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CLINICAL REVIEW
Translational medicine

Pulsatile arterial haemodynamics in heart failure

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Due to the cyclic function of the human heart, pressure and flow in the circulation are pulsatile rather than continuous. Addressing pulsatile haemodynamics starts with the most convenient measurement, brachial pulse pressure, which is widely available, related to development and treatment of heart failure (HF), but often confounded in patients with established HF. The next level of analysis consists of central (rather than brachial) pressures and, more importantly, of wave reflections. The latter are closely related to left ventricular late systolic afterload, ventricular remodelling, diastolic dysfunction, exercise capacity, and, in the long-term, the risk of new-onset HF. Wave reflection may also represent a suitable therapeutic target. Treatments for HF with preserved and reduced ejection fraction, based on a reduction of wave reflection, are emerging. A full understanding of ventricular-arterial coupling, however, requires dedicated analysis of time-resolved pressure and flow signals, which can be readily accomplished with contemporary non-invasive imaging and modelling techniques. This review provides a summary of our current understanding of pulsatile haemodynamics in HF.

Keywords Pulsatile haemodynamics • Pulse pressure • Afterload • Ventricular-arterial coupling

Introduction

Heart failure (HF) is an important clinical problem in developed countries, with high rates of hospitalization and mortality.[1] An increased brachial systolic blood pressure (bSBP) and brachial diastolic blood pressure (bDBP), starting at levels as low as 115 and 75 mmHg, respectively, predict incident HF across all adult age groups.[2] Consequently, reduction of incident HF was the most pronounced benefit of intensive BP lowering in the recently published SPRINT trial.[3]

Brachial systolic blood pressure and bDBP, introduced over a century ago, are among the most widely performed measurements in clinical medicine. Despite their wide use in daily practice, the complex relationship between the pump (i.e. the heart) and the arterial circulation cannot be fully understood from two isolated pressure points at the brachial artery for the following reasons: (i) physiologically, due to the pulsatile characteristics of the pump, BP is a curve rather than two extremes (SBP, DBP), with a defined amount of pressure [pulse pressure (PP)] fluctuating around a mean value [mean arterial pressure (MAP)]; the curve contains features that provide insights into arterial function.[4] (ii) Systolic blood pressure and PP increase from the ascending aorta to peripheral measurement sites, a phenomenon called pressure amplification, which is related to the mechanical properties of the arterial system. Therefore, brachial BPs do not necessarily reflect the pressures 'seen' on the heart. (iii) Most importantly, BP originates from the interaction of cardiac and arterial function and is the result of the flow generated by the heart and the afterload imposed by the arterial tree. Therefore, patients with identical BP may have substantially different afterload patterns due to differences in the blood flow generated by the left ventricle (LV). Therefore, LV afterload (arterial load) cannot be estimated without knowledge of both pressure and flow.

Broadly, arterial load has two components: steady (or 'resistive') load and pulsatile load. 'Steady' load [total peripheral resistance (TPR), largely determined by systemic microvascular resistance], along with cardiac output (CO), determines MAP ($MAP = CO \times TPR$), whereas pulsatile afterload is influenced by multiple arterial properties (aortic geometry and stiffness, timing, and magnitude of arterial wave reflections). This review focuses on the pulsatile component of cardiac afterload, its assessment, prognostic value, and therapeutic consequences.

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Non-invasive assessment and physiological background of the measurements

Pulse pressure

Brachial PP (bPP) is a widely used pulsatile haemodynamic index. It can be easily computed SBP minus DBP and is thus readily available. It is the result of left ventricular mechanical work interacting with the arterial tree and, as such, depends on stroke volume (SV) and forward flow on the one hand, and on aortic stiffness, size, and wave reflections on the other. When the LV chamber pump function is preserved and significant aortic valve disease is absent, a high PP is generally considered indicative of increased pulsatile afterload. In heart failure with reduced ejection fraction (HFrEF), PP is directly related to measures of LV function, such as EF, SV, CO, left ventricular (LV) d*p*/d*t*, and LV longitudinal axis shortening.[5] In other words, in HFrEF, a lower PP is often a consequence of a worse LV function. This needs to be taken into account when interpreting studies that assess the prognostic value of PP.

Due to its simplicity of measurement, several epidemiological studies have investigated the prognostic role of bPP, most of them demonstrating that a high bPP is associated with a poor prognosis. According to European Guidelines on Hypertension,[6] a bPP value ≥60 mmHg in elderly individuals with stiffer arteries reflects asymptomatic damage of the large arteries. As the BP wave travels from central aorta to peripheral sites (e.g. brachial artery), MAP drops only by 2 mmHg, whereas SBP and PP can increase markedly[4] [SBP and PP amplification (PPA)], particularly in younger adults. The *PPA* ratio (peripheral PP/central PP) is determined by complex interactions between many factors, including LV contractility and ejection duration, heart rate, arterial stiffness, arterial calibre (and taper), the timing and amplitude of wave reflections, and arteriolar tone (TPR). *Central PP* cannot be calculated from bPP by a simple formula but requires dedicated instruments that record the time-resolved waveforms at the carotid site or in more peripheral locations. In the absence of obstructive atherosclerotic carotid disease, the carotid pressure waveform is considered a reasonable 'direct' surrogate of the aortic pressure waveform, whereas more peripheral waveform recordings (brachial or radial) require mathematical algorithms to estimate the aortic pressure waveform. In all instances, the obtained aortic pressure waveform needs to be calibrated with peripheral mean and diastolic pressures, which unlike systolic pressure demonstrate little variation between the aorta and peripheral sites.[7] The technical details are beyond the scope of this manuscript and can be found in dedicated reviews.[8]

