

**Review**

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# Role of Pulsatile Hemodynamics in Acute Heart Failure: Implications for Type 1 Cardiorenal Syndrome

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**Key Words**

Acute heart failure syndrome · Cardiorenal syndrome · Vascular aging · Pulsatile hemodynamics

**Abstract**

Heart failure has become a major health problem worldwide with a substantial financial burden mainly from hospitalization due to acute heart failure syndrome (AHFS). A considerable number of patients hospitalized for the treatment of AHFS experience significant worsening of renal function, which is now recognized as type 1 cardiorenal syndrome (CRS) and is associated with worse outcomes. Currently known risk factors for acute CRS in AHFS include obesity, cachexia, hypertension, diabetes, proteinuria, uremic solute retention, anemia, and repeated subclinical acute kidney injury events. Venous renal congestion due to hemodynamic changes also contributes to type 1 CRS. Vascular aging and its aggravated pulsatile hemodynamics have been shown to be involved in the pathogenesis of AHFS. Suboptimal recovery of the perturbation of the pulsatile hemodynamics may predict 6-month post-discharge cardiovascular outcomes in patients hospitalized due to AHFS. Furthermore, on-admission pulsatile hemodynamics may also be helpful to identify and stratify patients with aggravated pulsatile hemodynamics who may benefit from customized therapy. There are close interplays and feedback loops between heart and kidney dysfunction. Increased arterial stiffness accelerates pulse wave velocity and causes an earlier return of the reflected wave, resulting in higher systolic, lower diastolic, and higher pulse pressure in the central aorta and renal arteries. Increased pulsatile hemodynamics have been associated with deterioration of renal function in subjects with a high coronary risk and patients with hypertension or chronic kidney disease. Thus, there is a potential role of vascular aging/pulsatile hemodynamics in the pathophysiological pathways of acute CRS in AHFS.

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## Introduction

Heart failure (HF) affects over 5 million Americans and 15 million Europeans and is a major health problem worldwide [1, 2]. The cost in the United States is over USD 34 billion per year, mainly related to hospitalizations, with similar financial burdens for many European countries [2, 3]. The incidence of HF increases sharply with age, and survival is dismal following the development of HF [4]. Optimal treatment of this disabling and fatal condition may require functional characterization of the failed left ventricle (LV) and its interaction with the arterial system [5].

Over the past decades, it has been demonstrated that there are close interplays and feedback loops between heart and kidney dysfunction. The kidneys are recognized as one of the organs that receive abundant blood supply. As much as 20% of cardiac output constitutes the renal blood flow, >90% of which is distributed to the renal cortex to maintain a high and stable glomerular filtration rate (GFR). There are efficient mechanisms of autoregulation in the cortex so that renal blood flow and GFR remain constant in the face of large variations in systemic blood pressure (BP) [6]. However, renal impairment in patients with HF is common and increasingly recognized as an independent risk factor for morbidity and mortality [7]. The Acute Decompensated Heart Failure National Registry (ADHERE), a large database of 105,388 patients with HF requiring hospitalization in the United States, reported that 30% of the patients had an additional diagnosis consistent with chronic kidney disease (CKD) [8]. Several studies have established that >70% of the patients experience some increase in their creatinine (Cr) level during hospitalization for HF, with approximately 20–30% of HF patients experiencing an increase of >0.3 mg/dl [9, 10]. Any change in Cr has been shown to be associated with longer length of stay, increased costs, and increased short-term and long-term mortality [9–11]. However, the degree of Cr rise during the treatment of acute heart failure syndrome (AHFS), defined as new-onset or gradually or rapidly worsening HF signs and symptoms requiring urgent therapy [12], has a highly variable effect on mortality that is dependent on the population studied [13, 14].

