

# Diuretics as pathogenetic treatment for heart failure

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**Abstract:** Increased intracardiac filling pressure or congestion causes symptoms and leads to hospital admissions in patients with heart failure, regardless of their systolic function. A history of hospital admission, in turn, predicts further hospitalizations and morbidity, and a higher number of hospitalizations determine higher mortality. Congestion is therefore the driving force of the natural history of heart failure. Congestion is the syndrome shared by heart failure with preserved and reduced systolic function. These two conditions have almost identical morbidity, mortality, and survival because the outcomes are driven by congestion. A small difference in favor of heart failure with preserved systolic function comes from decreased ejection fraction and left ventricular remodeling which is only present in heart failure with decreased systolic function. The magnitude of this difference reflects the contribution of decreased systolic function and ventricular remodeling to the progression of heart failure. The only treatment available for congestion is fluid removal via diuretics, ultrafiltration, or dialysis. It is the only treatment that works equally well for heart failure with reduced and preserved systolic function because it affects congestion, the main pathogenetic feature of the disease. Diuretics are pathogenetic therapy for heart failure.

**Keywords:** heart failure, diuretics, congestion, systolic function, diastolic function, ejection fraction

*To the memory of Kenneth Lee Baughman*

## Introduction

In the classic paradigm of heart failure, the downward spiral of disease progression starts with decreased cardiac output, resulting in kidney hypoperfusion with the activation of the renin–angiotensin–aldosterone axis, retention of sodium and water, stimulation of the sympathetic nervous system, vasoconstriction, and further hypoperfusion. This concept works well if an initial offense such as acute myocardial infarction, myocarditis, or idiopathic cardiomyopathy jeopardizes myocardial contractility. However, these cases do not represent the whole spectrum of heart failure. In fact, they represent only about half of all heart failure.

About one third to one half of heart failure patients have normal systolic function on the basis of left ventricular ejection fraction. Patients with heart failure with preserved systolic function do not have decreased cardiac output, and so do not fit into the classic paradigm of heart failure. One hypothesis explaining the origin of heart failure in these subsets of patients is based on the concept of decreased “effective blood flow”.<sup>1</sup> However, several studies by Maurer et al provided the evidence that blood flow is normal or increased in a substantial number of patients with heart failure with preserved systolic function.<sup>2,3</sup>

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Multiple studies have compared the natural course, morbidity, and mortality in heart failure with preserved and reduced systolic function. Patients with preserved ejection fraction are usually older, more frequently women, have less coronary disease and myocardial infarction, and have more atrial fibrillation and other comorbidities. They have higher systolic blood pressures and pulse pressures,<sup>4</sup> as well as a higher prevalence of left ventricular hypertrophy, aortic valve disease, and anemia.<sup>5</sup>

Despite multiple dissimilarities in patient populations, the reported mortality is either similar<sup>5-11</sup> or somewhat better in those with preserved systolic function.<sup>12,13</sup> In fact, the survival curves are identical in some studies, indicating that it is basically the same condition with the same natural course.

Symptoms in heart failure with preserved and reduced systolic function are similar, physical examination is also similar, and peak oxygen consumption ( $VO_2$ ) and the slope of the ventilation/carbon dioxide production ratio on the cardiopulmonary stress test is indistinguishable.<sup>14</sup> Even the financial burden is similar, in that patients with heart failure and normal ejection fraction consume as many health care resources as those with reduced ejection fraction.<sup>15</sup>

These observations can be explained only if we accept that the two groups of patients share a common syndrome which determines the course and prognosis to a much greater extent than all the dissimilarities, including systolic function. All the evidence indicates that this syndrome is congestion.

## Congestion causes heart failure symptoms regardless of ejection fraction

According to the Acute Decompensated Heart Failure National Registry (ADHERE), most patients admitted for heart failure are “wet” or congested, with dyspnea, rales, edema, radiological signs of fluid overload, or a combination of these features.<sup>16</sup> Current technologies providing continuous hemodynamic monitoring support these clinical observations with hard data from the measured parameters.