Wave reflections in the arterial tree

Left ventricular contraction generates a forward-travelling wave (incident or forward wave). The wave travels at a given speed [pulse wave velocity (PWV), ~5 to 15 m/s in humans] along the wall of the aorta and more distal conduit arteries and is partially reflected at sites of impedance mismatch (branching points, lumen diameter tapering, and change in local stiffness).[9] Innumerable reflections from distributed sites are transmitted back toward the heart, interacting to form a 'net' reflected wave. In young adults, aortic PWV is low, and the bulk of reflected waves arrive at the aortic root during diastole. With advancing age, PWV increases, and reflected waves arrive at the heart during mid-to-late systole.[10,11] In these conditions, wave reflections exert important unfavourable effects,[4] including (i) an increase in mid-to-late systolic load (relative to early systolic load); (ii) an increase in aortic SBP, although the degree of pressure augmentation vs. flow reduction depends on LV function; (iii) a decrease in DBP, including the area under the pressure waveform (pressure–time integral) in diastole, which is a key determinant of coronary blood flow. Importantly, reflected waves also re-reflect at the heart, contributing to an increase in the amplitude of the forward pressure wave, above and beyond the influence of the aortic root load and flow requirements.[12]

Methods to analyse waveforms

Pulse waveform analysis (*PWA*): The reflected wave causes a visible notch (inflection point) and an increase (i.e. augmentation) in late systolic pressure (*Figures 1* and *2*). *Augmented pressure* (*AP*), expressed in mmHg, is the increase in BP following the inflection point and is partially related to the effects of wave reflection on the aortic BP curve. *Augmentation index* (*AIx*) is the ratio between augmented pressure and pulse pressure (AIx = AP/cPP), typically expressed as a percentage. Both AIx and AP are higher with increasing age, lower heart rate (a relatively longer systolic period enables reflected waves to exert greater pressure augmentation during systole), smaller body height (shorter travel distance), female sex, and are lower following food ingestion and following exercise.[15] Pulse waveform analysis-derived indexes are dependent not only on the magnitude but also on the timing of wave reflection. To overcome this potential limitation and focus on the amount of wave reflection only, *wave separation analysis* (*WSA*) can be used, which requires simultaneously acquired pressure and flow waves at the same location to separate the pressure wave into its *forward* (*Pf*) and *backward* (*Pb*) components.[16] *Reflection magnitude* (RM) is the ratio of amplitudes of Pb/Pf. A more recent development is *wave intensity analysis* (*WIA*),[17] in which BP and flow velocity measured at the same arterial site are considered and a separation into forward and backward-travelling wavefronts can be achieved (*Figure 2*). Waves can originate either from the proximal (forward-travelling) or distal (backward-travelling) end of the circulation and can be either a compression ('pushing') or decompression ('sucking') wave. A compression wave will accelerate or decelerate blood flow depending on its origin: if it arises proximal to the site of measurement, it will increase pressure and accelerate flow, but compression waves of distal origin will increase pressure and decelerate blood flow.[18] Wave intensity analysis is a useful approach that complements WSA, but it overemphasizes high-frequency components of the pulse (i.e. rapid changes in pressure and flow waves) and thus tends to under-represent reflected waves (which are rich in low-frequency content). A key advantage of WIA may be related to the study of cardiac-derived compression and suction waves (rather than wave reflection *per se*): the early systolic S-compression wave peak is related to the maximum derivative of left ventricular pressure increase in early systole, while the D-late systolic forward-travelling suction wave peak is related to the time constant of pressure decay in late systole/early diastole.[19] Both may, therefore, provide insights into ventricular function[14] and LV-arterial coupling. *Wave power analysis*, a recently proposed technique based on volume flow rather