## Heart Failure and Vascular Aging

In subjects without HF, arterial load is increased among those with hypertension and is matched by increased end-systolic LV stiffness [15]. Increased end-systolic LV stiffness may be mediated by enhanced myocardial contractility or processes that increase passive myocardial stiffness, the latter may be responsible for the progression to preserved ejection fraction (EF) HF [15]. In patients with HF and impaired LV contractility, the ventriculoarterial coupling describes the efficiency of mechanical energetic transfer from the heart to the arteries [16]. Failure of an LV invariably generates reduced mechanical energy, and the efficiency of the transfer of the limited energy depends critically on whether or not the arterial tree is optimally adjusted to reduce loadings from its various segments. On the other hand, the ventriculoarterial coupling implies that afterloads generated from the various anatomical or physiological segments of the arterial tree may have an impact on the various components of the mechanical function of the failed LV during systole or diastole and may thus be involved in the deterioration of and decompensation into AHFS requiring hospitalization.

## Acute Heart Failure Syndrome and Vascular Aging

Over the past two decades, there have been significant advances in the treatment of chronic reduced EF HF with the application of drugs blocking the major neurohormonal responses to the initial injury as well as of cardiac devices such as biventricular pacing rectifying the abnormal conduction and contraction in a failed LV. However, HF remains associated with a persistently high mortality and morbidity. The post-discharge mortality and re-hospitalization rates for AHFS reach 10–20 and 20–30%, respectively, within 3–6 months [17, 18]. We have also shown that about one third of the patients ever been admitted for AHFS would have post-discharge adverse events within 6 months [19]. While the majority of the patients appear to respond well to initial therapies consisting of loop diuretics and vasoactive agents, the management of AHFS is challenging given the heterogeneity of the patient population [12, 17, 18], absence of a universally accepted definition, incomplete understanding of its pathophysiology, and lack of robust evidence-based guidelines. Furthermore, the hospitalization for AHFS per se is one of the most important predictors for post-discharge mortality and readmission in patients with chronic HF [20, 21].

Coronary artery disease (CAD), hypertension, valvular heart disease, and/or atrial fibrillation, as well as noncardiac conditions such as renal dysfunction, diabetes, anemia, and medications (for example, nonsteroidal anti-inflammatory drugs and/or glitazones) may contribute to the occurrence of AHFS [2, 12]. Early vascular aging, a well-known cardiovascular risk factor, usually manifests as increased arterial stiffness, wave reflection phenomenon, central BP, carotid intima-media thickness, and endothelial dysfunction [22]. Aortic pulse wave velocity (PWV) is the well-acknowledged gold standard measurement of aortic stiffness associated with cardiovascular mortality and morbidity in patients with hypertension or diabetes and in the elderly [23–25]. In addition, the wave reflection phenomenon and the local assessments of arterial stiffness such as distensibility, compliance, elastic modulus, and  $\beta$  stiffness index may also provide prognostic information. In brief, vascular aging impairs cardiac function through aggravated pulsatile hemodynamics and is associated with the development and the progression of HF [19, 26].

We have investigated the interval changes of pulsatile hemodynamics in patients hospitalized for AHFS [19]. We found that pulsatile hemodynamics result mainly from arterial stiffening and the wave reflection phenomenon, and both may be involved in the pathogenesis of AHFS. Suboptimal recovery of pulsatile hemodynamics may predict 6-month post-discharge cardiovascular outcomes in patients hospitalized for AHFS. While pre- or post-discharge pulsatile hemodynamics indicate the completeness of treatment for AHFS, on-admission pulsatile hemodynamics may also be helpful to identify and stratify patients with aggravated pulsatile hemodynamics who may benefit from customized therapies. Our further work have disclosed that on-admission measures of wave reflection intensity, including carotid augmented pressure,  $P_b$  (amplitude of the backward pressure from a decomposed carotid pressure wave), and carotid pulse pressure (PP), may be useful for predicting long-term outcomes in AHFS patients with either systolic HF or preserved EF HF [27]. The results support a major role of vascular aging/pulsatile hemodynamics, increased wave reflections in particular, in the pathogenesis of AHFS [27].