During heart failure exacerbations, right ventricular pressures increase by about 25%, starting several days prior to clinical deterioration. Heart failure management guided by this information resulted in reduction of hospitalizations, which dropped from 1.08 per patient-year to 0.47 per patient-year (57% reduction,  $P < 0.01$ ).<sup>17</sup> Similar hemodynamic changes were reported from the Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure trial (COMPASS-HF), in which

New York Heart Association (NYHA) III or IV patients were monitored by a Chronicle<sup>®</sup> implantable cardioverter device. In patients with normal and decreased systolic function, which differed according to multiple structural and hemodynamic parameters, the mechanism of exacerbation was exactly the same, ie, intracardiac pressures increased significantly before clinically evident volume overload episodes, and the percentage of pressure change from baseline was similar.<sup>18</sup> Furthermore, successful treatment of acute decompensated heart failure, regardless of systolic function, was associated with a decrease in diastolic pressures.<sup>19</sup> In summary, congestion is a syndrome shared by heart failure with normal and reduced systolic function. Congestion not only causes symptoms, but it also worsens the prognosis.

## Congestion causes pulmonary hypertension and cardiorenal syndrome

Two syndromes, ie, pulmonary hypertension and cardiorenal syndrome, are consistently associated with a poor prognosis in heart failure. Increased pulmonary pressure is linked to increased short-term and long-term mortality in heart failure. A 5-mmHg increase in right ventricular systolic pressure results in a 9% increase in mortality in heart failure with both normal and reduced ejection fraction.<sup>20</sup> Increased right ventricular systolic pressure is a stronger predictor of death than left ventricular ejection fraction.<sup>21</sup>

Several studies have indicated that the severity of diastolic rather than systolic cardiac dysfunction determines the degree of elevation of pulmonary arterial pressure. In individuals with normal ejection fraction and unknown heart failure status, mean pulmonary artery pressure was shown to be  $31.1 \pm 6$  mmHg in normal diastolic function,  $35.6 \pm 10.2$  mmHg in Grade 1 diastolic dysfunction (impaired relaxation),  $38.9 \pm 10.6$  mmHg in Grade 2 (pseudonormal), and  $55.1 \pm 11.4$  mmHg ( $P < 0.001$ ) in Grade 3 (restrictive pattern).<sup>22</sup> In untreated patients with dilated cardiomyopathy, the E wave deceleration rate and the degree of mitral regurgitation were the strongest independent predictors of pulmonary hypertension, while ejection fraction was only a minor contributor. The reversal of pulmonary hypertension after treatment with an angiotensin-converting enzyme inhibitor and diuretics occurred only in patients whose diastolic left ventricular function improved from restrictive or pseudonormal to impaired relaxation pattern.<sup>23</sup>

In left ventricular systolic dysfunction, pulmonary artery systolic pressure was elevated on echocardiography in most patients, ranging from 23 to 87 mmHg, and correlated with

parameters of diastolic dysfunction. Ejection fraction was not an independent predictor of pulmonary artery pressure.<sup>24</sup>

Cardiorenal syndrome also worsens the prognosis in heart failure. In ADHERE, 60% of patients had moderate or severe renal insufficiency. Mortality rates, length of hospitalization, need for mechanical ventilation, intensive care, and cardiopulmonary resuscitation all increase with the degree of baseline renal dysfunction.<sup>25</sup>

Mortality associated with renal dysfunction was higher in those with heart failure with normal rather than reduced systolic function.<sup>26</sup> The presence of at least moderate tricuspid regurgitation was associated with a lower glomerular filtration rate in heart failure, indicating that elevated renal venous pressure plays a role in cardiorenal syndrome.<sup>27</sup> In the Cleveland Clinic cohort, heart failure patients with worsening renal function had higher central venous pressure, both upon admission and after intensive medical therapy. Furthermore, the ability of central venous pressure to predict renal dysfunction was consistent across the spectrum of systemic blood pressure, pulmonary capillary wedge pressure, cardiac index, and estimated glomerular filtration rates.<sup>28</sup>

In summary, two conditions, ie, pulmonary hypertension and renal dysfunction, worsen the clinical course and prognosis in heart failure, and develop as a result of elevated filling pressures, or congestion.