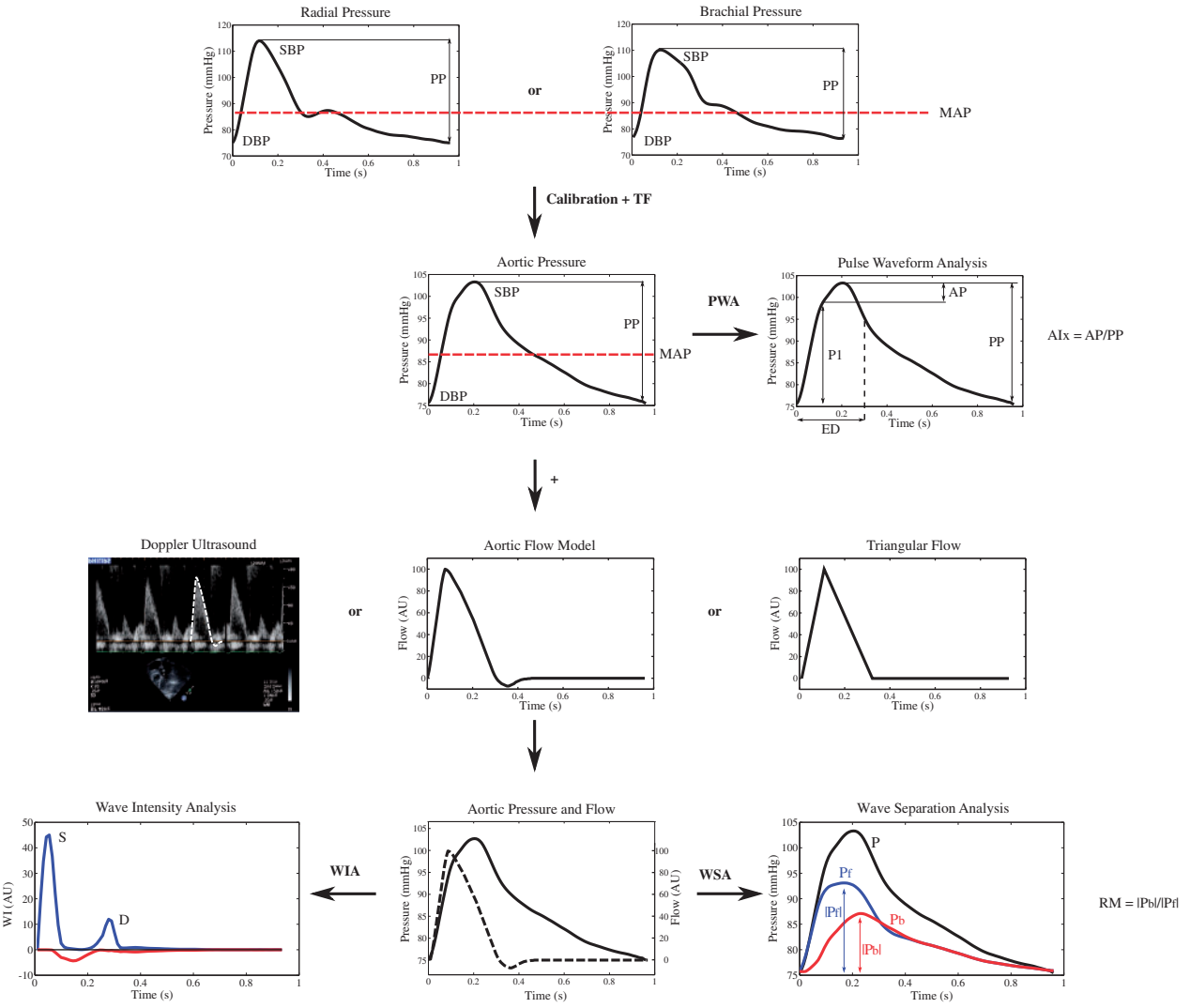

Figure 1 Assessment of pulsatile haemodynamics—overview. *Top line:* recording of signal-averaged radial or brachial pressure waveforms with tonometry or brachial cuff. *Second line:* following calibration with brachial pressures, aortic waveforms are calculated with a transfer function (TF). Pulse waveform analysis, based on pressure signals alone, yields measures of the first (P1) and second (P2) systolic peaks for computation of augmented pressure and augmentation index (AP, AIx). *Third line:* flow waveforms are obtained, either with Doppler recording of LV outflow (which equals aortic inflow), or as model-derived flow or triangular flow as a proxy. *Bottom line:* combined and time-aligned analysis of a pressure–flow pair is used for wave separation analysis, wave intensity analysis, and other analytical approaches (Courtesy of Bernhard Hametner, modified from Parragh *et al.*[13] and from Hametner *et al.*[14]). DBP, diastolic blood pressure; ED, ejection duration; MAP, mean arterial pressure; PP, pulse pressure; PWA, pulse waveform analysis, RM, reflection magnitude; SBP, systolic blood pressure; WIA, wave intensity analysis; WSA, wave separation analysis.

than flow velocity, has important advantages over WIA and requires further study in humans.[20]

Pulse wave velocity, characteristic impedance, total arterial compliance

Pulse wave velocity is the travel distance divided by transit time of the pulse between two recording sites. Carotid-femoral (cf) PWV is currently considered the gold standard metric of aortic stiffness.[21] Pulse wave velocity is not a direct measure of ventricular afterload, but is informative of arterial wall properties, and has important prognostic implications.[4,21,22] Proximal aortic impedance (Zc) is the slope of the pressure–flow relation in the absence of wave reflections and represents the pulsatile load imposed by the proximal aorta. It is highly dependent on proximal aortic size and also dependent on its stiffness. Total arterial compliance (TAC) represents the lumped compliance provided by the arterial tree. In the systemic circulation, it is largely determined by conduit arteries (including the aorta and more distal muscular conduit arteries).

Practical recording and devices

See Supplementary material online for details.

