Review Article

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The Role of Arterial Stiffness and Central Hemodynamics in Heart Failure

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ABSTRACT

Whereas traditional understanding of left ventricular afterload was focused on a steady-state circulation model with continuous pressures and flow, a more realistic concept is emerging, taking the pulsatile nature of the heart and the arterial system into account. The most simple measure of pulsatility is brachial pulse pressure, representing the pulsatility fluctuating around the mean blood pressure level. Brachial pulse pressure is widely available, fundamentally associated with the development and treatment of heart failure (HF), but its analysis is often confounded in patients with established HF. The next step of analysis consists of arterial stiffness, central (rather than brachial) pressures, and of wave reflections. The latter are closely related to left ventricular late systolic afterload, ventricular remodeling, diastolic dysfunction, exercise capacity, and, in the long term, the risk of new-onset HF. Wave reflection may also evolve as a suitable therapeutic target for HF with preserved and reduced ejection fraction. A full understanding of ventricular-arterial coupling, however, requires dedicated analysis of time-resolved pressure and flow signals. This review provides a summary of current understanding of pulsatile hemodynamics in HF.

INTRODUCTION

Heart failure (HF) is an increasing health problem globally and regionally,[1] with high rates of hospitalization and mortality.[2] An increased brachial systolic blood pressure (bSBP) and brachial diastolic blood pressure (bDBP), starting at levels as low as 115 and 75 mm Hg, respectively, predict incident HF across all adult age groups.[3] Arterial hypertension is an important predictor of both HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF).[4] 75% of patients hospitalized for decompensated HF have a history of hypertension.[5] Consequently, reduction of incident HF was the most pronounced benefit of intensive BP lowering in the Systolic Blood Pressure Intervention Trial (SPRINT).[6] In a recent meta-analysis, antihypertensive drug treatment in middle-aged patients[7] and in elderly patients with isolated systolic hypertension[8] lowered the risk for HF by almost 50%, in elderly patients with a history of myocardial infarction by 80%.

bSBP and bDBP, introduced over a century ago by Riva-Rocci et al.,[9] are among the most widely performed measurements in clinical medicine. Due to the pulsatile nature of the pump (i.e., the heart), BP is a curve rather than 2 extremes (systolic BP [SBP], diastolic BP [DBP]), with a certain 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, cardiac function, and their interplay.[10] Patients with identical brachial BPs may have substantially different afterload patterns and/or differences in the blood flow generated by the left ventricle (LV). LV afterload (arterial load) cannot be estimated without knowledge of both pressure and flow. Conceptually, arterial load has 2 components: steady (or "resistive") load, and pulsatile load. "Steady" load (total peripheral resistance [TPR] or systemic vascular resistance [SVR]) is largely determined by the radius of small arteries and arterioles, hence small vessel tone (and density). Together with cardiac output (CO), TPR determines MAP [MAP = CO × TPR]. In contrast, or rather complimentary, pulsatile afterload is influenced by multiple mechanical properties of the aorta, large and also small arteries (aortic stiffness and geometry, timing and magnitude of arterial wave reflections). The aim of this review is to provide a comprehensive overview of the role of the pulsatile component of cardiac afterload, its assessment, prognostic value, and therapeutic consequences.

WHICH MEASUREMENTS ARE AVAILABLE, AND WHAT IS THEIR PHYSIOLOGICAL BACKGROUND?

PP

Brachial PP (bPP) is a simple and widely used pulsatile hemodynamic index. It can be easily calculated as SBP minus DBP and is thus available with every BP measurement. It results from left ventricular ejection, interacting with the arterial tree. Therefore, the main determinants are cardiac (stroke volume [SV], forward flow) as well as arterial (aortic characteristic impedance, aortic and large artery stiffness, aortic and large artery size, wave reflections). Among the latter group, wave reflection seems to be prominent.[11] When LV function is preserved and significant aortic valve disease (particularly aortic regirgitation) is absent, a high PP is a marker of increased pulsatile afterload. In contrast, in HFrEF, PP is directly related to measures of LV function, such as ejection fraction (EF), SV, CO, left ventricular dp/dt, and LV longitudinal axis shortening.[12] In other words, in HFrEF, a lower PP is often a consequence of a worse LV function. This needs to be considered, when the prognostic value of PP is investigated. 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,[13][14] a bPP value ≥60 mmHg in elderly individuals reflects asymptomatic damage (stiffening) of the large arteries.

As the BP wave travels from central aorta to peripheral sites (e.g. brachial artery), MAP drops only by 2 mm Hg, and DBP is roughly equivalent, whereas SBP and PP can increase markedly[10] (SBP and PP amplification [PPA]), more pronounced in young individuals. The PPA[15] ratio (peripheral PP/central PP [cPP]) is determined by many factors, including LV contractility and ejection duration, heart rate, arterial stiffness, arterial caliber (and taper), the timing and amplitude of wave reflections, and arteriolar tone (TPR). cPP is different from bPP (cPP is lower than bPP) and cannot be calculated directly from bPP. One needs dedicated instruments that record pressure waveforms at the carotid artery 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, mainly so-called transfer functions, to "rebuild" the aortic pressure waveform. In a first step, the obtained peripheral pressure waveform is calibrated with brachial cuff BP. There are basically 2 options for calibrating the waveforms (bSBP and DBP versus MAP and DBP). Although the first method (SBP/DBP) is more popular, the second method (MAP/DBP) seems to be more accurate, particularly when MAP is directly determined by oscillometry.[16][17] Further technical details are beyond the scope of this manuscript and can be found in dedicated reviews.[18]