## Congestion worsens the course and prognosis in heart failure

Hospitalizations for heart failure occur due to volume overload or congestion. It was recently demonstrated that the risk of further hospitalizations and death increases progressively and independently with each episode of heart failure exacerbation, and the total number of heart failure hospitalizations is a strong predictor of mortality.<sup>29,30</sup> When pulmonary hypertension secondary to volume overload is present in chronic hemodialysis patients, it predicts high mortality.<sup>31</sup> Any sign of congestion adds to mortality. Mortality rates almost double from no signs to three or more signs of congestion (11% versus 20%, respectively;  $P < 0.0001$ ).<sup>32</sup>

The relationship between congestion and systolic function may be more complex than is currently thought. Myocardium easily accumulates interstitial fluid, and the resulting myocardial edema compromises contractility.<sup>33</sup> Extrapolating these findings, one can conclude that congestion, regardless of its origin, can result in decreased systolic function.

Congestion can facilitate electric instability of the heart. Elevated brain natriuretic peptide produced by a stretched

cardiac muscle has been associated with sudden cardiac death in hypervolemic patients.<sup>34</sup> Additional confirmation of the profound pathophysiological role of congestion can also be found in echocardiography.

## Severity of congestion reflected in diastolic but not systolic dysfunction

In daily clinical practice, left ventricular systolic function is often estimated using ejection fraction, yet little evidence supports the correlation of ejection fraction with actual hemodynamic parameters. In acute heart failure patients, only a weak correlation was found between cardiac index and ejection fraction ( $r = 0.25$ ;  $P = 0.0003$ ), and no correlation existed between ejection fraction and wedge pressure.<sup>35</sup> In another study, measurements of left ventricular systolic performance, ie, stroke work, ejection fraction, and contractility by  $dP/dt$ , did not differ significantly between patients with heart failure with normal systolic function and normal controls. The authors concluded that the underlying pathophysiology causing symptoms and signs of heart failure did not reflect abnormalities in left ventricular systolic properties, but more likely abnormalities in diastolic function, which was the predominant and necessary factor for the occurrence of heart failure in these patients.<sup>36</sup>

Unlike ejection fraction, diastolic dysfunction on echocardiography is closely correlated with intracardiac filling pressures. Abnormal echocardiographic diastolic parameters, especially an elevated  $E/e'$  ratio (ratio of peak velocity of early diastolic inflow to early diastolic mitral annular velocity), indicate elevated filling pressures.<sup>37-44</sup> In a large population-based study, patients with heart failure and preserved systolic function in Olmsted County, Minnesota, had markedly different left ventricular end-diastolic pressure and diastolic echo parameters, especially  $E/e'$ , compared with both normal controls and hypertensive patients, whereas cardiac index was similar in all three cohorts.<sup>45</sup>

A high  $E/e'$  ratio reflects elevated intracardiac pressures, regardless of etiology of heart failure and ejection fraction. Elevated filling pressures in healthy hearts produce a restrictive pattern on echocardiography. When intravenous fluids were given to healthy dogs, their echoes demonstrated restrictive left ventricular filling.<sup>46</sup>

Interestingly, in patients with very advanced systolic heart failure, the correlation between  $E/e'$  and wedge pressure becomes weaker. In a recent series from Cleveland Clinic, no correlation was found between  $E/e'$  ratio and wedge pressure in patients with larger left ventricular volumes, severely reduced cardiac indexes, or biventricular

pacemakers.<sup>47</sup> This likely means that congestion becomes less important than low cardiac output in very advanced heart failure.