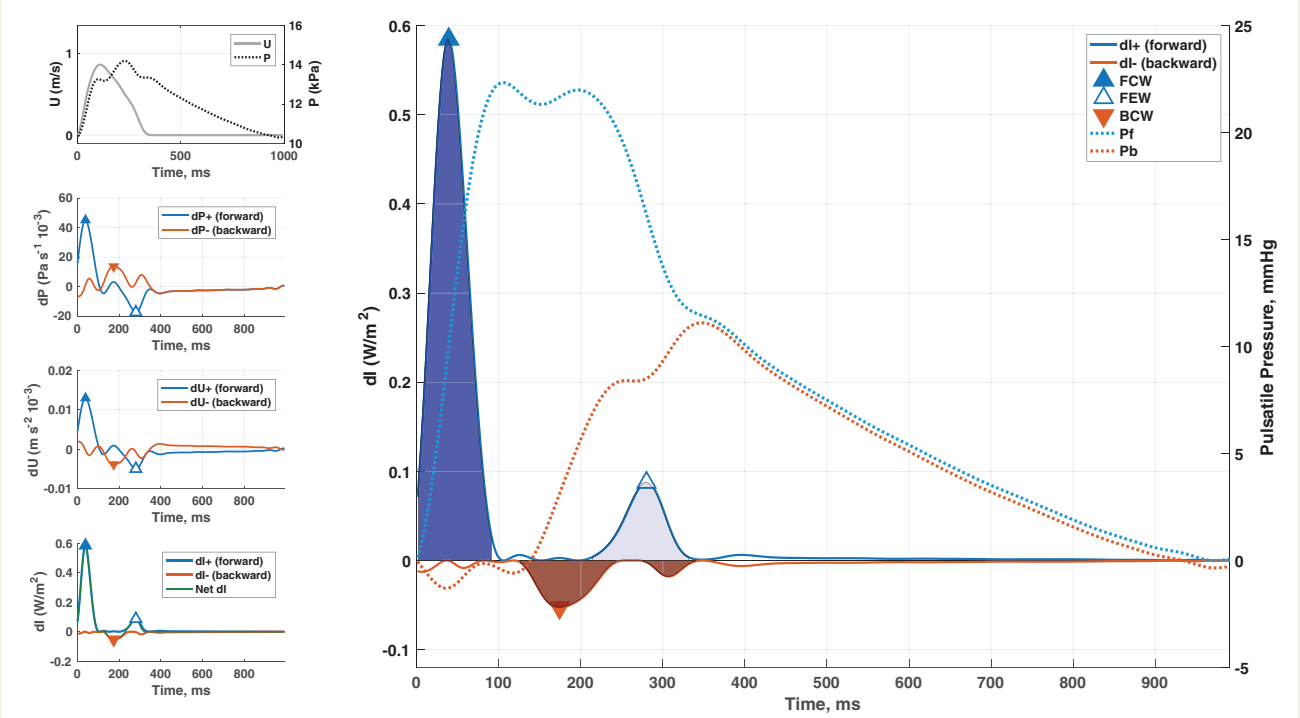

Figure 2 Wave separation analysis vs. wave intensity analysis. Identification of forward-travelling and backward travelling waves in the proximal aorta using wave intensity analysis. The method is based on the assessment of changes in pressure (P) and flow velocity (left panels), which can be multiplied to compute instantaneous wave intensity (left bottom panel). The right panel shows forward and backward wave intensity curves, which can be analysed to identify the timing and magnitude of key wave fronts: early systolic forward compression wave (dark blue), late systolic forward suction wave (light blue), and backward compression wave (red). The cumulative sum of forward and backward pressure changes (dP, used to computed wave intensity) are superimposed on the right *y*-axis. These curves (Pf, Pb) are equivalent to forward and backward waves obtained via classic wave separation analysis. It can be seen that wave intensity tends to markedly under-represent reflected waves, because it emphasizes rapid changes in pressure and flow (high frequencies), whereas reflected waves are enriched in lower frequencies. BCW, backward compression wave; FCW, forward compression wave; FEW, forward expansion suction wave.

The relationship between cardiac and arterial function

Myocardial vs. ventricular afterload

Left ventricular afterload can be defined as the hydraulic load imposed by the systemic circulation (i.e. relationship between pressure and flow as discussed above), whereas myocardial afterload is best defined as the myocardial wall stress (MWS) required to generate fibre shortening.[23–26] Myocardial afterload does not only depend on arterial load but also on the time-varying LV geometry during ejection, which in turn affects the relationship between MWS and LV chamber pressure. The time-varying LV geometry during ejection is dependent on: (i) LV volume at the beginning of LV contraction (i.e. end-diastolic volume), which in turn is determined by chronic LV remodelling and preload and (ii) the interaction between myocardial contraction, LV geometry, and arterial load throughout ejection.

In accordance with Laplace's law of the heart, MWS is lower for any given LV pressure, as the ratio of LV chamber volume to LV wall volume decreases. This is true not only in end-diastole or end-systole but throughout ejection (*Figure 3*). Among normotensive and hypertensive adults with a normal LV ejection fraction (EF), peak MWS typically occurs in early systole, when quasi-diastolic geometry coexists with systolic pressure.[27–29] This is followed by a marked change in the relationship between LV pressure and MWS during mid-systole, which determines a lower MWS for any given LV (and aortic) pressure (*Figure 3*).[28] This phenomenon appears ideal to protect cardiomyocytes against excessive load in mid-to-late systole[28,30] and depends on the dynamic reduction of LV chamber size relative to wall volume, and its magnitude is highly variable between individuals.[28] Subjects with lower ejection fraction,[28] concentric remodelling,[28] or those who demonstrate poor early systolic contraction (and ejection)[31] demonstrate less pronounced shifts in the pressure–stress relation.

Therefore, there is an important interaction between myocardial geometry, the myocardial contraction pattern, and the effect of wave reflections on LV hydraulic load (*Figure 4*). Wave reflections tend to increase mid-to-late systolic LV load and MWS,[27,28] but the time course of LV contraction impacts the degree to which cardiomyocytes are 'exposed' to the ill effects of wave reflections in mid-to-late systole, a period in which there appears to be particular vulnerability to the deleterious effects of increased afterload.[30,32–35] Time-varying MWS, therefore, provides highly relevant integrated information about myocardial-ventricular-arterial coupling.[4,27–29,36]

