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Deep Phenotyping of Systemic Arterial Hemodynamics in HFpEF (Part 2): Clinical and Therapeutic Considerations

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Abstract

Multiple phase III trials over the last few decades have failed to demonstrate a clear benefit of various pharmacologic interventions in heart failure with a preserved left ventricular (LV) ejection fraction (HFpEF). Therefore, a better understanding of its pathophysiology is important. An accompanying review describes key technical and physiologic aspects regarding the deep phenotyping of arterial hemodynamics in HFpEF. This review deals with the potential of this approach to enhance our clinical, translational, and therapeutic approach to HFpEF. Specifically, the role of arterial hemodynamics is discussed in relation to (1) the pathophysiology of left ventricular diastolic dysfunction, remodeling, and fibrosis, (2) impaired oxygen delivery to peripheral skeletal muscle, which affects peripheral oxygen extraction, (3) the frequent presence of comorbidities, such as renal failure and dementia in this population, and (4) the potential to enhance precision medicine approaches. A therapeutic approach to target arterial hemodynamic abnormalities that are prevalent in this population (particularly, with inorganic nitrate/nitrite) is also discussed.

Keywords

Heart failure with preserved ejection fraction; Arterial hemodynamics; Wave reflections; Afterload; Pulsatile load; Exercise intolerance; Comorbidities; Dementia; Renal disease

Introduction

The burden of heart failure has increased dramatically over the last several years [1, 2]. Approximately half of patients with heart failure (HF) have heart failure with a preserved left ventricular (LV) ejection fraction (HFpEF). Furthermore, the relative prevalence of HFpEF (as a proportion of the total burden of heart failure) appears to be increasing as the population ages [1, 3]. Patients with HFpEF demonstrate high mortality rates and an impaired quality of life [4, 5].

Multiple therapies that provide substantial clinical benefit in heart failure with reduced ejection fraction are available. However, multiple phase III trials over the last few decades have failed to demonstrate a clear benefit of various candidate pharmacologic interventions in HFpEF. Therefore, a better understanding of the processes that contribute to the pathophysiology of HFpEF is important. Detailed phenotyping of arterial hemodynamics provides important insights into the pathophysiology of LV remodeling and fibrosis, diastolic dys-function, and impaired oxygen delivery to peripheral skeletal muscle, all of which contribute to exercise intolerance, the cardinal feature of HFpEF. Furthermore, it has been proposed that HFpEF is a heterogeneous syndrome, with different degrees of contribution from various pathophysiological processes. This may unfavorably impact the average responses of this patient population to novel therapies tested in clinical trials. The utilization of better clinical phenotyping tools, which in turn may be used to “segment” the HFpEF population into relevant pathophysiologic categories, or simply to identify individuals with prominent specific abnormalities that are targeted by pharmacologic interventions, represents a promising approach to enhance our therapeutic approach to HFpEF.

An accompanying review describes key technical and physiologic aspects regarding the deep phenotyping of arterial hemodynamics in HFpEF. This review deals with the translational and clinical role of this approach and its potential to (1) provide important mechanistic insights regarding the pathophysiology of LV diastolic dysfunction, hypertrophy, and fibrosis, (2) provide insights into the pathophysiology and therapeutic approach to peripheral mechanisms of exercise intolerance in HFpEF, (3) explain, at least partially, the high prevalence of some comorbid conditions (such as kidney disease and dementia) that occur in HFpEF, and (4) identify specific abnormalities that can be targeted with pharmacologic therapy.

Arterial Load and the Left Ventricular Loading Sequence: Role in LV Remodeling

As described in the accompanying review, wave reflections occur at multiple sites of impedance mismatch, such as points of branching or change in wall diameter or material properties along the arterial tree. Innumerable reflections merge into a discrete reflected wave, which travels back to the heart [6–8]. The time of arrival of the reflected wave to the proximal aorta is strongly dependent on the pulse wave velocity (PWV) of conduit vessels, particularly the aorta, which transmits forward and backward traveling waves from and toward the LV, respectively [8–11]. Stiffer aortas, which exhibit greater PWV, conduct forward and backward traveling waves at greater velocities and therefore promote an earlier arrival of wave reflections to the LV [6, 8, 12–14]. As a consequence of the aortic stiffening that occurs with aging and various disease states, the hemodynamic effects of wave reflections shift from diastole to systole, with prominent effects during mid-to-late systole in older adults [8, 12], particularly in women [3, 6, 7, 12, 15–17] and in patients with HFpEF [18–20]. In these conditions, wave reflections can have a substantial impact on the LV loading sequence (increasing mid/late relative to early systolic load). Table 1 summarizes

some key hemodynamic events during early, mid, and late systole, which are important to understand the impact of wave reflections on the myocardium.

For any given level of systolic (peak) blood pressure, prominent mid-to-late systolic loading has been shown to exert deleterious effects on LV structure and function in animal models and has been associated with LV hypertrophy in humans [8, 21, 22]. Kobayashi et al. [21] used a Wistar rat model and performed constriction of either the ascending aorta or the suprarenal abdominal aorta. Constriction of the ascending aorta increased LV load in early systole (which mimics an increased proximal aortic characteristic impedance), whereas constriction of the descending aorta caused prominent mid-to-late systolic loading from a large reflected wave that originated at the distal aortic constriction site [21]. In this study, despite identical peak LV pressure levels in both groups, rats that underwent descending aortic banding (and were thus exposed to greater mid-to-late systolic load) demonstrated much greater LV hypertrophy than those undergoing ascending aortic banding (which were exposed to increased early systolic load) [21].