## Diastolic dysfunction predicts poor prognosis regardless of systolic function

Diastolic dysfunction predicts the prognosis in heart failure patients with both normal and decreased ejection fraction. In systolic heart failure, the primary endpoint of death, transplantation, or heart failure hospitalization was independently predicted by parameters of diastolic function, including shorter deceleration time, a lower ratio of pulmonary vein systolic to diastolic velocity, and increased E/e' levels.<sup>48,49</sup> In another study, the mitral E/e' ratio ( $P < 0.001$ ) and the Tei index (index of myocardial performance incorporating both systolic and diastolic time) but not the ejection fraction, were the only independent predictors of death or heart failure admission ( $P = 0.019$ ).<sup>50</sup> Within a cohort with severely decreased ejection fraction  $\leq 30\%$ , diastolic indexes of mitral inflow significantly predicted poor outcomes, while ejection fraction did not.<sup>51</sup> A restrictive filling pattern was the only independent predictor of death or appropriate defibrillator shock.<sup>52</sup> In pooled data from 3540 patients with heart failure across the entire spectrum of ejection fraction, a restrictive filling pattern was associated with a twofold increase in the risk of death, and was independent of ejection fraction, class, and age.<sup>53</sup> Diastolic dysfunction is also strongly and inversely associated with exercise capacity. Patients with a high E/e' have reduced exercise tolerance.<sup>54</sup>

Different studies have demonstrated that elevation of brain natriuretic peptide either correlates better with diastolic dysfunction than with systolic dysfunction, or correlates only with diastolic dysfunction, and does not correlate with ejection fraction at all.<sup>55</sup>

In summary, advanced diastolic dysfunction reflects the severity of congestion, and predicts morbidity and mortality in heart failure patients regardless of ejection fraction.

## Heart failure exists without systolic dysfunction, but not without diastolic dysfunction

Although approximately 30%–50% of patients with heart failure have normal systolic function, hardly any heart failure patients have normal diastolic function. In a series of 206 patients with clinical heart failure, diastolic dysfunction by echocardiography was present in  $>90\%$ , regardless of

ejection fraction.<sup>55</sup> In another series of 126 heart failure patients with ejection fraction  $<35\%$ , none had normal diastolic function.<sup>56</sup>

In the Olmstead County heart failure cohort, only 10% of patients with preserved ejection fraction and 5% of those with reduced ejection fraction had normal diastolic function.<sup>6</sup> In another study that enrolled randomly selected residents rather than heart failure patients, only one in 45 participants with a validated diagnosis of heart failure had normal diastolic function. In participants with an ejection fraction  $<50\%$ , only one fifth (20.5%) had normal diastolic function.<sup>57</sup>

According to the Mayo Clinic algorithm for diagnosing diastolic dysfunction,<sup>58</sup> ejection fraction  $<50\%$  is not compatible with normal diastolic function. If the E/A ratio is normal, it immediately places the patient in the “pseudonormal” range and presumes elevated filling pressures.

In summary, while systolic dysfunction may or may not be present in heart failure, diastolic dysfunction is universal. It reflects the presence of congestion which is common to heart failure with any degree of systolic function.

## Heart failure with reduced and preserved ejection fraction

Comparison of heart failure with preserved and reduced systolic function demonstrates that disease progression in these two cohorts is strikingly similar. A slight difference in the natural course and prognosis in favor of preserved systolic function has at least two explanations. The first one has to do with patient selection. In all the relevant published studies, patients were diagnosed as having heart failure with preserved systolic function according to clinical, most commonly the Framingham, criteria. Left ventricular filling pressure was neither measured by catheterization nor estimated by diastolic dysfunction on echocardiography. This could result in overdiagnosis of heart failure. In a study by Caruana et al,<sup>59</sup> 102 of 109 patients with normal ejection fraction diagnosed with heart failure by their internists had other conditions, including obesity, chronic obstructive pulmonary disease, and coronary artery disease, that could explain their symptoms, and only seven had heart failure. It is also possible that some cohorts representing heart failure with preserved systolic function are contaminated by patients having conditions other than heart failure. These patients may be partially responsible for slightly more favorable outcomes.