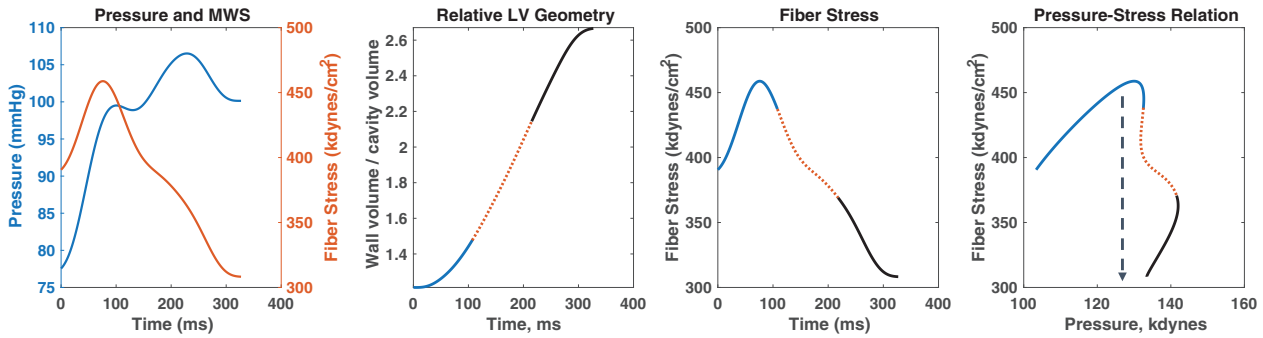

Figure 3 Time-resolved myocardial wall stress. The first panel shows the ejection-phase aortic pressure and myocardial wall stress (MWS) profiles. The second panel shows the time-resolved relative myocardial geometry (ratio of wall volume to cavity volume) that correlates with wall stress via the Laplace law; the first, second, and last thirds of systole are shown in blue, dotted red, and black lines, respectively. The third panel shows the ejection-phase myocardial wall stress, and the fourth panel shows pressure–MWS relation. It can be seen that myocardial wall stress peaks in early systole and subsequently decreases, even in the context of increasing pressure. This is due to a mid-systolic shift in the pressure–stress relation (dashed arrow) which favours lower MWS for any given pressure. This shift is due to the geometric reconfiguration of the LV (decreased cavity volume relative to LV wall volume) and is impaired in the presence of reductions in LV ejection fraction, concentric geometric remodelling, and reduced early systolic ejection (reduced early-phase ejection fraction). LV, left ventricular.

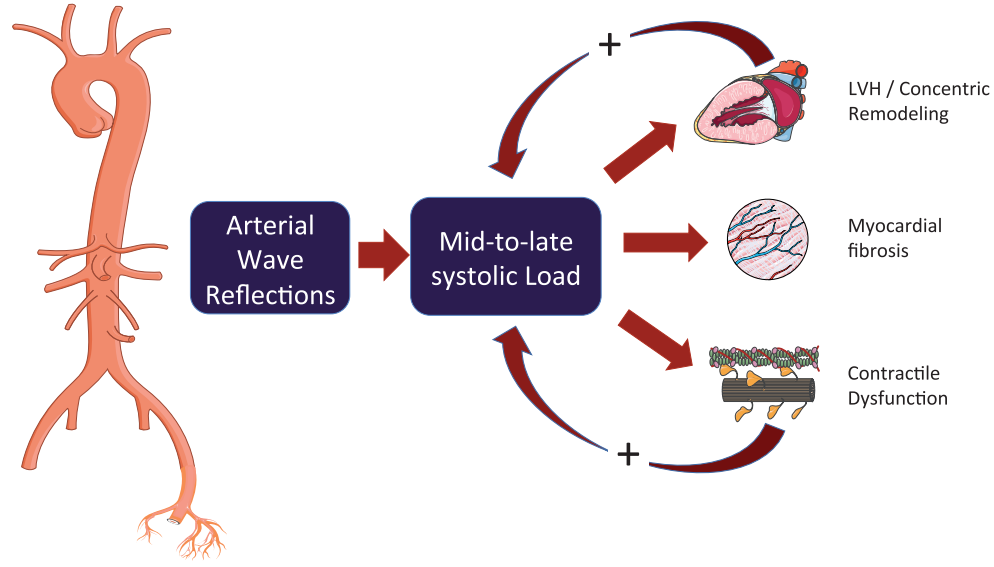

Figure 4 Wave reflections increase late systolic left ventricle load, which favours left ventricular remodelling and myocardial dysfunction. However, the effect of wave reflection on myocardial load is modulated by contraction pattern and the time course of myocardial wall stress. Left ventricles in which the mid-systolic shift in the pressure–stress relation is impaired (due to a reduced ejection fraction, concentric geometric remodelling, and/or reduced early systolic ejection) fail to protect cardiomyocytes against the load induced by wave reflections in late systole, a period of vulnerability to load. This may represent a vicious cycle that favours development and furthers progression of heart failure. Modified from Chirinos.[26] LVH, left ventricular hypertrophy.

In rotationally symmetric ventricles, time-resolved ejection-phase MWS can be estimated non-invasively with a combination of arterial tonometry and either Doppler echocardiography[28] or cardiac magnetic resonance imaging (MRI),[37] using the method described by Arts *et al.*[38] Myocardial wall stress can be used to more directly infer late systolic myocardial load. Prominent late systolic MWS is associated with impaired LV relaxation[29] and left atrial dysfunction.[37] Furthermore, peak systolic MWS is closely and linearly related to invasively measured myocardial oxygen consumption (MVO_2)[39] and therefore can be used to assess the mechanical efficiency of the cardiovascular (CV) system, with fewer assumptions than in the pressure–volume plane.