## Cardiorenal Syndrome

The phenomenon that HF is accompanied by renal failure is termed the cardiorenal syndrome (CRS) [28]. CRS has become a universal clinical challenge, implying both the development and worsening of renal insufficiency secondary to HF as well as harmful effects of

**Table 1.** Definitions of CRS subtypes

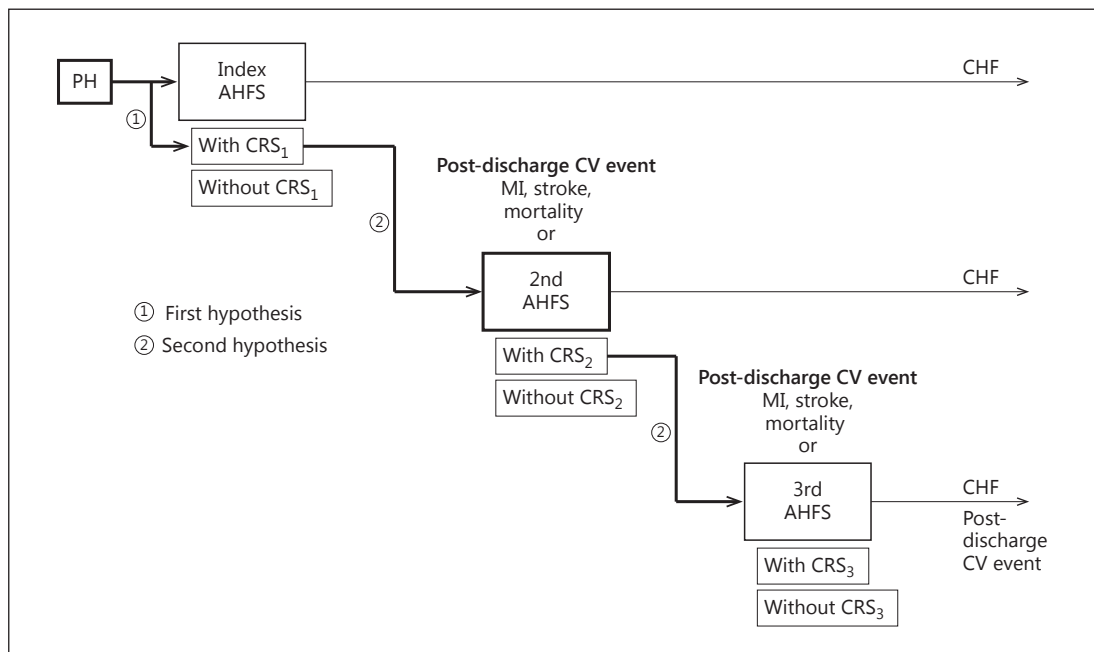
Type 1	Acute decompensated HF that leads to acute kidney injury
Type 2	Chronic HF that leads to chronic kidney disease
Type 3	Acute kidney injury that leads to acute cardiac dysfunction such as arrhythmia or HF
Type 4	Primary CKD contributes to cardiac dysfunction
Type 5	Secondary CRS, combined heart and kidney dysfunction due to systemic disorders such as sepsis and systemic lupus erythematosus

impaired renal function on the cardiovascular system [28]. CRS has recently been classified into five subtypes depending on the etiological and chronological interactions between cardiac and renal dysfunction (table 1) [28]. The mechanisms underlying CRS are multifactorial, including hemodynamic alterations, neurohormonal effects, and inflammation [29]. However, despite the increased awareness of CRS, further elucidation of its mechanisms and appropriate treatment approaches are clearly warranted. A substantial number of patients hospitalized for the treatment of AHFS experience significant worsening of renal function, which is associated with worse outcomes [29–31]. It remains unclear whether worsening renal function specifically contributes to poor outcomes or whether it is merely a marker of advanced cardiac and renal dysfunction [32].

CRS in AHFS is a particularly difficult condition to manage as treatment to relieve congestive symptoms of HF may lead to a further decline in renal function, which is a major independent predictor of long-term cardiac morbidity [30]. Several treatment strategies for decongestion in AHFS patients who develop CRS are currently under investigation, including invasive hemodynamic monitoring to guide therapy, use of continuous diuretic infusions, ultrafiltration, or novel therapies with adenosine or vasopressin receptor antagonists [33]. Surprisingly, in a randomized trial [30] involving patients hospitalized for AHFS, worsened renal function, and persistent congestion, the use of a stepped pharmacological therapy algorithm was superior to a strategy of ultrafiltration for the preservation of renal function at 96 h, with a similar amount of weight loss with the two approaches. Furthermore, ultrafiltration was associated with a higher rate of adverse events. Therefore, the underlying mechanisms of CRS in AHFS are complex and not fully understood [29, 31, 34]. Thus, there is a pressing need to continue the search for better strategies to manage acute CRS based on the new findings of its pathophysiology [34].