These findings are supported by observational human data. Hashimoto et al. [23] assessed changes in wave reflection magnitude occurring during antihypertensive therapy and observed that the reduction in wave reflections predicted regression of LV mass independently of blood pressure reduction. The association between reflected wave magnitude reduction and LV mass reduction was also independent of age, sex, and use of renin-angiotensin system inhibitors and was particularly strong in patients with LV hypertrophy at baseline. Of note, despite the fact that standard antihypertensive therapy reduced wave reflections on average, the change was highly variable, with reflection magnitude actually increasing in some subjects. In agreement with Hashimoto's findings, a relationship between reflection magnitude (approximated from measured pressure and an assumed physiologic flow waveform) and LV mass has been reported in large community-based studies that included normotensive and hypertensive individuals [15, 24]. Similarly, Quail et al. recently demonstrated that in patients with repaired aortic coarctation, reflection magnitude assessed from the ascending aortic distension waveform (a surrogate of the aortic pressure waveform) and measured aortic flow (using phase-contrast MRI) was independently associated with LV hypertrophy [25]. When interpreted in the context of available animal data, available human studies support a role for wave reflections in the development of LV hypertrophy, independent of absolute blood pressure levels.

Available studies also suggest a role for wave reflections and mid-to-late systolic load on LV fibrosis. In the previously mentioned study by Hashimoto et al. [23], the banding intervention that increased wave reflections, resulting in mid-to-late systolic LV loading, also caused more LV sub-endocardial fibrosis, compared to the intervention that increased load in early systole. A recently completed study sponsored by the American College of Radiology Network is assessing the role of wave reflections on diffuse LV fibrosis (measured by MRI T1 mapping sequences) among patients with severe aortic stenosis undergoing aortic valve replacement. In severe aortic stenosis (which often causes HFpEF with LV hypertrophy and diastolic dysfunction), relief of the severe LV pressure load occurs when aortic valve replacement is performed, "leaving" the patient's LV exposed to the underlying arterial load (including wave reflections) at much lower levels of absolute

pressure. This represents an ideal human model to study pressure-independent effects of the LV loading sequence.

Effect of Mid-to-Late Systolic Load on LV Diastolic Dysfunction

Multiple animal studies have demonstrated the deleterious effect of mid-to-late systolic load on LV relaxation [22, 26–30]. Hori et al. used a canine model to impose increased afterload by either (a) clamping the ascending aorta to induce early systolic load, (b) clamping the descending aorta to induce mid-to-late systolic load, and (c) intermittently clamping the ascending aorta in late systole. The authors demonstrated that, for a given increase in peak systolic LV pressure, clamps b and c (mid-to-late systolic loading interventions) prolonged *tau* (the gold standard index of diastolic relaxation) much more than early loading. In a subsequent study, Gillebert et al. [22], studied the effect of the timing of systolic load on LV relaxation in dogs, by inflating balloons in the ascending aorta at different times during ejection (inducing either early systolic load or mid-to-late systolic load). Their study demonstrated that, for a given increase in peak systolic LV pressure, mid-to-late systolic loading prolonged *tau* much more than early systolic inflation, further demonstrating a cause-effect relationship between mid-to-late systolic load and diastolic dysfunction [22]. These results are consistent with several other animal studies [27–32]. Interestingly, one study [33] did not find slowing of relaxation when load was applied selectively in very late systole (~20–50 ms before aortic valve closure), whereas load applied in mid-systole (~80–110 ms before aortic valve closure) significantly slowed relaxation. These results suggest that the effects of wave reflections are not necessarily deleterious in very late systole, unless the bulk of their effect “advances” into mid-systole (as they do in older adults with markedly increased aortic PWV). This is consistent with our understanding of the importance of mid-systole as a critical time during which LV contraction progressively shifts the pressure-stress relation and “protects” cardiomyocytes from the deleterious effects of wave reflection during late ejection [34–37] (Table 1).

In support of the large body of animal experimental findings demonstrating a cause-effect relationship between mid-to-late systolic load and impaired LV relaxation, several human studies demonstrate that indices of wave reflections and/ or mid-to-late systolic myocardial wall stress (MWS) are independently associated with diastolic dysfunction [18, 31, 34, 38–46], left atrial remodeling [40, 47, 48], decreased longitudinal systolic function (despite preserved EF) [42, 49], and elevated brain natriuretic peptide levels [41, 45, 50, 51].

Consistent with the effects of wave reflections on LV remodeling, fibrosis, and dysfunction, wave reflection magnitude [52, 53] and late systolic hypertension [54] have been shown to be strong independent predictors of incident HF in the Multi-Ethnic Study of Atherosclerosis (MESA). More data are required regarding the differential association between late systolic hypertension and incident HFpEF vs. heart failure with reduced ejection fraction.