Differences in the effects of arterial load in heart failure with preserved ejection fraction and heart failure with reduced ejection fraction

When LV pump function is preserved, the reflected wave typically induces a late systolic pressure peak in the pressure waveform, augmenting aortic pressure in mid-to-late systole. These features are prominent in patients with heart failure with preserved ejection fraction (HFpEF)[40–43] and may be useful in the diagnostic workup of the condition[41]: measures of pulsatile arterial function (including brachial PP, but favouring central haemodynamics) were as good as tissue Doppler echocardiography in separating patients with HFpEF from those without the condition in a population of patients with exertional dyspnoea. When LV pump function is reduced, however, wave reflection may exert more pronounced effects to decrease flow, with no apparent alteration in the appearance of the pressure waveform (when the latter is analysed in isolation). In patients with severe LV systolic dysfunction (LVEF ≤30%), wave reflections truncate flow, reduce SV, and induce a shortening of ejection duration.[13,44,45] In addition, forward waves are also altered: in patients with severely reduced EF (mean value 27.8%), WIA derived ratio of first to second systolic peak is reduced,[46] as compared to individuals with normal EF, and divided patients with HFrEF from controls with normal EF with an area under the curve of 0.879.[14]

Disadvantages of effective arterial elastance

Given the value of the pressure–volume plane to study LV chamber function and energetics, an 'extension' of the pressure–volume approach to assess arterial load and ventricular-arterial coupling was proposed, primarily to understand the determinants of SV.[47–50] In this proposed paradigm, arterial load is quantified as an 'effective arterial elastance' (E_A), which is computed as the ratio of end-systolic pressure to SV.

However, arterial load is time-varying, complex, and cannot be expressed as a single number.[9,25] E_A fails to capture key features of pulsatile load and ventricular-arterial coupling, particularly time-varying phenomena during ejection[51] and the LV loading sequence (early vs. late systolic load), which as reviewed above, is an important determinant of maladaptive remodelling, hypertrophy, diastolic dysfunction, atrial dysfunction, and HF risk.[9,29,33,40,52–55] In addition, the assumption that E_A is a lumped parameter of resistive and pulsatile arterial load, is in fact incorrect.[25,56–58] E_A is not a true elastance (i.e. the inverse of a compliance) and is almost exclusively dependent on vascular resistance (a microvascular, rather than a conduit artery property)[57] and heart rate.[57,58] E_A bears an almost perfect relationship to the product of TPR and heart rate, but demonstrates weak, inconsistent and in some cases, erratic/paradoxical relationships with gold standard measures of pulsatile load.[58] Importantly, E_A is not related to aortic wall stiffness[58]; therefore, an increase in E_A should not be interpreted as arterial 'stiffening' and, by extension, and parallel increase in E_A and E_{ES} should not be interpreted as a state of 'ventricular-arterial stiffening'.

The inability of E_A to properly capture pulsatile arterial load is explained by the multiple simplifying assumptions made during its original derivation (as previously discussed in detail),[24,25,57,58] which translate into important limitations to the application of this approach to characterize physiologic abnormalities and obtain useful clinical inferences. For example, in a recent study, measures of wave reflection, but not E_A or TPR, were significantly correlated with the invasively measured time constant of isovolumic relaxation, the gold standard index of diastolic relaxation.[59] Similarly, a recent study demonstrated that E_A did not predict incident HF in the Multiethnic Study of Atherosclerosis (MESA) cohort,[60] whereas wave reflections (RM) and late systolic load were strong predictors.[61,62] The use of E_A to assess pulsatile or 'global' arterial load is therefore strongly discouraged.

Clinical impact of pulsatile arterial load

Arterial load and left ventricular hypertrophy

Left ventricular hypertrophy (LVH) is an important marker of asymptomatic organ damage in hypertension[6] and an important intermediate step from hypertension to HF.[63] Animal models have shown that an increase in aortic stiffness without any change in TPR leads to LVH.[64] Moreover, late systolic loading resulted in much more prominent hypertrophy than early systolic loading in rats.[53] Humans with isolated systolic hypertension, a condition related to increased aortic stiffness, exhibit higher left ventricular mass (LVM) than those with systolic–diastolic hypertension. Moreover, LVM is more strongly related to PP than to MAP, underlining the importance of pulsatile phenomena.[65] This relationship is stronger for cPP,[66,67] in particular when measured over 24-h.[68] The relationship between LVM and arterial stiffness/wave reflections is apparent even in adolescents and young adults.[69] In a recent study including >4000 adults from the general population, the contribution of steady state load (TPR) and pulsatile haemdynamics (TAC, Pf, Pb) on LVM and geometry was investigated.[70] In multivariable models, systemic vascular resistance (SVR), TAC, and Pb were directly, and Pf was inversely associated with LVM, with wave reflection (Pb) demonstrating the strongest relationship, and SVR demonstrating a relatively weak relationship. In a longitudinal study in a family-based population sample, progression to LV concentric remodelling pattern over 4.7 years was independently associated with higher baseline cfPWV.[71] Moreover, in women, higher cPP at baseline predicted the longitudinal increase in LVM. Reductions in LVM, which have proven prognostic benefit, are more closely associated with reductions in wave reflection than with reductions in brachial BP.[54,72] When different drugs (angiotensin converting enzyme (ACE)-inhibitor-diuretic combination vs. a beta-blocker) were compared, those favourably affecting pulsatile haemodynamics (reducing cSBP and cPP) were superior in reducing LVM,[73] whereas both therapeutic regimens did not differ regarding steady state haemodynamics (CO and TPR).

Arterial load and exercise capacity

Consistent with the important role of pulsatile arterial load on the myocardium, pulsatile arterial properties have been shown to be associated with exercise capacity, as discussed in the Supplementary material online.

