Tonometry	Carotid	N	**Pr** peak‡ & amplitude‡, **Ks**‡, & **Kd**‡ predict CV mortality (19.8y FU)
	2211	53±12	46	Tonometry	Radial	Y	**Ks**‡ & **Kd**‡ predict **CV** mortality (10y FU)
Wang[54], 2017	168	64±15	66	Tonometry	Carotid	N	**Pxs** integral† predicts total mortality (9.9y FU)
Schneider[55], 2018	251	64±NA	71	Tonometry	Radial	NA	**Pxs** integral* predicts all-cause mortality & CV events (3.4y FU)
Fortier[48], 2019	260	70±NA	60	Tonometry	Carotid	N	**Pxs** integral† & **Ks**† predict all-cause & CV mortality. **Pxs** amplitude† & **Pr** integral† predicts all-cause mortality (2.6y FU)
Behnam[47], 2019	2539	63±11	42	Tonometry	Carotid	N	**Pr** amplitude‡**, Ks**‡ & **Kd**† predict CVD events (15.1y FU)
Reservoir pressure parameters and CV risk markers							
Sharman[19], 2009	16	62±10	82	Tonometry	Radial	N	**Pr** peak positively correlates with AIx
Davies[63], 2010	15	53±10	62	Catheter	Aorta	NA	**Pr** integral positively correlates with AIx
Piskorski[64], 2013	159	51±1	45	Tonometry	Radial	NA	**Pxs** & **Pr** integral positively correlates with AP
Climie[52], 2014	37	52±8	51	Tonometry	Radial	N	**Pxs** integral‡ negatively correlates MRI grey matter volume
Davies[41], 2014	2069	63±8	81	Tonometry	Radial	N	**Pxs** integral‡ positively correlates with cIMT. **Pr**‡ & **Pxs**‡ integral positively correlates with LVMI
Schultz[42], 2015	359	61±9	49	Tonometry	Radial	N	**Pr** integral‡ positively correlates with AP, AIx, & LVMI
Climie[53], 2017	33	57±9	55	Tonometry	Radial	N	Change in **Pxs** integral* negatively correlates with the change in eGFR
Armstrong[59], 2020	220	61±10	68	Catheter	Aorta & Brachial	N	**Kd**‡ negatively correlates with eGFR

Data are mean±SD unless stated otherwise. GTF = Y identifies those studies where a generalised transfer function was used to synthesise an aortic pressure waveform from a peripheral artery waveform. Studies were identified through snowballing and PubMed and Google scholar searches. Only statistically significant associations from published studies are presented here, see supplementary material eTable 1 and eFigure 2 for non-significant findings. ‡ indicates findings were at least independent of age, sex, and blood pressure (systolic or mean arterial pressure), † indicates findings were at least age and sex independent, and * indicates findings were at least independent of age. AIx, augmentation index; AP, augmentation pressure; cIMT, carotid intima media thickness; CV, cardiovascular; eGFR, estimated glomerular filtration rate; FU, follow up; GTF, generalised transfer function; Kd, diastolic rate constant; Ks, systolic rate constant; LVMI, left ventricular mass index; MRI, magnetic resonance imaging; Pxs, excess pressure; Pr, reservoir pressure; y, years.


Systolic pressure
120
Blood pressure (mmHg)
Pulse pressure
80
Diastolic pressure
Time
Conventional
blood pressure
assessment
120
80


120
80
Blood pressure (mmHg)
Pulse pressure
AP
P1
P2
Incisura
dP/dt
max
Mean arterial
pressure
Tr
Systolic duration
Diastolic duration


120
80
50
Blood pressure (mmHg)
Measured pressure
Reservoir pressure
Excess pressure
Systolic rate constant
Diastolic rate constant
P∞


Reservoir pressure
Aortic volume scaled
0.0
0.2
0.4
0.5
0.7
0.9
1.1
1.2
Time (seconds)
Aortic volume
R2 = 0.95
Reservoir pressure