Wave reflections in the arterial tree

Left ventricular ejection generates a forward-traveling wave (incident or forward wave). The wave travels at a given speed (pulse wave velocity [PWV], up to 5–15 m/sec 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, change in local stiffness).[19] Reflected pressure waves add to forward pressure, whereas reflected flow subtracts from forward flow.[19] Myriads of reflections from all over the body are transmitted back towards the heart, summarizing in the ascending aorta as one "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.[20][21] Under these conditions, wave reflections exert important unfavorable effects,[10] 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.[22] 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.[23] Wave reflections can be quantified in humans through several methods (**Figure 1**).[24-26]

Pulse waveform analysis (PWA): With this method, information about wave reflections is derived from analysis of the pressure waveform. The rationale behind is that analysis of the entire waveform might unravel information about the arterial system, which is additive to conventional BP (systolic and diastolic are the extreme points of the pressure curve). The principle of PWA is the following: the reflected wave causes a visible notch (inflection point) on the pressure curve, which occurs at the time of maximum flow.[19] Augmented pressure (AP), expressed in mmHg, is the difference between the second and first systolic peak on the pressure waveform. Augmentation index (AIx) is the ratio between AP and (central) PP (AIx=AP/cPP), typically expressed as a percentage. Thus, AP and AIx can be seen as the effect of wave reflection on the aortic pressure waveform. 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 exercise.[27] PWA-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.[28] As flow curves are much more laborious to aquire, compared to pressure curves, a validated simplification[29] uses aortic flow curves, which are estimated from pressure curves, based on 3 element Windkessel models and complex
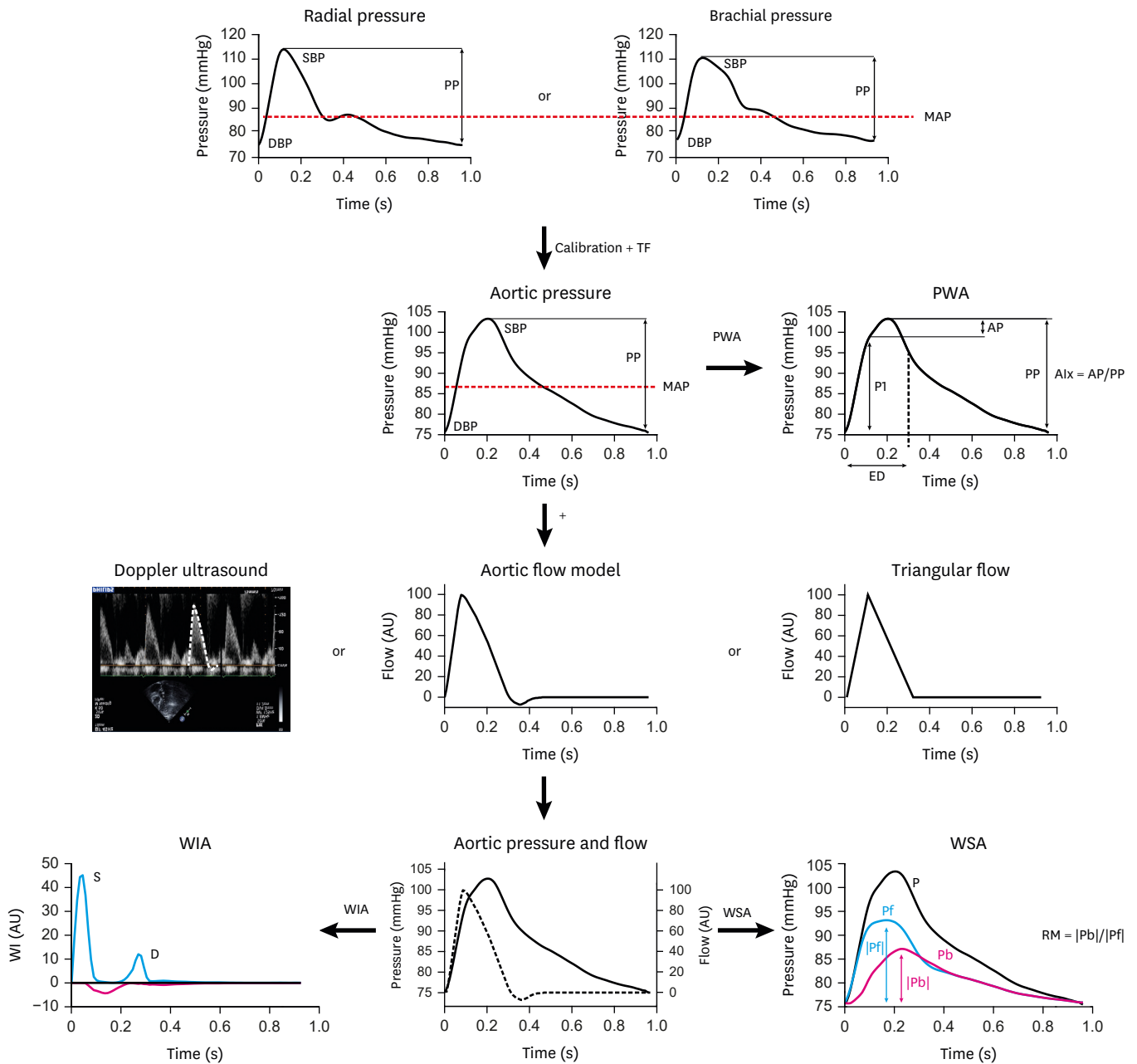
Figure 1. Assessment of pulsatile hemodynamics - overview. *Top line:* Recording of signal-averaged radial or brachial pressure waveforms with tonometry or brachial cuff. *Second line:* Following calibration with brachial pressures, aortic waveforms are calculated with a TF. Pulse waveform analysis, 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-deriven 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.
Modified from Parragh et al.[26] and Hametner et al.,[24] and reprinted with permission from Weber and Chirinos.[25]
AIx = augmentation index; AP = augmented pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure; Pb = amplitude backward wave; Pf = amplitude forward wave; PP = pulse pressure; PWA = pulse waveform analysis; RM = reflection magnitude; SBP = systolic blood pressure; TF = transfer function; WIA = wave intensity analysis; WSA = wave separation analysis.