Arterial load and risk of incident heart failure

In the Framingham study, bPP (and bSBP) were stronger predictors than DBP for congestive HF (CHF)[74] in middle-aged men and women.[75] In 5690 participants from the MESA study, RM was strongly and independently predictive of new-onset HF.[62] In particular, RM compared favourably to other risk factors for CHF as per various measures of model performance, reclassification, and discrimination and predicted CHF even in patients with normal BP. Along the same lines of evidence, independently of the absolute level of peak BP, late systolic hypertension was strongly associated with incident HF.[61] In the same population, and in contrast, SVR, TAC, and E_A did not predict HF, indicating the importance of the loading sequence.[60] In the Framingham Heart study, after adjustments for standard risk factors including MAP, cfPWV was independently associated with incident clinical HF[76] after a follow-up of 10.1 years. Moreover, greater cfPWV was associated with both HFpEF and HFrEF, although the findings did not achieve statistical significance, in part due to a modest number of HF events. In 2602 patients with chronic kidney disease (mean glomerular filtration rate (GFR) 45 mL/min/1.73 m^2), after a mean follow-up of 3.5 years, cfPWV as well as bSBP, cSBP, and PP predicted hospitalized HF, with cfPWV showing the best relationship.[77] In another community-based cohort of 2290 older adults (mean age 74 years),[78] cfPWV was associated with overall HF and HFrEF only in unadjusted analysis and, with respect to overall HF, only in partially, but not in fully adjusted models. Finally, in asymptomatic patients at risk for HF, worsening of arterial stiffness (increase in brachial-ankle PWV) within 5 years was associated with increased risk of incident HF.[79] In summary, available evidence supports a relationship between arterial stiffness and particularly, measures of wave reflection/late systolic load, and the risk of incident HF in the community.

Prognostic value of pulsatile haemodynamics in established heart failure

Due to the ease of assessment, most of the evidence available is related to bPP (Supplementary material online, *Table S1*). In advanced HFrEF, a lower bPP often is associated with a worse prognosis. In these patients, a low bPP is due to a poor LV function. In patients with less severe HFrEF, which can be indicated by higher bPP or higher SBP, the relationship may become direct (i.e. a higher bPP being associated with a worse prognosis). In these patients, PP is more reflective of arterial stiffness and increased pulsatile afterload. In HFpEF, the relationship between bPP and outcomes tends to be direct. In some studies, however, particularly in acute HFpEF, patients with the lowest bPPs also demonstrate a worse prognosis. These patients may have pronounced concentric remodelling with lower SVs, despite a preserved EF (which does not prove preserved myocardial contractility in HFpEF[80]).

Given the important confounding effect of LV function on PP, direct estimations of arterial load are likely to be more informative. One single-centre study demonstrated the adverse prognostic value of wave reflections in patients with acute decompensated HF.[81] Similarly, PWV as a more direct measure of arterial stiffness seems to be directly related to prognosis (HF hospitalization, CV, and all-cause mortality) in HFrEF and HFpEF.[82,83]

Therapeutic implications

Role of pulse pressure in heart failure with preserved ejection fraction studies

No proven effective pharmacologic treatment is currently available to reduce morbidity or mortality in patients with HFpEF (Supplementary material online, *Table S2*). Given the important pathophysiological role of impaired pulsatile haemodynamics in HFpEF, it is worth assessing haemodynamic characteristics of study populations in various trials, and the effects of interventions on pulsatile haemodynamics. Unfortunately, current evidence is largely limited to bPP. In two recent Phase II trials, ALDO-DHF[84] and in PARAMOUNT,[85] a substantial decrease in bPP was achieved in the active intervention arm (Spironolactone or Sacubitril-Valsartan, respectively), associated with an improvement in filling pressures or natriuretic peptides. In clinical endpoint trials, baseline bPP has generally been <60 mmHg, the cutoff defined by European Hypertension Guidelines,[6] suggesting that enrolled populations exhibited a relative paucity of pulsatile haemodynamic abnormalities demonstrated in other HFpEF studies. Moreover, in most clinical endpoint trials in HFpEF, bPP was not substantially reduced. For instance in the largest study (I-PRESERVE[86]), which showed a neutral outcome, bPP was lowered by only 1.7 mmHg by Irbesartan (and unchanged with placebo).

Wave reflections as a potential therapeutic target

In HFrEF, standard pharmacologic therapy may substantially reduce arterial load and wave reflections in some patients, although the response is variable and not readily judged by standard clinical parameters. A recent preliminary randomized study of arterial pressure waveform-guided therapy for HFrEF (aimed at reducing AIx) demonstrated that this strategy resulted in a greater improvement in peak oxygen consumption compared to standard care.[87] Drugs more often used in the active treatment group were aldosterone antagonists, hydralazine, and nitrates. Higher wave reflections at baseline and their larger decrease during treatment were associated with functional improvement.[88]

Not all vasodilators are equally effective at reducing wave reflections. In HFrEF, nitroprusside has been shown to reduce wave reflections at rest and during exercise.[89] Oral nitric oxide donors also reduce wave reflection in the acute setting. However, despite the well-documented acute effect on nitroglycerine and other organic nitrates on wave reflection,[90] the combination of isosorbide dinitrate and hydralazine administered chronically (24 weeks) did not reduce wave reflection in patients with HFpEF in a recent study.[91] This may be due to tolerance associated with long-term use.[92]