It should be noted that the effects of wave reflections on the myocardium are influenced by both their magnitude and the timing of their hemodynamic effects relative to LV ejection (Table 1). In older populations, both wave reflection magnitude and timing (from an

increased PWV) are likely important. Targeting wave reflection magnitude and phase with currently available therapies that modify muscular arterial properties represents a suitable therapeutic approach to improve chronic LV remodeling and dysfunction in HFpEF, using currently available agents. As discussed later in this review, it is also important that this modification in wave reflections be achieved without important reductions in systemic vascular resistance.

In summary, patients with HFpEF demonstrate a malignant pulsatile hemodynamic profile, characterized by increased aortic PWV and prominent mid-to-late systolic hemodynamic effects of wave reflections, which likely contributes to LV hypertrophy and dysfunction in this condition. Of note, these pulsatile hemodynamic abnormalities are not necessarily corrected by standard blood pressure control, but may be targeted with tailored therapy, independent of blood pressure reduction per se.

Cellular Processes in the Myocardium

The cellular processes that mediate the deleterious effects of wave reflections on the myocardium are poorly understood. The effect of mid-to-late systolic load on diastolic relaxation and chronic LV remodeling are likely due to intrinsic differences in cellular processes at different phases of systole (Table 1). During early ejection, active development of fiber cross-bridges occurs in the electrically activated myocardium and peak MWS occurs [37], which is followed by a transition from contraction to relaxation. The transition from contraction to relaxation occurs very early during ejection in dogs (~34% after the initiation of mechanical systole and ~16% into the duration of ejection) [55]. In humans, the time to peak MWS, which reflects the time of peak force development (and after which force first starts to decline), has been proposed as a marker of the time to the onset of relaxation [44]. This normally occurs ~70–100 ms into ejection [36, 37, 42].

The immediate effects of afterload on diastolic relaxation have been explained on the basis of the differential effect of early vs. mid-to-late systolic load on the number of interacting cross-bridges. Loading during active cross-bridge formation in early systole increases the number of interacting cross-bridges (cooperative activity), a physiological mechanism that favors matching of the number of cross-bridges with systolic load [22, 56]. However, when increased load occurs after the onset of myocardial relaxation, the number of interacting cross-bridges can no longer adapt. Under these circumstances, a mismatch between the number of cross-bridges and load may occur, increasing the stress imposed on individual cross-bridges and decreasing cross-bridge cycling.

However, a complex interplay between cross-bridge recruitment, cooperative activity, cross-bridge inactivation, and cross-bridge cycling rate is likely at play [34, 44, 55, 56]. Recently, the course of ejection in early systole (which depends at least partially on myocardial contractility) has been shown to correlate with the subsequent course of MWS [44]. As mentioned earlier (and discussed in more detail in the accompanying review), under normal conditions, brisk force development and fiber shortening occur in early systole, resulting in LV ejection and a dynamic reconfiguration of LV geometry that results in a mid-systolic reduction in MWS relative to LV pressure [37], thus protecting the cardiomyocytes against

excessive load in mid-to-late systole (a period of increased vulnerability). The phenomenon of shortening deactivation (which is associated with reduced calcium sensitivity of the contractile apparatus) decreases force development after early systolic rapid shortening and increases the relaxation rate of muscle [34, 44]. This represents a perfect “match” to this normal physiology, because sustained myocardial force development in mid-to-late systole is unnecessary to preserve fiber shortening and LV ejection against the load imposed by wave reflections. However, in the presence of contractile abnormalities that compromise early ejection, the mid-systolic dynamic geometric reconfiguration of the LV that favors a reduced MWS relative to pressure is impaired. In these conditions, shortening deactivation does not operate fully, such that force development continues or increases in mid-to-late systole, tending to preserve the overall EF on one hand, but impairing relaxation on the other [34, 44].

Shah and Wasserstrom suggested a role for disorganization and disruption of transverse (T-) tubules, which are important for the spatial alignment between L-type calcium channels and the sarcoplasmic reticulum [53]. Disrupted T-tubules lead to inefficient calcium cycling, myocardial dysfunction, and calcium overload in cardiomyocytes due to deficient calcium reuptake [53, 57]. These abnormalities are deleterious in their own right, but may also conspire with impaired shortening deactivation to sustain contraction and prolong relaxation.

The differential effect of time-varying myocardial afterload on cellular and molecular processes taking place in early vs. mid-to-late ejection should be a focus of further research. In particular, the molecular mediators of the long-term effects of mid-to-late systolic load on maladaptive remodeling and the pharmacologic effects of common drugs that may affect the time course of myocardial contraction require further study. In addition, the role of comorbidities is not well understood and requires further research. As suggested by Shah and Wasserstrom, long-standing hypertension and comorbidities such as coronary artery disease, obesity, and chronic kidney disease may affect the normal contraction pattern that normally protects myocytes from the effects of wave reflection [37, 53]. The impact of wave reflections on LV remodeling and dysfunction are summarized in Fig. 1.

