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.

Renal insufficiency (i.e., an estimated glomerular filtration rate (GFR) < 60.0 mL/min/1.73 m²) 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 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 vasomotor or vasodilatory. 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.
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 antihypertensives on central blood pressure and brachial blood pressure: The effects of various antihypertensives 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), α-blocking agents, and nitrates, reduce the central blood pressure more effectively than the brachial blood pressure [48,49]. On the other hand, β-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 +perindopril and atenolol ±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 [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 ≥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].
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 HFP EF 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 nitrroglycerin improves LV systolic diastolic function in HFP EF patients [48,77].

Is cardiac contractility normal in HFP EF?

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 HFP EF, Ees is ≥Ea and EF is maintained at ≥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 HFP EF 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 HFP EF 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 HFP EF. This process suggests that HFP EF will have a poor prognosis [80]. It has not been identified whether HFP EF 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 5: Comparison of LV morphology and function in patients with HFP EF or HFrEF. 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 HFP EF (solid lines) than in people with normal hearts, and HFrEF patients typically exhibit an end-diastolic pressure-volume relationship shifted upwards and to the left (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' = transmural 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 HFP EF?

Epidemiologic studies have shown that 40% to 50% of patients with heart failure have HFP EF, 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 HFP EF, particularly in elderly women [58]. Patients with HFP EF are assumed to have vascular disease with arterial stiffening as well as cardiac disease, because this condition is often accepted to arise from hypertension. HFP EF derived from arterial stiffening 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, HFP EF should be considered to have a different pathogenesis from HFrEF [54,56,57,72].

In HFP EF, ventricular–arterial disease leads to afterload mismatch, which results in decompenation of LV end–systolic elastance (Ees) for arterial stiffness and augmentation of central PP [73–75].
by adding the re... Figure 6: Relationship between end-systolic elastance and effective arterial elastance in patients with HFpEF. The increase of Ees is overcome by elevation of central pulse pressure (CPP, central PP = central pulse pressure; AP = augmentation pressure; other abbreviations are as in... Ees = end-systolic elastance; EDPVR = end-diastolic pressure-volume relation; PP = peripheral PP; LVEDP = left ventricular end-diastolic pressure; Ea = effective arterial elastance; LV = left ventricular; SV = stroke volume; LVEDV = left ventricular end-diastolic volume; RAA = renin-angiotensin-aldosterone system. The contribution of other abbreviations is described in figure 5 [56,71,79].

Potential therapeutic strategies targeting abnormal ventricular-arterial stiffening in HFpEF

At present, the use of ARBs, ACEIs, mineralocorticoid receptor antagonists (MRA), and β-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.

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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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