However, there is another factor determining the difference. Decreased ejection fraction and left ventricular remodeling are present in heart failure with reduced systolic function, but

are absent in preserved systolic function. Decreased ejection fraction and left ventricular remodeling creates an excess mortality in heart failure with reduced systolic function. It adds electrical instability, leading to a higher rate of sudden cardiac death, in this subset of patients. Sudden cardiac death occurs more frequently in those with decreased ejection fraction than in those with normal ejection fraction (21% versus 16%, respectively),<sup>60</sup> or even versus 2% as per the Duke Databank for Cardiovascular Disease.<sup>61</sup>

The ultimate treatment for heart failure with reduced systolic function is a left ventricular assist device or heart transplantation, which is practically never utilized in heart failure with normal systolic function, except for specific cases of restrictive or hypertrophic obstructive cardiomyopathy. It is likely that, at some point in time, left ventricular dilatation and remodeling reaches a critical limit and becomes the driving force of the downward spiral of terminal heart failure. The angiotensin-converting enzyme inhibitors and beta-blockers work in systolic heart failure because they slow down and partially reverse left ventricular remodeling. Without such remodeling, as in heart failure with preserved systolic function, they do not have a substrate to work on. All clinical trials testing drugs used successfully in reduced ejection fraction failed to demonstrate their benefit in the subset with preserved systolic function. The difference in morbidity and mortality between heart failure with preserved and reduced ejection fraction measures the contribution of the low output syndrome, together with electric instability created by left ventricular remodeling, to the natural course of heart failure.

Advances in heart failure treatment from 1991 to 2001 have led to better survival in patients with reduced, but not preserved, systolic function. The one-year survival rate trended toward worsening in the preserved systolic function group, but improved in the group with depressed ejection fraction (from 87.7% to 81.0% and from 76% to 84%, respectively).<sup>62</sup> This occurred because, while new treatment modalities were implemented for left ventricular remodeling and sudden cardiac death (features unique to heart failure with decreased systolic function), treatment for congestion remained the same, ie, with diuretics.

## Diuretics are the universal treatment for heart failure

If the common denominator of heart failure is decreased output, the mainstay of heart failure treatment should be inotropic agents. However, the role of inotropes in heart

failure is limited. They are mostly used at the extreme of the heart failure spectrum, ie, those with severely impaired systolic function.

Because the common feature of heart failure is congestion, the mainstay of heart failure treatment is decongestion, or diuretics. In inpatient or outpatient settings and in systolic or diastolic heart failure, diuretics are invariably the top prescribed drug. In ADHERE, diuretics were used in 64.8% and 65.5% on hospital admission, 67% and 78.8% during hospitalization, and 79.5% and 83.7% on discharge in patients with heart failure with preserved and reduced ejection fraction, respectively.<sup>63</sup>

Several studies have attempted to randomize heart failure patients to diuretics or no diuretics, primarily through diuretic withdrawal in patients with already established treatment for heart failure. Richardson et al,<sup>64</sup> Cowley et al,<sup>65</sup> van Kraaij et al,<sup>66</sup> Mathur et al,<sup>67</sup> Andrews et al,<sup>68</sup> and Grinstead et al<sup>69</sup> have all demonstrated that patients with heart failure deteriorate so quickly after discontinuation of diuretics that they have to be reinstated on diuretic therapy within weeks.