### Vascular Aging – The Link between the Heart and Kidneys

BP measured at the central aorta is usually lower than BP measured at the brachial artery due to the progressive amplification of PP along the arterial tree [35]. PP amplification indicates the effectiveness of energy transfer and the augmentation by the locally reflected pressure wave, and, in addition, is an evaluation of arterial compliance [36–38]. Increased arterial stiffness accelerates PWV and causes an earlier return of the reflected wave, resulting in higher systolic BP, lower diastolic BP, and higher PP in the central aorta. Such changes in central hemodynamics would adversely have an impact on renal perfusion [39]. In normal individuals, the amplitude of wave reflection but not aortic PWV may be associated with filtration fraction and urinary albumin-creatinine ratio independently of systemic BP; both are signs of increased glomerular pressure [40]. In patients with a high risk of CAD, plasma



**Fig. 1.** Hypothetical framework for the role of pulsatile hemodynamics (PH) in the pathogenesis of CRS in patients hospitalized for AHFS. The first hypothesis states that the perturbation of PH causes both AHFS and CRS. The second hypothesis states that the development of type 1 CRS accelerates the occurrence of post-discharge cardiovascular (CV) events, including myocardial infarction (MI), stroke, mortality, and rehospitalization due to AHFS. Arrows point from cause to effect. CHF = Chronic heart failure.

Cr was significantly related to PP in the ascending aorta and the abdominal aorta on the level of renal arteries, and to aortic PWV [41]. In a cohort of 133 patients with CKD stages 3 and 4, aortic PWV was independently associated with the rate of change in renal function [42]. In another cohort of 145 CKD stage 3–5 patients, an independent association between brachial-ankle PWV and renal function decline and progression to commencement of dialysis or death was shown [43]. In addition to brachial-ankle PWV, LVEF was also negatively associated with the GFR slope, and higher brachial-ankle PWV and LVEF <40% were independently associated with progression to the renal end point [44]. Thus, central pulsatile hemodynamics may be a common basis for the associations among CKD, stroke, and CAD [39]. The underlying mechanism linking aortic stiffening and renal microvascular damage has been recently suggested by Hashimoto and Ito [36, 45]. In 133 patients with hypertension, central PP was closely related to changes in renal hemodynamics (resistive index of renal segmental artery) and urinary albumin excretion. It is likely that increased central PP causes renal microvascular damage through altered renal hemodynamics resulting from increased peripheral resistance and/or increased flow pulsation [36, 45].

### Perspective: Potential Role of Pulsatile Hemodynamics in Type 1 Cardiorenal Syndrome

Based on the current understanding of the risk factors for acute CRS in AHFS, these include obesity, cachexia, hypertension, diabetes, proteinuria, uremic solute retention, anemia, and repeated subclinical acute kidney injury events [29]. In the hospitalized patient,

hemodynamic changes leading to venous renal congestion, neurohormonal activation, hypothalamic-pituitary stress reaction, inflammation and immune cell signaling, systemic endotoxemic exposure from the gut, superimposed infection, and iatrogenesis all may contribute to acute CRS [29]. However, the potential role of vascular aging/pulsatile hemodynamics in the pathophysiological pathways of acute CRS in AHFS has not been explored [29].

In perspective, we propose that vascular aging/pulsatile hemodynamics may be a major independent determinant of the deterioration of renal function and the development of CRS in patients with AHFS. We further hypothesize that CRS independently accelerates the clinical aggravation and development of post-discharge adverse events. The hypothetical framework is shown in figure 1. Future studies are definitely needed to prove the concept and expand our armament to target type 1 CRS.

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### Disclosure Statement

The authors have no conflicts of interest to declared.

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