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## Review Article

# The pathophysiology of chronic cardiorenal disease based on central hemodynamics

## Abstract

As patients with chronic kidney disease (CKD) and chronic heart failure (CHF) increase, there is concern about a future heart failure pandemic. Deterioration of renal function is an independent prognostic factor for CHF after decongestion. Interactions between renal disease and cardiac disease are increasing, including nephrosclerosis and heart failure with preserved ejection fraction (HFpEF), which are both derived from augmentation of central pulse pressure by age-related arterial stiffening. Thus, it is necessary to treat multiple underlying diseases of cardiorenal syndrome simultaneously. However, an effective therapeutic strategy for HFpEF has not been established. This review reconsiders the pathophysiology of chronic cardiorenal disease related to arterial stiffening from the viewpoint of central hemodynamics and explores treatment options.

## Introduction

Compared with the peripheral blood pressure, the central blood pressure is more closely related to organ changes that are representative of arteriosclerosis and renal dysfunction, including left ventricular (LV) mass and common carotid artery intima-media thickness (IMT) [1-4]. In addition, central blood pressure has been shown to be a predictor of cardiovascular events [1,5-7]. It has been suggested that elevation of central blood pressure has a key role in the linkage of heart and kidney disease, and central blood pressure may be a predictor of the progression of hypertension [8]. Accordingly, antihypertensive agents that more effectively reduce central blood pressure could be useful for prevention or improvement of organ damage.

The prevalence of heart failure is increasing worldwide and an accelerated increase in people with heart failure has been predicted in the future [9,10]. In particular, heart failure with preserved ejection fraction (HFpEF) is common among elderly persons [11-14].

Chronic kidney disease (CKD) is a prognostic factor for heart failure [15-17] and it is also increasing worldwide, along with underlying diseases such as hypertension and age-related nephrosclerosis [18,19]. There has also been an increase of diabetic kidney disease (DKD), which is defined as atypical diabetic nephropathy characterized by mild proteinuria with deterioration of renal function and nephrosclerosis [20-23].

Renal insufficiency (i.e., an estimated glomerular filtration rate (GFR) < 60.0 mL/min/1.73 m<sup>2</sup>) is common in patients with chronic heart failure (CHF), and approximately 36% of CHF patients also have renal insufficiency [16]. Moreover, renal dysfunction (assessed by GFR) is independently associated with an elevated risk of all cause death, cardiovascular death, and hospitalization for heart failure in patients with CHF and a preserved or reduced EF [16].

Cardiorenal syndrome (CRS) is the term for the bidirectional pathophysiological interaction between cardiac and renal dysfunction, and it is classified into 5 types in consideration of whether the condition is acute, chronic, or secondary [24]. Worsening renal function (WRF) occurs in approximately one third of patients admitted to hospital with acute decompensated heart failure (ADHF), and is associated with an increased length of stay, a higher readmission rate, and worse short-term and long-term survival [25-28]. Therefore, a treatment strategy is needed for ADHF and acute CRS (type 1). With aging of the population, it is predicted that there will also be an increase of chronic CRS (type 2), chronic renocardiac syndrome (type 4), and secondary CRS (type 5) derived from arteriosclerosis.

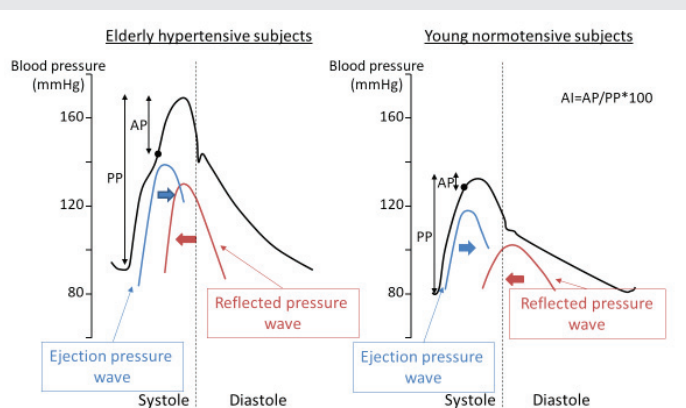
Thus, ventricular-arterial-renal interactions are becoming an issue of increasing interest with large clinical implications. This article reviews the pathophysiology of renal and cardiac damage (HFpEF) related to arterial stiffening from the perspective of central hemodynamics, and also discusses potential therapeutic options for reducing central pulse pressure [PP].