mathematical modeling. Reflection magnitude (RM) is the ratio of amplitudes of Pb/Pf. A more recent development is wave intensity analysis (WIA),[30] 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. Waves can originate either from the

proximal (forward-traveling) or distal (backward-traveling) 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.[31] WIA 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 traveling suction wave peak is related to the time constant of pressure decay in late systole/early diastole.[32] Both may, therefore, provide insights into ventricular function[24] and LV-arterial coupling.

PWV, characteristic impedance, total arterial compliance (TAC)

PWV is the travel distance divided by transit time of the pulse between two recording sites. Whereas mainly pressure waves are recorded for PWV measurement with tonometric probes or piezoelectric sensors,[10] also volume waves, recorded with impedance cardiography, can be used.[33] Carotid-femoral PWV (cfPWV) is currently considered the gold-standard metric of (regional) aortic stiffness,[34] and is more popular in Europe. In Asian countries, brachial-ankle PWV (baPWV),[35] recorded with cuffs at the arms and legs, is more common. PWV is not a direct measure of ventricular afterload, but is informative of arterial wall properties, and has far-reaching prognostic implications.[10][34][36] 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. 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). Arterial functional parameters used to describe pulsatile hemodynamics and arterial stiffness are summarized in **Table 1**. The anatomic conceptualization of the various measurements of LV afterload[25] is depicted in **Figure 2**.

Table 1. Arterial functional parameters used to describe pulsatile hemodynamics and arterial stiffness

Measure	Advantage	Disadvantage	Measurement technique	Prognostic value for heart failure
Brachial PP	Simple	Depends on cardiac and arterial function	Brachial cuff	+++ (direct or inverse)
Central PP	The PP "seen" by the heart and central organs	Depends on cardiac and arterial function	Radial/brachial waveforms (tonometry or cuff), calibrated with brachial BP, and TF → central pressure waveform	+
PWA: AIx, AP	Physiological rationale	Depends on cardiac and arterial function, heart rate, sex, height, etc.	Automated analysis of the central pressure waveform	+
WSA: Pb, RM	Physiological rationale	Needs pressure and flow waveforms	Automated analysis of the central pressure and flow waveform	++
WIA	Physiological rationale	Needs pressure and flow waveforms; sensitive to waveform quality	Automated analysis of the central pressure and flow waveform	−
cfPWV	Relatively robust measurement	Depends on actual BP; determination of travel distance on body surface only an estimate	Tonometry, piezo-electronic sensors, cuffs	++
baPWV	Relatively robust measurement	Depends on actual BP; determination of travel distance is "virtual"	Cuffs	+

AIx = augmentation Index; AP = augmented pressure; baPWV = brachial-ankle pulse wave velocity; BP = blood pressure; cfPWV = carotid-femoral pulse wave velocity; Pb = amplitude backward wave; PP = pulse pressure; PWA = pulse waveform analysis; RM = reflection magnitude; TF = transfer function; WIA = wave intensity analysis; WSA = wave separation analysis.
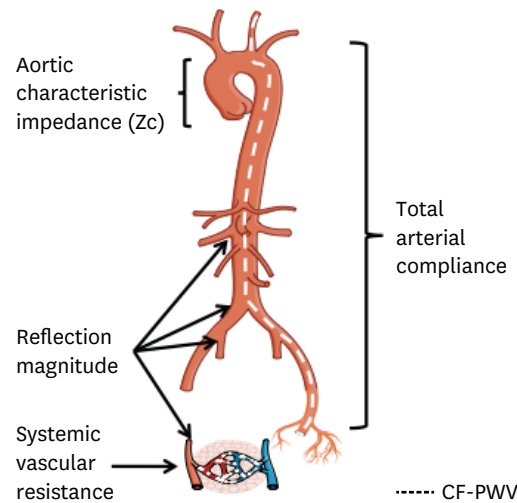
Figure 2. Anatomic origin of arterial properties that impact LV afterload. Although arterial load results from complex interaction between various arterial segments, in general, specific loading patterns can be attributed to anatomic sites. cfPWV, a measure of large artery wall stiffness, is also shown, although this is not a measure of LV load *per se*.
Modified from Chirinos and Segers.[40] and reprinted with permission from Weber and Chirinos.[25]
cfPWV = carotid-femoral pulse wave velocity; LV = left ventricle.

THE RELATIONSHIP BETWEEN CARDIAC AND ARTERIAL FUNCTION ("VENTRICULO-ARTERIAL (VA) COUPLING")

Traditionally, the invasive assessment of pressure and volume in the LV has been used to study VA coupling.[37] By connecting all end-systolic points of pressure-volume loops obtained during various loading conditions, the so-called 'end-systolic pressure volume relation' (ESPVR) line is retrieved. This relation is roughly linear within physiologic ranges, sensitive to inotropic changes, and insensitive to afterload, and the respective line slope has been termed as end-systolic elastance (Ees).[38] The intersection between the ESPVR (upper left-hand corner of the P-V loop) and a line drawn from the end-diastolic volume on the horizontal axis identifies a second line. The respective slope represents the end-systolic pressure to SV ratio, named effective arterial elastance (Ea). Stroke work generation is maximal when the Ea/Ees ratio equals 1, while maximal cardiac efficiency is achieved when the Ea/Ees ratio equals 0.5.[39]