There is increasing interest in the role of inorganic nitrate and nitrite as potential therapeutic agents in HF. These agents harness the endogenous nitrate–nitrite–NO pathway, in which inorganic nitrate (derived from dietary ingestion or from the oxidation of endogenous NO) undergoes a regulated two-step reduction process to NO

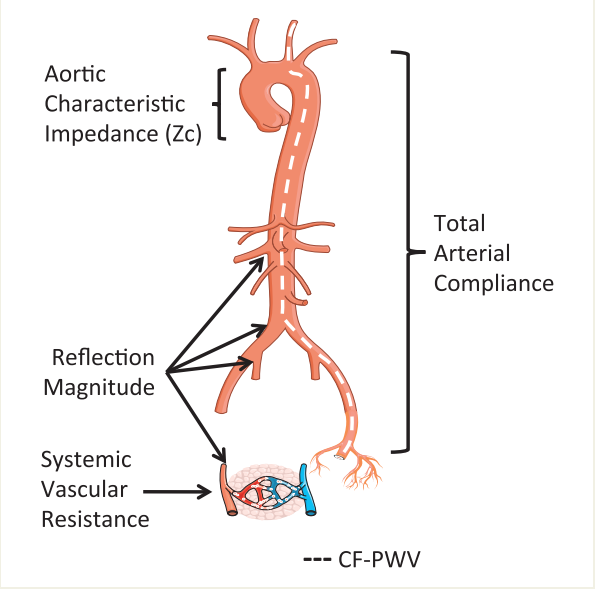

Figure 5 Anatomic origin of arterial properties that impact left ventricular afterload. Although arterial load results from complex interaction between various arterial segments, in general, specific loading patterns can be attributed to anatomic sites. cf-PWV, a measure of large artery wall stiffness, is also shown, although this is not a measure of LV load *per se*. Modified from Chirinos and Segers[23]. cf-PWV, carotid-femoral pulse wave velocity.

(nitrate→nitrite→NO). In addition to the well-known hypoxia/acidosis-dependent microvascular reduction of nitrite to NO (which favours microvascular vasodilation during exercise), a normoxia-dependent reduction pathway that operates in the wall of conduit muscular systemic arteries has recently been described.[93] Normoxia-dependent activation accounts for the high selectivity of inorganic nitrate and nitrite for conduit muscular arteries, and the recently described effect of exogenously administered inorganic nitrate/nitrite on arterial wave reflection.[41,93–95] Among patients with HFpEF, exogenous inorganic nitrate has been shown to reduce late systolic LV load by wave reflections, and to shift the reflected wave into diastole, during which it boosts coronary perfusion pressure, improving the myocardial oxygen supply–demand ratio.[41,94] Unlike organic nitrates, these effects were achieved without significantly reducing MAP or cerebrovascular resistance and without increasing pulsatile power penetration into the cerebrovascular circulation.[94,96]

Several Phase IIa studies have suggested a therapeutic potential of inorganic nitrate/nitrite in HFpEF[41,94,95,97] and non-ischaemic HFrEF.[98–100] So far, mainly an improvement in exercise haemodynamics[101] and exercise capacity[42] has been shown. The main agents being investigated are inhaled sodium nitrite and potassium nitrate. Inhaled sodium nitrite has a very short half (<40 min), and its intermittent administration results in pronounced circulating nitrite level fluctuations, which are unlikely to exert sustained therapeutic effects throughout the day. This issue may underlie the negative results in the INDIE trial [NCT02742129], which studied inhaled inorganic nitrite in HFpEF. Inorganic nitrates, on the other hand, have a much longer half-life, which allows for dosing with milder circulating level fluctuations. The KNO_3CK OUT HFpEF [NCT02840799] with potassium nitrate will provide further insights into the role of this approach and pharmacologic differences between these agents in HFpEF. The effects of soluble guanylate cyclase stimulators/activators on pulsatile load and wave reflections are critical areas of future research.

Outlook

Non-invasive techniques are now available to comprehensively characterize arterial pulsatile haemodynamics in the clinic (*Figure 5*). The availability of contemporary modelling techniques, the ongoing shift towards personalized medicine, and the emergence of drugs that may favourably target pulsatile LV load independently of blood pressure, provide a framework for the clinical translation of arterial haemodynamics into therapeutic approaches. However, it is essential that mechanistic studies continue and that future trials incorporate deeper phenotyping of arterial haemodynamics (which can now be done with minimal patient burden even in multicentre trials), in order to truly advance our clinical approach to the treatment of HF using these concepts. In particular, despite its popularity, AIx appears to be inferior to WSA-based parameters as RM[62] or Pb.[88] Therefore, WSA should be more broadly applied in future studies. Finally, several haemodynamic principles and analytic techniques (such as wave separation, wave intensity, and wave power analyses) can be applied in sites other than the aorta,[69,102] which can provide important insights into cerebrovascular and coronary haemodynamics in patients with HF.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Conflict of interest: T.W. received a research grant for a multicentre study from i.e.m., Stolberg, Germany. J.A.C. has received consulting honoraria from Bristol-Myers Squibb, OPKO Healthcare, Fukuda Denshi, Microsoft, Ironwood Pharmaceuticals, Sanifit, Pfizer, Bayer, Vital Labs, and Merck. He received research grants from National Institutes of Health, American College of Radiology Network, Fukuda-Denshi, Bristol-Myers Squibb, Microsoft, and device loans from AtCor Medical and Uscom. J.A.C. is named as inventor in a University of Pennsylvania patent application for the use of inorganic nitrates/nitrites for the treatment of heart failure and preserved ejection fraction.

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