## Central blood pressure

**Components of central blood pressure:** Central blood pressure has been noted as an index of the overall health of the arterial tree [29]. It is constituted by the ejection pressure wave that spreads from the heart to periphery and the reflected pressure wave that spreads in reverse from the peripheral arteries to the central region. When the reflected pressure wave is added to the ejection pressure wave during late systole, and the central pulse pressure wave is amplified by the augmentation pressure [AP] [30].

Young persons with normal blood pressure have distensible arteries, but elderly persons with hypertension do not. Loss of aortic distensibility due to arterial stiffening results in an increase of the central PP due to elevation of the central systolic blood pressure and a decline of the central diastolic blood pressure with loss of the cushion and Windkessel effects, because the reflected pressure wave moves faster and the reflected wave thus shifts from diastole to late systole. In elderly hypertensive persons, the augmentation pressure [AP] and the central pulse pressure wave are amplified as a consequence of the reflected pressure wave moving to late systole. In contrast, the reflected pressure wave is slower and appears during diastole in young normotensive persons because of the flexibility and distensibility of their arteries (Figure 1) [29,31]. The interaction between the ejection pressure and the reflected pressure is assessed by pulse wave analysis and is expressed as the augmentation index [AI]. In elderly persons with increased arterial stiffness, the central systolic blood pressure is generally determined by the reflected pressure wave, whereas the brachial systolic blood pressure measures the ejection pressure wave (Figure 2).

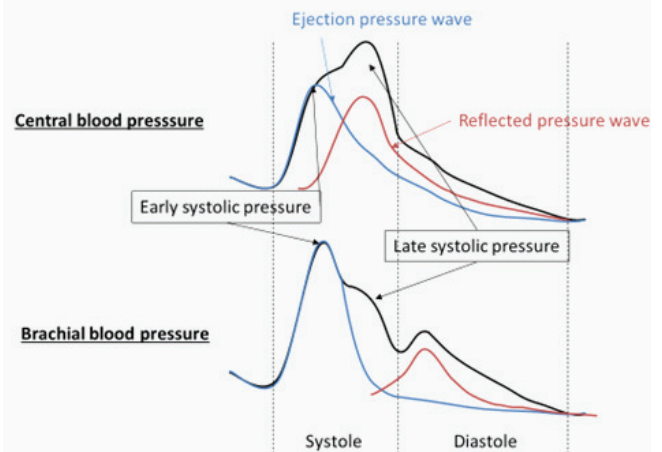
**Clinical implications:** The AI of central blood pressure is determined by the pulse wave velocity, which reflects segmental arterial elasticity and peripheral reflectance. Elevation of the central PP and AI lead increased LV afterload and decreased coronary perfusion due to a decline of diastolic pressure, and thus are more closely related to cardiovascular target organ damage and cardiovascular events compared



**Figure 1:** Speed of return of the reflected pressure wave to the central aorta in young normotensive and elderly hypertensive subjects.

Note the marked increase of AP during late systole in elderly hypertensive subjects due to faster return of the reflected pressure wave.

AP; augmentation pressure, PP pulse pressure, AI; augmentation index [29,31].



**Figure 2:** Difference of central and brachial blood pressures in elderly subjects with increased vascular stiffness. In elderly subjects with increased vascular stiffness, the central systolic blood pressure measures blood pressure due to the reflected pressure wave, whereas the brachial systolic blood pressure measures blood pressure due to the ejection pressure wave.

with the brachial pressure. [1-4]. The central blood pressure reflects LV afterload, and thus is also more closely related to production of brain natriuretic peptide (BNP), a marker of cardiac workload and hypertrophy, relative to the brachial blood pressure [2,32]. Therefore, central PP is considered to be a risk indicator that is more pathophysiologically relevant to the pathogenesis of cardiovascular disease than the peripheral pressure [1,5,7,33-35]. For example, central blood pressure is superior for prediction of new-onset hypertension during follow-up of persons with high normal blood pressure [8].