However, arterial load is time-varying (i.e. not stable across the cardiac cycle), complex and cannot be expressed as a single number.[19][25][40] Ea is not a true elastance (i.e., the inverse of a compliance) and is almost exclusively dependent on TPR and heart rate,[41][42] but demonstrates weak, inconsistent and in some cases, erratic/paradoxical relationships with gold-standard measures of pulsatile load.[41] Importantly, Ea is not related to aortic wall stiffness[41]; therefore, an increase in Ea should not be interpreted as arterial "stiffening" and, by extension, and parallel increase in Ea and Ees should not be interpreted as a state of "ventricular-arterial stiffening".[25] As a consequence, Ea did not predict incident HF in the Multi-Ethnic Study of Atherosclerosis (MESA) cohort,[43] whereas wave reflections (RM) and late systolic load were strong predictors.[44][45]

A more comprehensive approach to investigate VA coupling takes time-varying changes (i.e., the changes that occur during the cardiac cycle) of LV and arterial function and their
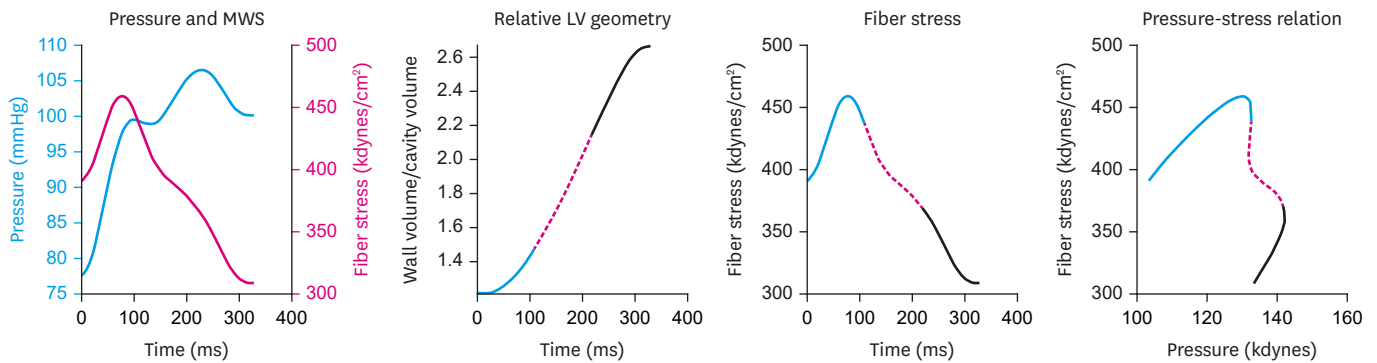
Figure 3. Time-resolved MWS. The first panel shows the ejection-phase aortic pressure and MWS profiles. The second panel shows the time-resolved relative myocardial geometry (ratio of wall volume to cavity volume) that correlates with wall stress via the Laplace law; the first, second and last thirds of systole are shown in blue, dotted red and black lines, respectively. The third panel shows the ejection-phase MWS, and the 4th panel shows pressure-MWS relation. It can be seen that MWS 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, which favors 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 remodeling, and reduced early systolic ejection (reduced early-phase ejection fraction).
Reprinted with permission from Weber and Chirinos.[25]
LV = left ventricle; MWS = myocardial wall stress.

interplay into account (**Figure 3**). LV 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 fiber shortening.[25] The time-varying LV geometry during ejection is dependent on: (1) LV volume at the beginning of LV contraction (i.e., end-diastolic volume), which in turn is determined by chronic LV remodeling and preload; (2) the interaction between myocardial contraction, LV geometry and arterial load throughout ejection.[25] 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 throughout the whole ejection period. Among normotensive and hypertensive adults with a normal LVEF, peak MWS typically occurs in early systole, when quasi-diastolic geometry coexists with systolic pressure.[46-48]. 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.[47] This phenomenon appears ideal to protect cardiomyocytes against excessive load in mid-to-late systole,[47][49] and depends on the dynamic reduction of LV chamber size relative to wall volume, and its magnitude is highly variable between individuals.[47] Subjects with lower EF,[47] concentric remodeling,[47] or those who demonstrate poor early systolic contraction (and ejection)[50] demonstrate less pronounced shifts in the pressure-stress relation and are, thus, more vulnerable to increases in late systolic load.

With respect to arterial function, an increase in late systolic load apparently has the worst impact on cardiac function.[51] Epidemiologically, HFpEF is most prevalent among elderly women, most of them have hypertension, diabetes, or both, and often coronary artery disease. These comorbidities exactly resemble conditions with increased arterial stiffness/wave reflections.[51] Functionally, an increase in late systolic pressure leads to an impairment of diastolic function in experimental animals[52] and in humans.[53][54] In detail, in a study comprising 336 patients undergoing invasive coronary angiography,[53] early diastolic velocity (E′), as assessed by tissue Doppler echocardiography (TDE), showed a strong, negative correlation with AP, PWV, and Zc. Higher filling pressures of the LV were associated with increased wave reflections (AIx, AP) and arterial stiffness (PWV, Zc).