Hemodynamic Role of the Microvasculature in HFpEF

As discussed in the first part of this review, increased LV systolic stiffness can be necessary to preserve the ejection fraction in HFpEF, but results in increased blood pressure lability [58]. In the setting of a stiff LV, reductions in effective arterial elastance (which is primarily influenced by systemic vascular resistance) will lead to proportionally greater blood pressure decrease vs. a stroke volume increase (Fig. 2). Furthermore, an increased LV systolic stiffness at rest will impair the chamber contractile reserve (and stroke volume reserve) during exercise. This is particularly problematic in this condition, because patients with HFpEF demonstrate an impaired microvasculature, with blunted vasodilatory reserve [59–62]. This constellation of abnormalities presents a unique challenge for vasoactive therapeutic strategies, because important reductions in systemic vascular resistance in this population may result in important side effects (such as dizziness and hypotension). However, enhancing vasodilatory reserve (i.e., a reduction in systemic vascular resistance with exercise) is a logical goal to enhance aerobic capacity, as discussed below.

In addition to the role of vasodilatory reserve on arterial load and ventricular-arterial coupling during exercise, the abnormal vasodilatory reserve present in HFpEF has profound implications for peripheral oxygen delivery and utilization (Fig. 2). Vasodilatory responses during exercise mediate the peripheral redistribution of flow to working muscle, which is a key component of the normal hemodynamic response to exercise [63], and depend on local vasodilatory mechanisms in locomotive muscle, allowing it to effectively “compete” for the available cardiac output [63]. Given the increase in metabolic demands imposed by active skeletal muscle contraction, vasodilation occurs as an adaptive response to a developing imbalance between oxygen supply and demand [63, 64]. Hypoxic vasodilation is an important mechanism that ensures an adequate increase in local blood flow to fulfill the need for delivery of oxygen to metabolically active tissue [63, 64]. Skeletal muscle vasodilation during exercise allows the local vasculature to overcome humoral and reflex-mediated vasoconstriction [63]. In particular, “functional sympatholysis” must occur in exercising muscle to overcome the intense systemic sympathetic vasoconstrictive response. Nitric oxide bio-availability and release is a key mechanism mediating this response [63, 64]. Importantly, impaired microvascular responses within skeletal muscle can have dramatic consequences for oxygen extraction, creating a marked imbalance between oxygen delivery and requirement in muscle, which results in a large oxygen deficit, accentuated intracellular metabolic perturbations, and enhanced glycogenolysis even at low levels of activity [63].

The importance of flow distribution *within* muscle should also be noted. Although blood flow toward locomotive muscle groups is clearly important during exercise, blood flow within active muscles is not homogeneous, being greater in highly oxidative muscles, which normally demonstrate greater vaso-dilatation [65, 66]. Hypoxic vasodilation favors preferential vasodilation in tissues with high oxidative capacity, which seems important to optimize the matching of oxygen supply and demand [63, 64]. Dysregulation of these control processes provides an excess of flow and therefore oxygen delivery to muscles with less oxidative capacity, reducing muscle and whole-body fractional oxygen extraction [66]. However, regardless of the oxidative capacity per se, blood flow in muscle is also important to “wash out” metabolites (such as hydrogen ions) produced during exercise, preventing an excessive sympathetic activation from metaboreflex responses. The role of flow distribution within muscle in HFpEF requires further research.

In addition to the importance of microvascular function for skeletal muscle perfusion and oxygen extraction, abnormalities of the coronary microcirculation in HFpEF are increasingly recognized [67–70]. Patients with HFpEF demonstrate myocardial microvascular rarefaction and impaired coronary flow reserve [67–70]. Impaired myocardial microvascular reserve may impair diastolic perfusion during exercise, worsening diastolic function and exercise intolerance. Inflammation has been proposed as a key determinant of coronary microvascular dysfunction [71, 72]. However, microvascular dysfunction in the coronary bed seems to represent part of systemic microvascular dysfunction. More research is required to understand the determinants and the implications of coronary microvascular dysfunction in HFpEF. Similarly, the relative role of microvascular rarefaction vs. abnormal vasodilatory responses in individual small vessels, as determinants of abnormal microvascular function in HFpEF, requires further study.

In summary, systemic microvascular dysfunction in HFpEF requires a therapeutic approach that does not reduce resting systemic vascular resistance, but is able to significantly reduce vascular resistance in exercising muscle (and in the myocardium) during exercise, while preserving microvascular constriction in other vascular beds, to allow for an efficient cardiac output redistribution and adequate matching of oxygen supply and demand.

Macrovascular-Microvascular Cross-Talk: Role of Large Arterial Pulsatile Hemodynamics in Microvascular Dysfunction and HFpEF Comorbidities

There is an increasing recognition of the role of large artery stiffness and abnormal arterial pulsatile hemodynamics on microvascular disease, which is relevant for the damage of target organs such as the brain and the kidney [13, 73–77]. Cognitive dysfunction/dementia and renal dysfunction are highly prevalent in HFpEF and can significantly influence prognosis [78–82].

Aortic stiffening and increased wave reflections have important adverse consequences on microvascular pressure and flow. Conduit arteries normally exert a powerful cushioning function, which results in nearly steady flow in the microvasculature despite the intermittent LV ejection. Aortic stiffening results in a loss of this cushioning function and promotes increased pulsatility in the microvasculature, particularly in organs that demonstrate low microvascular resistance (such as the brain and the kidney). Excessive pulsatile pressure (with resulting barotrauma) and pulsatile flow (with excessive pulsatile shear forces from increased pulsatile flow velocity) can result in microvascular damage in these organs. Consistent with these principles, accumulating evidence links cerebral microvascular disease and renal disease with increased aortic stiffness [13, 73, 75, 76]. Vascular beds with increased resistance (such as skeletal muscle) are relatively (but not entirely) protected from increased central pulsatility. Increased arterial stiffness is also associated with impaired microvascular dysfunction (post-ischemic vasodilation) in the forearm vascular bed [74]. As discussed above, axial skeletal muscle microvascular function (vasodilatory reserve) is key for exercise-induced vasodilation, flow redistribution, and oxygen extraction during exercise.