**Relationship among central blood pressure, renal hemodynamics, and organ damage:** Elevation of the central PP is considered to exacerbate renal dysfunction, including an increase of albuminuria, as it has a direct influence on renal hemodynamics [1,3,4,32,36-38]. The parameter used most widely for noninvasive evaluation of renal hemodynamics as a significant predictor of progressive renal dysfunction is the resistive index (RI), which is derived from the pulsatile flow-velocity waveform [4,39-43]. An increase of the RI is related to elevation of the central PP and the AI [4], and is also associated with renal microvascular damage [4,36,44-46]. In persons with normal flexible and distensible arteries, the PP from the central aorta is gradually absorbed by renal arterioles including the afferent arterioles, finally resulting in non-pulsatile flow in the efferent arterioles to maintain a constant intraglomerular pressure. Autoregulation to constantly maintain the intraglomerular pressure at approximately 60 mmHg depends on adjustment of pressure in the afferent and efferent arterioles by vasoconstriction or vasodilation. It involves secretion of renin, tubular glomerular feedback, myogenic responses, and sympathetic nervous system activity. This mechanism keeps the intraglomerular pressure around 60 mmHg, even if the systolic blood pressure varies widely from 90 to 180 mmHg [47]. One of the key reasons for progression of renal damage due to elevation of central blood pressure is considered to be afferent arteriole dysfunction, although the details are still unclear. All blood entering the glomerulus passes through the afferent

arteriole and it acts as a gatekeeper that regulates renal blood flow by active contraction or dilatation. However, when the PP cannot be absorbed by the afferent arterioles, it reaches the efferent arterioles (Figure 3) [29]. As a result, the glomerular capillary walls are affected and hyperfiltration due to elevation of the intraglomerular pressure becomes persistent, leading to albuminuria. Thus, abnormal central hemodynamics lead to abnormal renal hemodynamics and hypertensive renal damage seems to occur due to elevation of the central PP.

**Differing effect of antihypertensive agents on central blood pressure and brachial blood pressure:** The effects of various antihypertensive agents differ between the aorta and the brachial artery. Vasodilators, including Ca channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs),  $\alpha$ -blockers, and nitrates, reduce the central blood pressure more effectively than the brachial blood pressure [48,49]. On the other hand,  $\beta$ -blockers have a weak effect on the central blood pressure [50].

The most pivotal study examining the relative importance of central and brachial blood pressures has been the Conduit Artery Function Evaluation (CAFÉ) study of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) [5]. Although brachial blood pressure was similarly reduced in both the amlodipine  $\pm$ perinopril and atenolol  $\pm$ thiazide arms of the CAFÉ study, there was significantly greater reduction of central systolic pressure and PP (due to reduction of reflected pressure wave) with amlodipine-based treatment. In addition, changes in the indicators of cardiovascular target organ damage, including left ventricular mass and IMT, are more dependent on reduction of central blood pressure than brachial blood pressure, and improvement due to antihypertensive therapy depends on the extent of central blood pressure reduction rather than a decrease of brachial pressure [1,2,51]. These reports suggest that measuring central blood pressure to monitor treatment would be useful for prevention of cardiovascular disease.

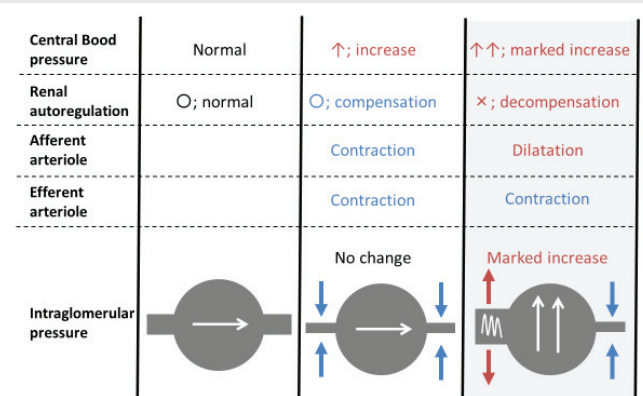
Currently, a cut-off value for normal/abnormal central blood pressure has not been established, although it was recently proposed that 130/90 mmHg could be a cut-off value for central blood pressure by investigation of a Taiwanese database [52].