To summarize the chapter, there is an important interaction between myocardial geometry, the myocardial contraction pattern, and the effect of wave reflections on LV hydraulic load. Wave reflections tend to increase mid-to-late systolic LV load and MWS,[46][47] 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).[49][52][55-57] In other words, mid-to-late systolic load on the LV, imposed by increased wave reflections, is deleterious and may lead to HF,[45] particularly in a susceptible LV with delayed early systolic contraction, which can be observed in hypertensive patients with left ventricular hypertrophy (LVH) and/or diastolic dysfunction.[50]

Differences in the effects of arterial load in HFpEF and HFrEF

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 (**Figure 4**). These features are prominent in patients with HFpEF,[53][58-60] and may be useful in the diagnostic workup of the condition[58]: measures of pulsatile arterial function (including bPP, but favoring central hemodynamics) were as good as TDE in separating patients with HFpEF from those without the condition in a population of patients with exertional dyspnea. When LV pump function is reduced, however, wave reflection may exert more pronounced effects to decrease flow, initially with no apparent alteration in the appearance of the pressure waveform (when the latter is analyzed in isolation). In patients with severe LV systolic dysfunction (LVEF ≤30%), wave reflections truncate flow, reduce SV and induce a shortening of ejection duration.[26][61][62] In these patients, PWA-derived measures of wave reflection (AIx, AP) are typically very low (**Figure 4**).[12][63] 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 (S/D ratio) is reduced,[64] as compared to individuals with normal EF, and could be used to divide patients with HFrEF from controls with normal EF with an area under the curve of 0.879.[24]
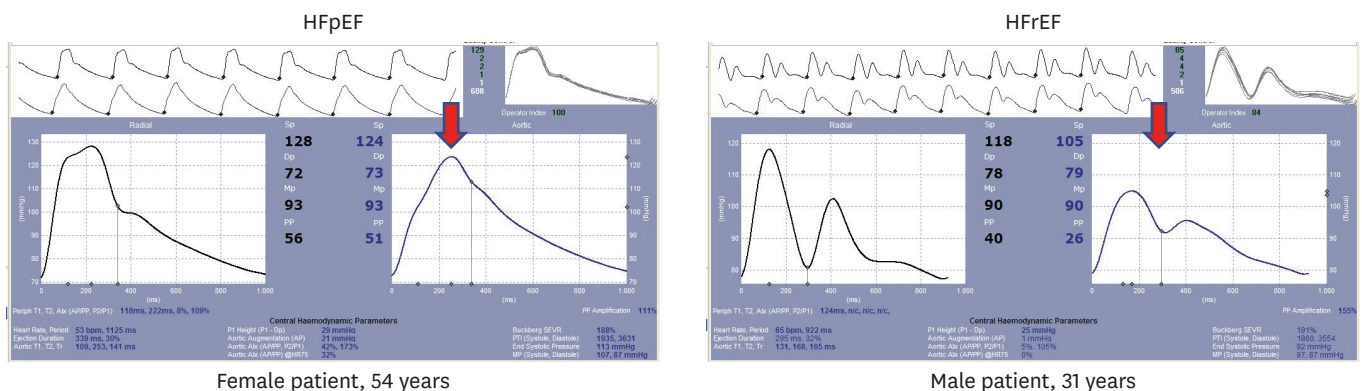
Figure 4. Pressure waveforms in HFpEF versus HFrEF. Radial pressure waves are shown as obtained, aortic pressure waves were derived with a valid transfer function. Note the striking differences in waveforms, which cannot be attributed to the small differences in brachial BP (128/72 mm Hg in HFpEF versus 118/78 mm Hg in HFrEF). In HFpEF, a striking late-systolic peak is visible, which is completely missing in HFrEF (arrows). Corresponding aortic AIx, normalized for heart rate 75, is 32% in HFpEF vs. 0% in HFrEF, respectively.
AIx = augmentation index; BP = blood pressure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction.

WHICH ARE THE CONSEQUENCES OF INCREASED ARTERIAL STIFFNESS AND CENTRAL HEMODYNAMICS?

LV hypertrophy

LVH is a marker of asymptomatic organ damage in hypertension[13] and an important intermediate step from hypertension to HF.[65] In animal models, an increase in aortic stiffness without any change in TPR leads to LVH.[66] Moreover, late systolic loading resulted in much more prominent hypertrophy than early systolic loading in rats.[67] Patients with isolated systolic hypertension, a condition characterized by increased aortic stiffness, show higher LV mass than those with systolic-diastolic hypertension. Moreover, LV mass is more strongly related to PP than to MAP, underlining the importance of pulsatile phenomena.[68] This relationship is stronger for cPP,[69)70] in particular when measured over 24-hours.[71] The relationship between LV mass and arterial stiffness/wave reflections can be seen even in adolescents and young adults.[72] In a recent analysis from the population-based MESA, including more than 4,000 adults, the contribution of steady state (SVR) and pulsatile hemodynamics (TAC, Pf, Pb) on LV mass and geometry was investigated.[73] In multivariable models, 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 remodeling pattern over 4.7 years was independently associated with higher baseline cfPWV.[74] Moreover, in women, higher cPP at baseline predicted the longitudinal increase in LV mass. Reductions in LV mass, which have proven prognostic benefit, are more closely associated with reductions in wave reflection than with reductions in brachial BP.[75)76] When different drugs (ACE-inhibitor-diuretic combination versus a beta-blocker) were compared, those favourably affecting pulsatile hemodynamics (reducing cSBP and cPP) were superior in reducing LV mass,[77] whereas both therapeutic regimens did not differ regarding steady state hemodynamics (CO and SVR).

Impaired 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, both in the general population and in patients with HF (HFrEF and HFpEF).

An inverse relationship between late systolic pressure augmentation and a reduced aerobic capacity in the general population was described in the Baltimore Longitudinal Study of Aging,[78] in healthy men,[79] in athletes,[80] and in patients undergoing cardiac rehabilitation.[81] More recently, Broufa et al.[82] demonstrated that pulsatile hemodynamic indices (including Pb and AIx) are independently related to peak oxygen uptake (peak VO$_2$) in adults with exertional dyspnea and preserved LV systolic function.