Richardson et al<sup>64</sup> substituted captopril for furosemide in symptomatic heart failure in a double-blind, randomized study. Of 14 patients taken off diuretics, four (28.6%) developed pulmonary edema or severe dyspnea and required immediate reinstatement of furosemide within eight weeks. In another study, patients who were on diuretics for heart failure could only tolerate withdrawal of this medication for a median duration of six weeks.<sup>66</sup> Mathur et al<sup>67</sup> conducted a randomized, double-blind, crossover, placebo-controlled trial lasting 16 weeks and found that none of the heart failure patients included could stay off diuretics. Grinstead et al<sup>69</sup> demonstrated that 20 (71%) of 41 stable heart failure patients taken off diuretics and randomized to lisinopril or placebo had to be restarted on diuretics due to worsening congestion within 12 weeks (median 15 days), with no difference between the lisinopril and placebo arms of the study. Finally, a meta-analysis of loop diuretics in heart failure found a statistically significant survival benefit of these drugs, even though many studies included in this analysis did not enroll patients with symptomatic heart failure, as demonstrated in a previous review.<sup>70</sup>

Several studies, most of which were retrospective, demonstrated that use of diuretics or higher doses of diuretics are associated with a poorer prognosis in general and higher mortality in particular, even after adjustments for multiple comorbidities.<sup>71-73</sup> In none of these studies were patients randomized to receive loop diuretics versus no diuretics or

placebo. Loop diuretics were prescribed by the physician guided by symptoms, ie, congestion. Simple adjustment for NYHA class cannot correct this selection bias because NYHA classification takes into account primarily signs of left ventricular dysfunction (dyspnea) but does not include edema, ascites, and anasarca, which reflect primarily right ventricular failure. Meanwhile, diuretics are prescribed for both conditions. Therefore, the diuretic dose reflects the severity of heart failure better than all other comorbidities taken together because the empiric dose of loop diuretics is matched to the severity of congestion. In the absence of directly measured intracardiac pressures, the dose of loop diuretics is the best measure of congestion we have. The higher the requirement for diuretics, the higher is the morbidity and mortality. No large prospective, randomized, placebo-controlled trials in heart failure have justified the use of diuretics. Such trials cannot be conducted because patients with heart failure do not survive without diuretics. A recent subanalysis of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness study (ESCAPE) demonstrated reduced mortality in patients with systolic heart failure undergoing more aggressive diuresis, even though this was achieved at the cost of worsening renal function.<sup>74</sup>

## Conclusion

Heart failure as a syndrome develops when there is an elevation in left ventricular filling pressure. Clinically it presents as congestion, regardless of etiology and systolic function. Congestion is a common denominator shared by all patients with heart failure. It can be identified invasively by direct measurement of intracardiac pressures, or noninvasively by signs of diastolic dysfunction on echocardiography. The severity of congestion determines symptoms, morbidity, natural course of the disease, and mortality in heart failure, as well as major complications, including pulmonary hypertension and cardiorenal syndrome. The best available treatment for congestion is diuretics which work equally well in heart failure with preserved and reduced systolic function.

Many patients with heart failure develop elevated left ventricular filling pressures and congestion as a result of decreased systolic function. Their natural course is somewhat worse because, in addition to congestion, they have left ventricular remodeling and decreased cardiac output, as well as electrical instability, resulting in ventricular tachycardia, ventricular fibrillation, and sudden cardiac death. Besides diuretics, they can benefit from other treatments either

reversing left ventricular remodeling or preventing sudden cardiac death, including angiotensin-converting enzyme inhibitors, beta-blockers, aldosterone antagonists, cardiac resynchronization therapy, defibrillators, left ventricular assist devices, and heart transplantation.

Further advances in heart failure treatment should be expected from better monitoring of intracardiac pressures and more accurate and timely decongestion. This will improve the clinical course of all heart failure patients with normal or decreased ejection fraction. It will also result in less severe complications, eg, cardiorenal syndrome and pulmonary hypertension, which could further improve survival. Clinical trials targeting these syndromes should not focus only on patients with preserved or reduced systolic function but rather on all heart failure population.

## Disclosure

The author reports no conflict of interest in this work.

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