It has been suggested that measurement of central pressure could be medically cost effective because guiding management of hypertension based on central blood pressure results in a significantly different therapeutic pathway compared with conventional cuff blood pressure measurement, using less medication to achieve blood pressure control and avoiding adverse effects on LV mass, aortic stiffness, or quality of life [53]. Accordingly, it is necessary for the central blood pressure level that prevents cardiovascular target organ damage to be determined by large-scale controlled studies in the future.

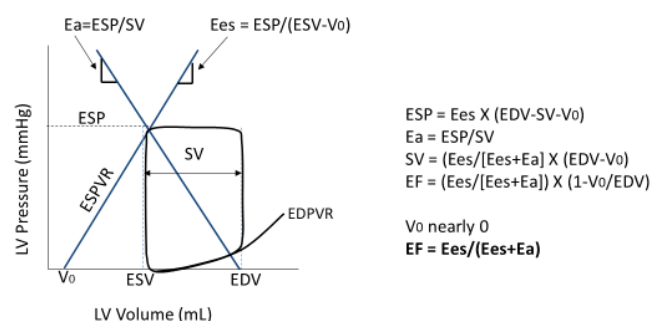
### Relationship between central blood pressure and HFpEF

**Clinical features of HFpEF:** Among all patients with heart failure, those with HFpEF are increasing due to aging of

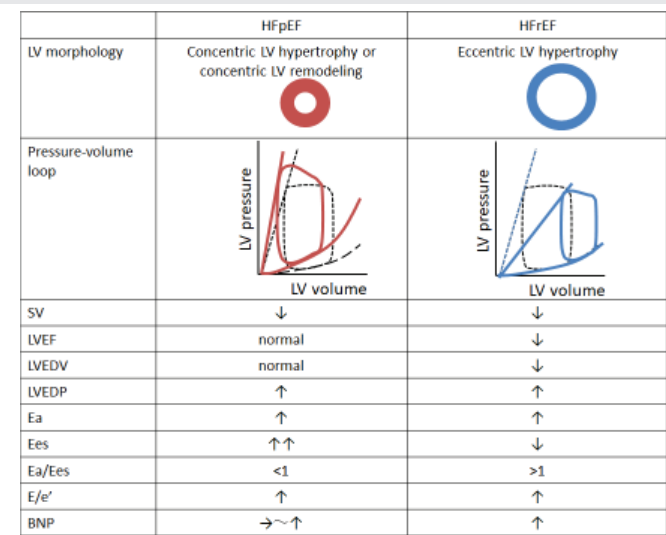
the population, and the combination of HFpEF with CHF is common. These patients do not have a good prognosis, like patients who have heart failure with reduced EF (HFrEF), and effective treatment has not yet been established [14,54]. Compared to HFrEF patients, HFpEF patients are more likely to be elderly women and to have hypertensive heart disease as the underlying disorder [55-58]. HFrEF is associated with deterioration of systolic function on top of diastolic dysfunction, so that LV end-diastolic volume increases to maintain stroke volume, resulting in elevation of LV end-diastolic pressure [59-61]. Conversely, HFpEF is related to diastolic dysfunction and elevation of LV end-diastolic pressure [EDP] occurs without an increase of LV end-diastolic volume (EDV) (Figure 4,5). Diagnosis of HFpEF is difficult clinically, but no increase of LV EDV and LVEF  $\geq$ 50% are requirements [62]. HFpEF can cause pulmonary congestion due to elevation of LV EDP derived from increased LV chamber stiffness, in the setting of excessive LV preload or afterload and increased heart rate during exercise [63,64]. BNP may be normal in up to 30% of patients with HFpEF [65,66], especially those who are obese [67] or only have exertional symptoms [68].