Studies in HFrEF patients also demonstrate a significant relationship between arterial pulsatile hemodynamics and exercise capacity.[83] Specifically, in patients with dilated cardiomyopathy, PWV is inversely and independently associated with peak VO$_2$.[84)85] Patients with HFrEF due to idiopathic dilated cardiomyopathy demonstrate an impairment in the reduction in wave reflections during exercise, with a smaller reduction in wave reflections for any given reduction in SVR, compared to normal controls.[86] This could increase myocardial work during exercise and contribute to exercise intolerance.

Hundley et al.[87] first demonstrated that patients with HFpEF exhibit increased aortic stiffness, which was in turn strongly associated with a lower aerobic capacity. Patients

with HFpEF have higher large artery stiffness at rest, which is inversely related to exercise capacity.[88] Measurements taken at rest may underestimate the impact of pulsatile hemodynamics.[89] Indeed, HFpEF patients also show an abnormal increase of wave reflections,[89][90] carotid stiffness,[91] aortic PWV[91] and an abnormal decrease of TAC[89] during exercise. The combination of increased pulsatile load and impaired vasodilatory reserve seems to be associated with impaired SV and CO reserve, and with increased LV filling pressures during exercise.[89-91]

Risk of incident HF

In the Framingham study and in the East Boston Senior Health project, bPP (and bSBP) were stronger predictors than DBP for congestive HF (CHF) in middle-aged men and women (**Table 2**).[45][92-98] In 5,690 participants from MESA, wave reflection (RM) was strongly and independently predictive of new-onset HF.[45] In particular, RM compared favorably to other risk factors for CHF in various statistical measures of clinical utility, and predicted CHF even in patients with normal BP. Along the same lines of evidence, late systolic hypertension was strongly associated with incident HF.[44] In contrast, SVR, TAC and E_A did not predict HF, indicating the importance of pulsatile over steady state hemodynamics and of late systolic load.[43] In the Framingham Heart study, after adjustments for standard risk factors including MAP, cfPWV was independently associated with incident clinical HF[94] after a follow-up of 10.1 years. Moreover, a higher cfPWV was associated with both HFpEF and HFrEF. In 2,602 patients with chronic kidney disease (mean GFR 45 mL/min/1.73m²), 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.[95] In another community-based cohort of 2,290 older adults (mean age 74 years),[96] 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 baPWV) within 5 years was associated with increased risk of incident HF.[97] In summary, available evidence supports a relationship between arterial stiffness and measures of wave reflection/late systolic load, and the risk of incident HF in the community.

Risk in established HF

Due to the ease of assessment, most of the evidence available is related to bPP (**Table 3**).[99-116] In advanced HFrEF, a low bPP is due to poor LV function, and, in term, associated with a worse prognosis.[99][108] 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

Table 2. Prognostic value of arterial parameters for incident HF

Study acronym	Setting/population	First author	Sample size	Mean age years	FU duration years	Arterial measurement	Study endpoint
Framingham	General population	Haider et al.[92]	2,024	61	17.4	bPP	CHF
East Boston Senior health project	General population	Chae et al.[93]	1,621	77.9	3.8	bPP	CHF
MESA	General population	Chirinos et al.[44]	5,960	62	7.6	RM	CHF; hard CVEs
CRIC	Chronic Kidney disease (eGFR 45)	Chirinos et al.[95]	2,602	59.9	3.5	cfPWV	Hospitalized HF
Framingham	General population	Tsao et al.[94]	2,539	64	10.1	cfPWV	HF
Health ABC	Older adults	Pandey et al.[96]	2,290	73.5	11.4	cfPWV	Hospitalized HF*
-	Asymptomatic with HF risk factors	Aisu et al.[97]	456	-	4.9	baPWV	Hospitalized HF
-	Acute STEMI patients	Feistritzer et al.[98]	160	62	1.2	PWV (MRI)	CVE including CHF

bPP = brachial pulse pressure; baPWV = brachial-ankle pulse wave velocity; cfPWV = carotid-femoral pulse wave velocity; CHF = congestive heart failure; CRIC = Chronic Renal Insufficiency Cohort; CVE = cardiovascular event; FU = follow-up; eGFR = estimated glomerular filtration rate; Health ABC = Health, Aging, and Body Composition; HF = heart failure; MESA = Multi-Ethnic Study of Atherosclerosis; MRI = magnetic resonance imaging; PWV = pulse wave velocity; RM = reflection magnitude; STEMI = ST elevation myocardial infarction.
*Not significant result following multivariable adjustment.

Table 3. Prognostic value of measures of pulsatile hemodynamics in established HF