Wave reflections are also important for microvascular dysfunction. Wave reflections from the lower body increase central (aortic) pressure pulsatility and thus promote microvascular pulsatility in target organs such as the brain. A controversial proposition has suggested a protective role for wave reflection in microvascular disease. This is based on the observation that aging is associated with a disproportionate increase in aortic stiffness relative to muscular arterial stiffness, promoting impedance matching and a reduction in wave reflection in first-order arterial bifurcations in older adults [75]. Loss of wave reflection proximal to target organs (such as at the aorta-carotid interface) has thus been proposed as a mechanism for excessive pulsatile power transmission to the distal circulation. However, impedance matching is not only dependent on wall stiffness but is also strongly dependent on vessel size [83]. Therefore, despite substantial differences in pulse wave velocity between the aorta and muscular arteries, optimization of the size ratio between parent and daughter vessels in the arterial tree [83] optimizes impedance matching in individual first-order bifurcations even before the aorta stiffens with age. The configuration of parent and daughter

arterial branches, which appears perfectly designed to favor forward energy transmission, is also responsible for the fact that reflections at single bifurcations tend to be quite small, relative to the composite reflected wave arising from the sum of millions of tiny reflections elsewhere. For example, in the study by Mitchell et al., 90% of reflection coefficient values at the aortacarotid interface were between 0 and 15% [75]. These reflection coefficients correspond to power transmission coefficients as high as 97.75 to 100%, indicating that such reflections return as little as 0 to 2.75% of the pulsatile energy to the parent branch. It is also worth noting that reflections at a single interface increase pulse (and systolic) pressure in the distal branches, which is hardly “protective” for the target organs.

As discussed in the first part of this review, the “bulk” of wave reflections arises from locations distal to the upper body first-order bifurcations and in fact, the larger reflected wave returning from arterial locations distal to the aortic arch penetrates the carotid artery as a “forward” wave (thus increasing pressure and flow in the carotid bed) [13, 84]. The innumerable reflections from arterial locations distal to the aortic arch form a larger composite reflected wave, which thus demonstrates a larger reflection coefficient and carries a much larger amount of reflected power than the single reflection at the aorta-carotid interface. Furthermore, impedance matching at the aortic-carotid interface paradoxically promotes the penetration of the reflected wave returning from the lower body into the carotid territory. Moreover, arteries upstream of the cerebral microvasculature appear to attenuate high-frequency flow pulsations (such as those contained in the early systolic carotid flow peak produced by the initial cardiac contraction), much more effectively than low-frequency oscillations (largely compose the reflected wave from the lower body) [13, 84]. Therefore, the pulsatile energy from reflected wave arising in the lower body appears to more effectively penetrate into the cerebral microvasculature [13, 84]. The role of wave reflection on pulsatile pressure, flow, and power penetration into the carotid territory is schematized in Fig. 3.

Aortic stiffness and abnormal pulsatile arterial hemodynamics are also deleterious for the kidney. The loss of renal autoregulation (because of altered myogenic tone) is a feature of aging, hypertension, and diabetes [85–88], all of which are commonly present in patients with HFpEF. Loss of autoregulation favors the transmission of higher pulsatile pressure and flow to the renal microcirculation, leading to glomerulosclerosis. Available data suggests that systemic wave reflections are also deleterious to the kidney, which is expected to the degree that they increase aortic pressure pulsatility [89]. Measures of wave reflection have been shown to predict a poor prognosis in patients with established renal disease [90, 91]. Similarly, augmentation index is positively associated with a faster progression of established kidney disease [92, 93], and backward wave amplitude is independently associated with a lower glomerular filtration rate [94] and with faster renal function decline over time in the general population, even after adjustment for forward wave amplitude [95]. Furthermore, measures of wave reflection correlate positively (not negatively) with renal resistive index (a measure of renal microvascular dysfunction) [96].

Clearly, the preponderance of evidence indicates that systemic wave reflections are deleterious to target organs. In fact, vasodilators that reduce wave reflection (such as calcium channel blockers) have been shown to reduce cognitive decline in older adults with systolic

hypertension [13, 73, 97]. This effect on cognitive function is not true for all antihypertensive agents and is likely independent on the effects of these drugs on brachial blood pressure.

Finally, wave reflections and pulsatile hemodynamics also interact with coronary microvascular function to determine myocardial perfusion and perfusion reserve. As discussed above, impaired myocardial microvascular reserve may impair diastolic perfusion during exercise, contributing to diastolic dysfunction and exercise intolerance. It is well known that coronary perfusion occurs predominantly during diastole. Therefore, a wide aortic pulse pressure (with a relatively low diastolic pressure) is unfavorable for the coronary perfusion gradient and can be worsened by reductions in mean arterial pressure. Poorly timed (premature) wave reflections contribute to the systolic pressure-time integral, with lesser contributions to the diastolic pressure-time integral. It is well known that the ratio of diastolic/systolic pressure time integrals (also called Buckberg index) is a key hemodynamic determinant of the ratio of myocardial oxygen supply vs. demand [98]. Therefore, wave reflections may conspire with coronary microvascular dysfunction to impair coronary flow during exercise. Improving the timing of wave reflections during exercise may represent a suitable therapeutic approach to improve myocardial oxygen supply and demand in HFpEF.