**Figure 3:** Decompensation of renal autoregulation and increased intraglomerular pressure due to marked elevation of the central blood pressure. Marked elevation of the central blood pressure overcomes renal autoregulation because the high pulse pressure cannot be absorbed by the renal vessels before the afferent arterioles, so that intraglomerular pressure is increased markedly. Eventually, albuminuria occurs and the glomerular filtration rate decreases.



**Figure 4:** Relationship between end-systolic elastance and effective arterial elastance. EF can be calculated from Ees and Ea if  $V_0 = 0$ . LV = left ventricular; ESP = end-systolic pressure; EDV = end-diastolic volume; ESV = end-systolic volume; SV; stroke volume; Ea = effective arterial elastance; Ees = end-systolic elastance;  $V_0$  = the zero volume intercept of the end-systolic pressure-volume line; ESPVR = end-systolic pressure-volume relationship; EDPVR = end-diastolic pressure-volume relation; EF = ejection fraction [78].



**Figure 5:** Comparison of LV morphology and function in patients with HFrEF or HFpEF.

The slope of the end-systolic pressure-volume relationship [end-systolic elastance], which is obtained by recording pressure-volume loops at different preload levels, is steeper in patients with HFpEF [solid lines] than in people with normal hearts, and HFpEF patients typically exhibit an end-diastolic pressure-volume relationship shifted upwards and to the left [solid lines] [dashed lines = normal hearts]. In contrast, the slope of the end-systolic pressure-volume relationship is typically less steep in patients with HFrEF [solid lines] than in people with normal hearts [dashed lines]. LV = left ventricular; SV = stroke volume; LVEF; left ventricular ejection fraction; LVEDV; left ventricular end-diastolic volume; LVEDP = left ventricular end-diastolic pressure; Ea = effective arterial elastance; Ees = end-systolic elastance; E/e' = transmitral peak velocity during early relaxation to early diastolic peak mitral annulus velocity; BNP = brain natriuretic peptide [61,63,67].

### Is arterial afterload due to augmentation of central PP the main pathophysiology of HFpEF?

Epidemiologic studies have shown that 40% to 50% of patients with heart failure have HFpEF, and that they are older than those with HFrEF and are more often female [54,58,69]. Moreover, a community study has demonstrated that advancing age and female gender are associated with increased vascular and ventricular systolic diastolic stiffness, even in the absence of cardiovascular disease, suggesting the combination of ventricular-vascular stiffness may contribute to the increased prevalence of HFpEF, particularly in elderly women [58]. Patients with HFpEF are assumed to have vascular disease with arterial stiffening as well as cardiac disease, because this condition is often accepted to arise from hypertension. HFpEF derived from arterial stiffness is pathophysiologically and clinically characterized by the failure of compensation due to ventricular-arterial coupling (i.e., ventricular-arterial coupling disease) [57,70], indicating that this is a key determinant of cardiovascular health. It has been observed that age-related vascular stiffening, which can have a marked effect on ventricular-arterial coupling, is accompanied by changes of LV stiffness and diastolic compliance [71]. Accordingly, HFpEF should be considered to have a different pathogenesis from HFrEF [54,56,57,72].

In HFpEF, ventricular-arterial disease leads to afterload mismatch, which results in decompensation of LV end-systolic elastance (Ees) for arterial stiffness and augmentation of central PP [73-75].

Effective arterial elastance (Ea) is an indicator of arterial stiffness that is defined by the negative slope between the end-systolic pressure-volume point and EDV [i.e., the ratio of end-systolic pressure to stroke volume (SV) shown in Figure 4]. Ees is an index of LV contractility that is also described by the slope of the end-systolic pressure-volume relationship (ESPVR) (Figure 4). In elderly patients with hypertension, central PP is boosted by an increase of the reflected pressure wave during late systole [29]. Elevation of Ea derived from this increase of central PP causes a change in the LV loading sequence with an increase of the late-systolic load, resulting in abnormal ventricular-arterial coupling and an eventual increase of Ees with LV hypertrophy. Furthermore, an increase of late systolic loading may incrementally impair early diastolic relaxation [76,77]. Thus, an increase of the cardiac arterial afterload with elevation of central PP causes secondary cardiac dysfunction [57], and is considered to underlie the pathophysiology of HFpEF in the elderly [76].