Study	First author	Setting/population	Sample size	Age	EF	Brachial SBP/DBP/PP mmHg	Relationship with outcome
Brachial PP							
-	Fagard et al.[99]	Advanced chronic HF	284	51.5	25.5	114/75,739	Inverse (all-cause mortality)
PRIME	Voors et al.[100]	Advanced chronic HF NYHA III and IV	1,901	65	26	107/73 and 133/77; (above/below median PP) mean PP: 47	Inverse (all-cause mortality)
VMAC	Aronson and Burger[101]	Hospitalized decompensated HF	489	59/60/67 (PP Tertiles)	21/26/34 (PP Tertiles)	105/70/34; 119/68/51; 141/65/75 (PP tertiles)	Inverse (all-cause mortality)
HIJC-HF	Kawashiro et al.[102]	Hospitalized congestive HF	3,169	69.8	42	NA	Inverse (all-cause mortality increased with PP ≤30 mmHg)
MAGGIC meta-analysis	Jackson et al.[103]	HFrEF	22,038	60–69 (PP quintiles)	27–34 (PP quintiles)	106–156/75–79 (PP quintiles) mean PP: 52	Inverse (all-cause mortality) consistent findings in acute and chronic HFrEF
-	Yildiran et al.[104]	HF NYHA I–IV	225	56.5	25–35	98–127/66–83/31–46	Inverse (CV death)
CAPRICORN	Petrie et al.[105]	LV dysfunction (EF ≤40) after acute MI	1,995	63	33	121/74/47	Inverse (all-cause mortality)
DIG	Maeder and Kaye[106]	Stable HF	6,792 (HFrEF)	63	29	126/75/51	Inverse (all-cause mortality)
EPHESUS	Regnault et al.[107]	3–14 days after acute MI with LF dysfunction (EF ≤40) and HF	6,613	64	33	119/72/47	Inverse (all-cause mortality, CV death, CV death + hosp)
-	Schillaci et al.[108]	Outpatients with congestive HF	8,660	64	<30: 20% >30: 41% NA: 39%	132/79/53	Inverse (all-cause mortality, CV mortality)
SAVE	Mitchell et al.[109]	Impaired EF following MI (no overt HF)	2,231	59.5	31	112–113/70/42–43	Direct (all-cause mortality; recurrent MI)
SOLVD	Domanski et al.[110]	LV dysfunction (EF ≤35); asymptomatic or symptomatic (NYHA 1.7)	6,781	55–64	26–28	109–144/77–78/32–67	Direct (all-cause mortality, CV mortality)
DCH cohort	Lip et al.[111]	Incident HF	2,159	58.9	NA	149/86.5/62.6	Non-significant direct (stroke)
GWTG-HF	Laskey et al.[112]	Hospitalized HFrEF (EF <40)	40,421	80	35–53 (PP quartiles)	139/73	U-shaped (inverse at PP <50 mmHg, direct at PP ≥50 mmHg) (all-cause mortality)
GWTG-HF	Laskey et al.[112]	Hospitalized HFpEF (EF ≥40)					Direct (all cause mortality)
DIG	Maeder and Kaye[106]	Stable HF	988 (HFpEF)	67	55	138/77/61	J-shaped (all-cause mortality; HF hospitalization)
MAGGIC metaanalysis	Jackson et al.[103]	HFpEF	5,008	65–73 (PP quintiles)	58–60 (PP quintiles)	115–172/77–80 (PP quintiles) mean PP: 62	Direct (only unadjusted analysis) Inverse (subgroup with acute HFpEF)
-	Tokitsu et al.[116]	Hospitalized HFpEF	512	71.7	63	134/73/61	U-shaped (total CV events, HF events)
Wave reflections							
-	Sung et al.[113]	Acute heart failure NYHA III and IV	120	72	41.2/42.9	141/81/60; 149/80/69	Direct (cPP, Pb, AP) (HF hospitalization, MI, stroke, death); consistent effect in HFrEF and HFpEF
Pulse wave velocity							
EPHESUS	Regnault et al.[107]	3–14 days after acute MI with LF dysfunction (EF ≤40) and HF	306	61	34	118/74/89	Direct (cfPWV) (all-cause mortality, CV mortality)
-	Bonapace et al.[115]	HF and EF ≤45%	156				Direct (aortic PWV)
-	Meguro et al.[114]	Stable HF NYHA II–III	72	68	53	129/75/54	Direct (baPWV) (HF hospitalisation, cardiac death)

AP = augmented pressure; baPWV = brachial-ankle pulse wave velocity; CAPRICORN = Carvedilol Post-Infarct Survival Control in LV Dysfunction; cfPWV = carotid-femoral pulse wave velocity; cPP = central pulse pressure; DBP = diastolic blood pressure; DCH = Diet, Cancer and Health; DIG = Digitalis Investigator Group; EF = ejection fraction; EPHESUS = Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; GWTG-HF = Get With The Guidelines-Heart Failure; other abbreviations see **Tables 1,2** HIJC-HF = Heart Institute of Japan–Department of Cardiology Heart Failure; LV = left ventricle; MAGGIC = Meta-Analysis Global Group in Chronic Heart Failure; MI = myocardial infarction; Pb = amplitude backward wave; PP = pulse pressure; PRIME = Prospective Randomized study of Ibopamine on Mortality and Efficacy; SAVE = Survival and Ventricular Enlargement; SBP = systolic blood pressure; SOLVD = Studies on Left Ventricular Dysfunction; VMAC = Vasodilation in the Management of Acute Congestive HF.

with a worse prognosis).[109-111] In these patients, a higher PP is due to increased pulsatile afterload. In HFpEF, the relationship between bPP and outcomes tends to be direct.[103][112] In some studies, however, particularly in acute HFpEF, patients with the lowest bPPs also demonstrate a worse prognosis.[106][112] These patients may have pronounced concentric remodeling with lower SVs, despite a preserved EF (which does not prove preserved myocardial contractility in HFpEF).[117]

Given the fact that PP depends on both arterial and LV function, direct measurements of arterial properties are likely to be more informative. One single-center study demonstrated the adverse prognostic value of wave reflections in patients with acute decompensated HF.[113] Likewise, cfPWV, a direct measure of arterial stiffness, was directly related to prognosis (HF hospitalization, CV and all-cause mortality) in HFrEF and HFpEF.[107)113-415]

THERAPEUTIC IMPLICATIONS

HFrEF

In HFrEF, guideline-directed pharmacologic therapy[2] may substantially improve arterial properties and wave reflections. However, study results have been somewhat inconsistent so far. Whereas ACE-inhibitors have been shown to improve arterial stiffness (PWV) additive to the effect of BP lowering in hypertensives,[118] such data are not available (yet ?) in HF patients. Omapatrilat, a composite ACE-inhibitor/neprilysin inhibitor, has been shown to reduce Zc, as compared to enalapril, in patients with isolated systolic hypertension.[119] The successor drug, sacubitril-valsartan, was compared against enalapril in 464 patients with HFrEF (< 40%), but the primary outcome, a change in Zc, was not significantly different between both drugs.[120]