In summary, a host of arterial hemodynamic abnormalities are present in HFpEF, which play a role into the pathophysiology of LV remodeling, dysfunction, abnormal myocardial oxygen supply and demand, exercise intolerance, and the frequent presence of some comorbidities. (Fig. 4) The arterial tree, therefore, represents an important therapeutic target in this condition.

Therapeutic Implications

The arterial hemodynamic characteristics of HFpEF dictate a set of “ideal” characteristics for a hemodynamic intervention in this condition, namely, one that (1) reduces wave reflections and mid-to-late systolic load at rest (which could improve diastolic function and exert long-term, “disease-modifying” effects on LV maladaptive remodeling), (2) does not significantly reduce mean arterial or systemic vascular resistance at rest, avoiding hypotension, (3) enhances exercise-induced vasodilation (reduction in SVR) to reduce LV afterload during exercise, (4) has selectivity for enhancing local vasodilation in hypoxic/acidotic environments, in order to match blood flow to metabolic demands (i.e., directing blood flow to exercising muscle), and (5) does not vasodilate low-resistance microvascular beds, due to their vulnerability to the prominent central pulsatility seen in this older population.

The endogenous nitrate-nitrite-NO pathway mediates a series of effects via normoxic vasodilation of conduit muscular arteries [99] (which thus operates both at rest and during exercise) in combination with selective microvascular dilation in hypoxic/acidotic conditions (such as occurs in exercising muscle) [100–103] that seem ideal to improve the arterial hemodynamic abnormalities that are prevalent in HFpEF. Interestingly, two separate studies have recently demonstrated that patients with HFpEF exhibit a reduced circulating NO metabolite pool [104, 105] (composed largely of nitrate and to a lesser extent nitrite), which

may limit the intrinsic activity of this pathway. As reviewed in detail elsewhere [100, 102], exogenous inorganic nitrate supplementation represents a promising therapeutic approach in HFpEF.

Interestingly, organic nitrates do not share the ideal vasoactive characteristics exhibited by inorganic nitrate. In contrast to inorganic nitrate, organic nitrates in HFpEF (1) induce a less consistent reduction in wave reflection, (2) can markedly reduce mean arterial pressure at rest, (3) lack the selective vasodilatory effect during exercise in exercising muscle, (4) exert prominent cerebrovascular vasodilatory effects, which accounts for the high incidence of headaches (and may also expose the already susceptible cerebrovascular microvasculature to excessive pressure and flow pulsatility), (5) induce tolerance or pseudo-tolerance, and (6) increase oxidative stress [102, 106, 107]. In a recent multi-center trial, isosorbide mononitrate reduced outpatient activity in a dose-dependent manner in this population [108]. In another recent trial [109], isosorbide dinitrate, with or without hydralazine, failed to improve wave reflections, LV remodeling, or the 6-min walk distance in HFpEF. Furthermore, in the isosorbide dinitrate-hydralazine arm, an increase in wave reflections at 24 weeks was seen, which was associated with worsened 6-min walk distance and an increased myocardial T1 (assessed by MRI T1 mapping), indicating adverse interstitial remodeling/ fibrosis. In both trials, organic nitrates were poorly tolerated. This is in sharp contrast with available studies which consistently suggest a favorable effect of inorganic nitrate/nitrite on exercise capacity or various hemodynamic parameters [100–102, 110 – 114].

The arterial hemodynamic effects of other drugs, such as neprilysin inhibitors and soluble guanylate cyclase stimulators, are not well understood and require further study.

Role in Precision Medicine

Whereas the concepts relating arterial hemodynamics with various aspects of the pathophysiology of HFpEF have been described in general, HFpEF is likely a heterogeneous syndrome, with different degrees of contribution from different pathophysiological processes in specific patients. This may unfavorably impact the average responses of this patient population to therapies tested in clinical trials. Characterizing arterial hemodynamics through “deep phenotyping” can provide a means to match specific therapies with patients or subsets of patients. A detailed characterization of pulsatile arterial hemodynamic function can now be achieved at the bedside using relatively simple tools, such as echocardiography and arterial tonometry, followed by computer-assisted hemodynamic modeling. Similarly, non-invasive methods to assess microvascular function and vasodilatory reserve are available.

Tools to phenotype arterial hemodynamic function can be utilized to “segment” the HFpEF population into relevant pathophysiologic categories. Achieving this goal would require careful measurements of these phenotypes in a relatively large representative sample of HFpEF patients, followed by the application of computational techniques to find patterns of clustering of abnormal arterial hemodynamics. Such subgroups may demonstrate unique clinical characteristics, responses to therapy, and/or risk for adverse outcomes or side effects

to specific drugs. Future patients in turn could be assigned to specific subsets based on parsimonious phenotypic markers, facilitating the translation of this classification into clinical practice. The latter could in turn allow for better treatment strategies, risk stratification, and targeted enrollment of specific patient subgroups into clinical trials. Approaches to segment the HFpEF population into clinical subtypes have been successfully applied using comprehensive general phenotypes [115, 116] and could further benefit from deeper phenotyping of arterial function and ventricular-arterial interactions.