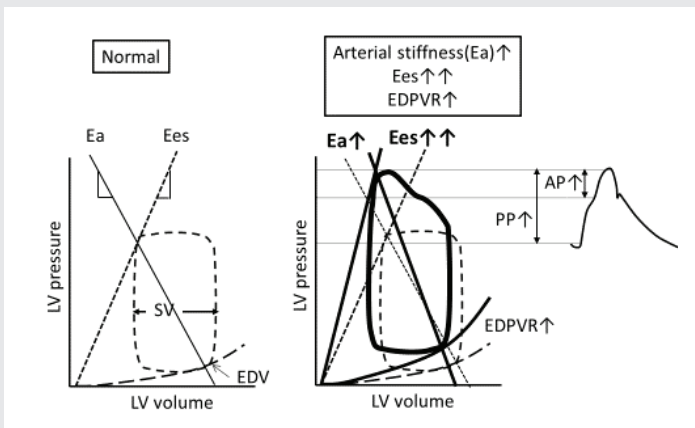
Treatments that can reduce late systolic vascular loading and arterial stiffness may be useful for patients with diastolic dysfunction by changing the loading conditions, which could explain why nitroglycerin improves LV systolic diastolic function in HFpEF patients [48,77].

### Is cardiac contractility normal in HFpEF?

EF can be expressed as a function of Ees and Ea in the following formula (Figure 4) [78]:  $EF = Ees / (Ees + Ea)$

If  $Ees = Ea$ , the value of EF becomes 0.5. In patients with HFrEF, EF decreases below 0.5 and Ees is lower than Ea. On the other hand, in patients with HFpEF, Ees is  $\geq Ea$  and EF is maintained at  $\geq 0.5$ .

Under physiological conditions, the Ea/Ees ratio is maintained at about 1 to preserve SV. Even if Ea increases substantially with advancing age, Ees also increases to keep the Ea/Ees ratio around 1, and this coupling is compensated [57,70,71]. On the other hand, the Ea/Ees ratio is  $<1$  in HFpEF because the increase of Ees exceeds that of Ea [Figures 5, 6] [56,79]. Although Ees is elevated in hypertensive heart disease depending on increase of Ea, the heart still has the reserve force to augment Ees for maintenance of the LV ejection fraction. In contrast, the excessive rise of Ees over Ea in HFpEF reflects impaired myocardial contractility and an increase of passive myocardial stiffness, which is followed by structural changes such as hypertrophy and fibrosis with the gradual progression of HFpEF. This process suggests that HFpEF will have a poor prognosis [80]. It has not been identified whether HFpEF with a normal EF shows myocardial contractility. In heart failure with a reduced or preserved EF, a substantial increase of Ees irrespective of the increase/decrease of Ea causes failure of ventricular-arterial coupling or afterload mismatch, resulting in a decrease of SV. In addition, excessive augmentation of Ees is followed by myocardial structural changes (hypertrophy and fibrosis), leading to more marked elevation of diastolic elastance in comparison with HFrEF, which can easily precipitate pulmonary congestion due to an abrupt increase of LV end-diastolic pressure during exercise



**Figure 6:** Relationship between end-systolic elastance and effective arterial elastance in patients with HFpEF. The increase of Ees is overcome by elevation of Ea for preservation of EF. Elevation of ESP [end-systolic pressure] is mediated by adding the reflected pulse pressure to central pressure due to arterial stiffness. Central pulse pressure is increased along with the augmentation index [AI]. LV = left ventricular; SV = stroke volume; LVEDV; left ventricular end-diastolic volume; LVEDP = left ventricular end-diastolic pressure; Ea = effective arterial elastance; Ees = end-systolic elastance; EDPVR = end-diastolic pressure-volume relation; PP = central pulse pressure; AP; augmentation pressure; other abbreviations are as in figure 5 [56,71,79].

[64,81]. Furthermore, arterial stiffening and LV remodeling by activation of the sympathetic nervous system and renin-angiotensin-aldosterone [RAA] system lead to progression of ventricular-arterial coupling disease [82].