A small randomized study of arterial pressure waveform-guided therapy for HFrEF (aimed at reducing AIx) was performed in a total of 50 patients (EF 38–39%, predominantly NYHA II, brachial BP in the lower normal range). The main therapeutic changes in the active group, based on a prespecified algorithm, were the more frequent use of spironolactone, nitrates, and hydralazine, in addition to guideline-based treatment with ACE-inhibitors/angiotensin-receptor-blockers and beta-blockers. The outcome was a greater improvement in peak VO$_2$ in the active group, compared to standard care, while AIx was reduced in both groups without a significant difference.[121] Higher measures of pulsatile hemodynamics and wave reflections (cPP, AP, Pf, Pb) at baseline, and their larger decrease during treatment were associated with functional improvement, defined as increase in 6 minute walk test.[122] These findings were not apparent from brachial BP. Thus, central aortic waveform analysis may allow an individualized treatment regimen for patients with HFrEF.[37]

Another relatively novel drug class which shows promise in the prevention and treatment of HF are sodium glucose cotransporter 2 inhibitors.[123] Recently, the effect of dapagliflozin was tested against placebo in 4,744 patients with HFrEF (EF roughly 31%).[124] It was observed that the risk of worsening HF or death from cardiovascular causes was lower among those who received dapagliflozin than among those who received placebo, regardless of the presence or absence of diabetes. The results were confirmed in a quite similar setting, but somewhat more advanced HF, for empagliflozin.[125] In the context of this review article it is of interest, that empagliflozin has been shown to improve pulsatile vascular function (cSBP, cPP, reflected wave amplitude) in a double-blind cross-over study,[126] as compared to placebo, suggesting a possible mechanistic explanation for the clinical benefit.

HFpEF

No treatment has yet been shown, convincingly, to reduce morbidity or mortality in patients with HFpEF.[2] Although it has been repeatedly shown[51][58][127] that increased arterial stiffness and increased pulsatile hemodynamics are hallmarks of HFpEF, results of treatment trials based on the improvement of vascular properties have been mixed so far.

Despite the well-documented acute effect on nitroglycerin and other organic nitrates on wave reflection,[128] isosorbide dinitrate, alone or in combination with hydralazine, administered chronically (24 weeks) in a small study did neither reduce wave reflection (RM) nor increase exercise tolerance (6-minute walk test) in patients with HFpEF.[129] This may be due to tolerance associated with long-term use.[130] Following the same lines, treatment with isosorbide mononitrate did not improve exercise capacity in patients with HFpEF, as compared to placebo.[131] In addition to organic nitrates, inorganic nitrates and nitrite have been investigated as treatments for HFpEF as well. These agents take advantage of the endogenous nitrate-nitrite-NO pathway, in which inorganic nitrate (derived from dietary ingestion or from the oxidation of endogenous NO) undergoes a regulated 2-step reduction process to NO (nitrate → nitrite → NO). In addition to the well-known hypoxia/acidosis-dependent microvascular reduction of nitrite to NO (which favors microvascular vasodilation during exercise), a normoxia-dependent reduction pathway that operates in the wall of conduit muscular systemic arteries has recently been described.[132] 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.[59][89][132][133] In a small study in 17 patients with HFpEF, a single dose of NO_3^- rich beetroot juice reduced late systolic LV load (AIx) and increased exercise capacity.[59] Also, acute sodium nitrite infusion improves exercise hemodynamics in HFpEF.[134] Accordingly, one week of daily dosing with beetroot juice (6.1 mmol inorganic nitrate) significantly improved submaximal aerobic endurance in elderly HFPEF patients.[135] Unlike organic nitrates, these effects were achieved without significantly reducing MAP or cerebrovascular resistance and without increasing pulsatile power penetration into the cerebrovascular circulation.[133][136] Inhaled sodium nitrite, on the other hand, has a very short half (<40 minutes) and its intermittent administration results in pronounced circulating nitrite level fluctuations, which are unlikely to exert sustained therapeutic effects throughout the day. Accordingly, inhaled inorganic nitrite was not effective in improving exercise capacity in patients with HFpEF.[137]

Regarding large morbidity/mortality trials, current evidence is largely limited to bPP. In 2 recent phase II trials, Aldosterone Receptor Blockade in Diastolic Heart Failure (ALDO-DHF)trial[138] and Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion (PARAMOUNT) trial[139] 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,[140-142] baseline bPP has generally been <60 mmHg, the cutoff defined by European Hypertension Guidelines,[13] suggesting that enrolled populations exhibited a relative paucity (or already successful treatment at baseline) of pulsatile hemodynamic abnormalities, which are otherwise typical for HFpEF patients.[58] Moreover, in most clinical endpoint trials in HFpEF, bPP was not substantially reduced. For instance in one of the the largest studies (Irbesartan in Heart Failure with Preserved Ejection Fraction Study[140]), which showed a neutral outcome, bPP was lowered by only 1.7 mm Hg by Irbesartan (and unchanged with placebo).

CONCLUSION

Arterial stiffness and central hemodynamics contributed significantly to our current understanding of HF, both HFrEF and HFpEF. Arterial pulsatile hemodynamics are key to comprehensively describe VA interactions, and have clinically relevant prognostic implications. What is currently missing in the concept of translational medicine are widely available drugs for reduction of pulsatile load and arterial destiffening. This would undoubtedly translate into clinical benefits in patients with HF.

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