Application of deep phenotyping of arterial hemodynamics in randomized trials of novel therapies would also be highly informative. This is particularly useful in early phase (I and II) trials, which could better characterize the hemodynamic effects of novel drugs, allowing better informed designs for phase III trials or iterative assessments of efficacy in additional phase II trials when overall results are “negative” but plausible signals are identified suggesting that specific pathophysiologic patterns or phenotypic subgroups of participants are favorably impacted by the drug. Even if the pharmacologic effects of specific novel drugs on arterial hemodynamics are well known (which is rare), deep phenotyping of arterial hemodynamics can be very useful, because it is likely that trial participants displaying relevant phenotypic abnormalities at baseline will respond more favorably to therapies that target those abnormalities. For instance, subjects who exhibit prominent wave reflections at baseline may respond more favorably to therapies that blunt wave reflections, improve endothelial function, or affect muscular artery properties. Although the application of comprehensive arterial phenotyping in clinical trials has been limited by the cost and the availability of necessary equipment to characterize arterial hemodynamics in multicenter studies, relatively inexpensive, non-invasive and operator-independent techniques for this purpose are now available. The latter may also facilitate application of deep phenotypic assessments in clinical practice, but this can only be justified once “actionable” phenotypic “readouts” are identified, ultimately improving patient care.

A related approach for the application of these techniques would be to prospectively identify individuals with prominent specific abnormalities presumed to be impacted by specific pharmacologic interventions, for targeted enrollment into early phase trials, as opposed to a relatively indiscriminate enrollment of patients with HFpEF. This approach differs from the parsimonious identification of patient subsets discussed above, because it implies phenotyping every potential subject precisely, defining thresholds in specific metrics for enrollment. For example, an early phase trial of a drug that presumably de-stiffens the aorta should logically enroll patients with increased aortic pulse wave velocity to begin with and ideally exclude those who likely have HFpEF on the basis of other physiologic abnormalities (such as primary myocardial processes in the absence of prominent pulsatile hemodynamic abnormalities).

Finally, a better understanding of arterial hemodynamics in general may guide therapeutic approaches using commonly available drugs. For instance, whereas some therapies (such as inorganic nitrate/nitrite) may be able to target multiple relevant arterial abnormalities present in HFpEF [101, 102], young hypertensive patients with HFpEF who may not exhibit markedly abnormal pulsatile hemodynamics, or stiff arteries, may benefit from the use of drugs that lower systemic vascular resistance, whereas older patients with stiff arteries, wide

pulse pressure, and normal systemic vascular resistance at rest may predictably develop important side effects related to hypotension with the same drugs. However, we should be cautious about making assumptions based on simple logic, as this has often led to erroneous predictions in this disease. In particular, the effects of common drugs based on studies in non-HFpEF populations should not be freely extrapolated to HFpEF, since this population (or subsets of it) may demonstrate unexpected responses. For example, whereas organic nitrates have been shown to reduce wave reflection in hypertension, as mentioned above, chronic administration of isosorbide dinitrate in HFpEF did not impact reflection magnitude, whereas the combination of isosorbide dinitrate with hydralazine was associated with increased wave reflections, reduced 6-min distance, and adverse myocardial remodeling in a recent trial [109].

Conclusions

Compelling evidence from animal and human studies strongly suggest that wave reflections cause adverse diastolic dysfunction and maladaptive LV remodeling. In addition, increased aortic stiffness and abnormal pulsatile hemodynamics are linked to microvascular disease in the brain, the kidney, and the axial microvasculature. Hemodynamic goals for our therapeutic approach to HFpEF should include the reduction in systemic wave reflections and central pressure pulsatility, without causing reductions in systemic or cerebrovascular resistance at rest, while enhancing the vasodilatory response to exercise in exercising muscle. This combination of tailored arterial hemodynamic effects may not only improve exercise capacity in the short term but may also exert favorable long-term disease-modifying effects on the LV and potentially of other target organs. Interventions that safely reverse large artery stiffening represent the “holy grail” of pulsatile arterial hemodynamics, but such interventions are unlikely to be available in the near future.

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Fig. 1.

Role of arterial wave reflections and late systolic load on LV remodeling and diastolic dysfunction. Arterial wave reflections selectively increase mid-to-late systolic LV load. Late systolic LV load from wave reflections promotes LV hypertrophy, fibrosis, and myocardial dysfunction (longitudinal systolic dysfunction and slow relaxation). The effect of wave reflections on the myocardium is strongly influenced by the LV contraction pattern. Normally, systolic ejection determines a dynamic reconfiguration of LV geometry that reduces myocardial wall stress relative to LV pressure in mid-systole, thus protecting the cardiomyocytes against excessive load in late systole. Concentric LV hypertrophy/remodeling and impaired contractility (even in the presence of a normal EF) are associated with a blunted mid-systolic shift in the pressure-MWS relation, which is less effective to protect cardiomyocytes to load during a period of increased vulnerability. This may represent a “vicious circle” that facilitates the development and progression of HFpEF

Fig. 2.