### Potential therapeutic strategies targeting abnormal ventricular-arterial stiffening in HFpEF

At present, the use of ARBs, ACEIs, mineralocorticoid receptor antagonists (MRAs), and  $\beta$ -blockers has been established for HFrEF, but not for HFpEF [82–85]. Because the RAA system is activated, elevation of central blood pressure followed by increased arterial stiffness causes ventricular remodeling due to excessive afterload, resulting in progression of heart failure. Therefore, vasodilators (ARBs, ACEIs, and CCBs) are considered to be more effective for reducing the central PP in HFpEF with increased arterial stiffness to manage CHF after decongestion.

### Treatment of chronic CRS for preservation of cardiac and renal function

It is important to use diuretics for decongestion when ADHF or acute exacerbation of CHF occurs regardless of whether a patient has HFpEF and HFrEF. At the same time, renal congestion due to volume overload (i.e., excessive renal afterload) causes WRF [86–88] complicated by elevation of central and renal venous pressures, which should also be treated with diuretics.

Repeated exacerbation and improvement of heart failure leads to residual damage, and cardiac function cannot recover fully to the previous state despite treatment for heart failure. As a result of recurrent episodes, the prognosis of heart failure deteriorates in an additive fashion [89]. Thus, the objective of treating CHF is to maintain cardiac and renal function or delay progression of dysfunction without acute exacerbations.

The therapeutic strategy for CHF, especially HFpEF, involves reducing afterload (i.e., afterload mismatch) to maintain ventricular performance. CCBs and/or ARBs are useful antihypertensive agents that lower central PP by vasodilatation. The increase of proteinuria mediated by elevation of intraglomerular pressure can be treated by using ARBs that dilate the renal efferent arterioles. When high-dose loop diuretics are used continuously to treat CHF without congestion, the RAA system is activated, leading to renal impairment along with exacerbation of CHF by progression of LV remodeling [82]. Reducing the daily dosage/number of doses of loop diuretics by using long-acting agents is important for minimizing RAA system activity. In addition, use of a selective vasopressin-2 receptor antagonist may be favorable for renal protection because it induces water diuresis that does not activate the RAA system [90] while maintaining renal hemodynamics [91]. In the future, investigations should be performed to determine the optimum diuretic dosages and combinations adjusted by the pathophysiologic state of heart failure and renal function. Improving vascular distensibility including vasodilatation by nitric oxygen (NO) is also attractive [57]. However, it is necessary to consider hemodynamic treatment that not only reduces afterload on the heart but also renal afterload during heart failure.

WRF is frequent among patients hospitalized for heart failure [28,92,93]. The prevalence of WRF is comparable in HFpEF and HFrEF, being associated with baseline CKD, the history of hypertension and diabetes, age, and diuretic use [94], which are also underlying lifestyle-related diseases for HFpEF. It seems that HFpEF may arise secondary to the aging process and lifestyle-related diseases associated with arterial stiffening and LV remodeling. Therefore, a strategy for preventing HFpEF (for which there is no established treatment) may involve early prevention of various lifestyle-related diseases associated with aging.

### Conclusions

Clarifying the pathophysiology of ventricular-arterial-renal interactions with advancing age is very important in relation to developing therapeutic strategies for chronic CRS. Elevation of the central systolic blood pressure with an increase of PP promotes LV remodeling, LV hypertrophy, and renal impairment, leading to a worse cardiovascular prognosis compared with elevation of the peripheral systolic blood pressure. Measurement of the central pressure is required clinically to better identify the mechanisms of ventricular-arterial-renal interactions.

The therapeutic strategy for CHF, especially HFpEF, should involve reducing afterload (i.e., afterload mismatch) to maintain ventricular performance. CCBs and/or ARBs are useful antihypertensive agents that lower central PP by vasodilatation. Moreover, regular exercise, proper caloric intake without excessive amounts of salt and management of body weight without obesity from adolescence may be needed to slow the rate of progression of arterial stiffness at an accelerating pace as aging. To establish an effective therapeutic strategy for cardiorenal disease based on central hemodynamics, it is

necessary for the central blood pressure level that prevents cardiovascular target organ damage to be determined by large-scale controlled studies in the future.

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