Role of microvascular hemodynamic function in hemodynamics at rest and during exercise. At rest (*left panels*), the ventricular-arterial system of patients with HFpEF is characterized by increased LV systolic stiffness (i.e., increased E_{ES} , *upper left panel, red line*). Therefore, any therapeutic intervention that reduces vascular resistance at rest (*black curved arrow*) (which is the key arterial determinant of “effective arterial elastance,” represented in green lines) will induce a large pressure decrease (*blue arrow*) relative to the increase in stroke volume (*orange arrow*). Furthermore, given the presence of stiff conduit arteries and premature wave reflections that augment systolic, rather than diastolic, aortic pressure, a reduction in mean arterial pressure may decrease diastolic arterial pressure excessively (*left lower panel*), leading to a reduction of perfusion pressure in key organs. During exercise (*right panels*), however, a reduction in vascular resistance is essential. A combination of vasoconstriction in most vascular beds (splanchnic vasculature, non-exercising muscle, etc.) along with vasodilation in exercising muscle (local functional sympatholysis) is key for the optimization of the cardiac output distribution and oxygen supply-demand matching in the periphery. In addition, the lack of reduction in SVR during exercise increases LV load and contributes to the limitation in cardiac output reserve. Microvascular function is also essential for enhancing coronary perfusion during exercise. However, pulsatile hemodynamics also affect myocardial oxygen demand (workload) and supply (diastolic perfusion pressure) during exercise (see text). *MAP* mean arterial pressure; *DBP* diastolic blood pressure

Fig. 3. Effect of wave reflection on pulsatile pressure, flow, and power pulsatility into the carotid territory. The *left-sided panel* represents the effect of the forward traveling wave from the ascending aorta (*blue arrows*) into the aortic arch and carotid territory. The *left-sided panel* represents the effect of the reflected wave from the lower body traveling up the descending aorta (*red arrows*). Although a small reflection occurs at the aortic-carotid interface, the bulk of wave reflections arising from the lower body penetrate the carotid as a forward wave, increasing pressure and flow pulsatility in the carotid territory. Paradoxically, impedance matching at the aortic-carotid interface reduces local reflection but also promotes the penetration of distal reflected waves into the carotid territory

Fig. 4.

Role of arterial hemodynamic dysfunction in HFpEF. Abnormal macrovascular and microvascular hemodynamic dysfunction promotes LV diastolic dysfunction and LV maladaptive remodeling (hypertrophy, fibrosis) and causes a reduced vasodilatory reserve during exercise, which in turn impairs coronary flow, peripheral flow redistribution, oxygen delivery, and extraction in exercising muscle. Abnormal pulsatile arterial hemodynamics also contribute to microvascular disease in the brain and the kidney (dementia, chronic kidney disease, which are frequently encountered comorbidities in HFpEF)

Table 1
Key events during early, mid, and late systole relevant for understanding the impact of the LV systolic loading sequence on the myocardium

Early systole (isovolumic contraction and ~1st third of ejection)	Mid-systole (~2nd third of ejection)	Late systole (~last third of ejection)
<ul style="list-style-type: none"> Transition from isometric contraction to the early ejection phase, during which peak myocardial wall stress develops (~70–100 ms after aortic valve opening in humans), followed by the onset of myocardial relaxation. Prior to the onset of relaxation, active cross-bridge formation occurs. Myocytes can partially adapt to load by increasing the number of interacting cross-bridges (cooperative activity). Fiber shortening during this period results in (1) initiation of length-dependent deactivation (“shortening deactivation”) of cardiomyocytes and (2) dynamic changes in LV geometry that favor a subsequent reduction in myocardial wall stress relative to LV pressure. Arterial load is governed by aortic root characteristic impedance (Z_c). Although wave reflections can arrive to the aorta in early systole, their net load during this period is small. 	<ul style="list-style-type: none"> Continued LVEjection determines a progressive shift in the pressure-stress relation, such that myocardial wall stress progressively decreases for any given LV cavity pressure. Shortening deactivation reduces the force of contraction and wall stress decreases. Despite this, increasing pressure may occur, given the shifting pressure-stress relation. This is a period of increased vulnerability to load, because it follows the onset of relaxation (and cross-bridges can no longer adapt to load), but precedes the full development of the shift in the pressure-stress relation (which protects cardiomyocytes from excessive wall stress). Premature wave reflections exert significant hemodynamic load on the LV (and the cardiomyocytes) during this period. 	<ul style="list-style-type: none"> Normally, (1) the shift in the pressure-stress relationship has fully developed, (2) myocardial wall stress/force development and the velocity of fiber shortening continue to decrease, and (3) the end of the action potential promotes full relaxation. Wave reflections exert significant hydraulic load on the LV, but when early-phase ejection and the mid-systolic shift in the pressure-stress relation are preserved, LV wall stress is low (cardiomyocytes are “protected” from wave reflections). However, when earlier systolic phenomena are abnormal (i.e., impaired early-phase ejection from decreased contractility or increased load, impaired mid-systolic shift in the pressure-stress relation due to LV concentric hypertrophy/remodeling or decreased contractility), cardiomyocytes continue to be vulnerable to the effects of wave reflections. A sustained contraction pattern may be present (as a result of deficient shortening deactivation), tending to preserve the overall EF on one hand, but impair relaxation on the other.