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Pathophysiology and Precision Medicine Guided Treatment of Congestive Heart Failure

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Abstract

This paper is based on retrospective and observational data from the author's 14 years of practice as a general cardiologist in a rural community hospital, which reported 62 cases with initial encounters as inpatients and followed as outpatients over 14 years, which applied the knowledge of physiology and pathophysiology to everyday practice in treating congestive heart failure (CHF). The 62 patients were reported to have had a normal life with a significantly lower readmission rate [1]. This paper illustrates the application of the author's understanding of the physiology and pathophysiology of cardiovascular and renal systems to the treatment of CHF patients. It intends to arouse attention in cardiology regarding our current treatment of CHF patients. It is hoped that this paper will help us improve the quality of life of millions of patients suffering from CHF and lower admission and readmission rates of CHF patients and the cost of CHF treatment by tens of billions of dollars annually.

Keywords

Congestive Heart Failure, Beta-Blocker, Diuretics

Congestive heart failure (CHF) is a medical condition in which the cardiovascular system of the body is unable to meet the metabolic needs of the human body for everyday activities. It is a cardiovascular system dysfunction resulting in abnormal fluid metabolism and related symptoms, such as pulmonary and lower extremity edema. It causes significant morbidity and mortality of the patient and excessive socioeconomic burden. There are 8 million patients diagnosed with CHF, and 15% of them require inpatient care in US every year. 15% of the patient population requiring inpatient care is a highly vulnerable population and has poor prognosis,

with nearly 1 in 4 readmitted within 30 days of discharge. Approximately half are readmitted within six months [2]-[4]. By 2030, US heart failure costs are expected to be at least 70 billion dollars per year, with 75% - 80% (52.5 - 56 billion dollars) of the direct costs for heart failure attributable to inpatient hospital stays [2] [5]-[7] without counting the indirect costs. If we decrease the admission rate by 50%, there will be more than 25 billion dollars in yearly savings in direct health care costs. We could even do better [1].

Improved treatment of CHF is essential for improving patients' quality of life and lowering healthcare costs. Our focus should be on the 15% of patients requiring inpatient care and preventing 75% of outpatients from progressing into the inpatient population. Effective treatment of CHF starts with a better understanding of the cardiovascular system's physiology and pathophysiology, which we learned in the medical schools. We need to focus on correcting cardiovascular system dysfunction instead of treating the fluid overload and related symptoms.

The symptom of CHF is thought to be due to fluid overload resulting in lower extremity and pulmonary edema. Therefore, treatment of CHF largely centers on achieving and maintaining euvolemia by using diuretics, which has been the cornerstone for treating CHF since the 1960s and is still recommended by professional associations [8] [9]. By promoting diuresis, diuretics aim to relieve these symptoms and prevent CHF exacerbations. 70% - 80% of CHF patients are on diuretics, which has been the first-line medication for the treatment of CHF for many years. However, while diuretics effectively reduce fluid overload and related symptoms, they do not address the root cause of CHF, which is dysfunction of the cardiovascular system, leading to frequent fluid overload resulting in hospital admission and readmission. Instead, overuse of diuretics may increase the mortality and hospitalization of CHF patients [10] [11]. Understanding the interaction between diuretics and the cardiovascular-renal system is essential to grasp their role in CHF management.

The CHF has been divided into two groups: congestive heart failure with reduced left ventricular systolic function (HFrEF)and congestive heart failure with preserved left ventricular systolic function (HFpEF). The exacerbation of both types of CHF presents similar clinical symptoms: shortness of breath, pulmonary edema, and lower extremity edema. It has been thought that HFrLV is mainly due to systolic dysfunction and HFpEF due to diastolic dysfunction. Their clinical presentations are very similar, which is fluid overload. However, the systolic function in HFpLV is normal and unchanged before and after CHF exacerbation, and the systolic function in HFrLV is decreased at baseline, which is unchanged or even decreased after acute CHF exacerbation with resolution of the symptoms after treatment. It suggests that the systolic function of the left ventricular function is not, at least, the leading cause of CHF exacerbation. The diastolic dysfunction of the left ventricle is the cause, which is why they present with similar symptoms.

The cardiovascular and renal systems work in tandem to regulate the water balance of the human body. The cardiovascular system provides blood flow to the

kidneys, which manages water excretion to maintain homeostasis. This self-regulating system adjusts urine output in response to changes in the fluid status of the human body, preserving adequate blood volume and pressure. However, in CHF patients, this balance becomes delicate. When diuretics are introduced, especially in patients with decreased fluid intake, intravascular volume can be excessively depleted by diuresis, leading to overactivation of the catecholamine system, followed by vasoconstriction, hypertension, increased heart rate, and the wall tension of the left ventricle, which will reduce kidney perfusion and urine output. Increases in heart rate, blood pressure, and wall tension of the left ventricle led to worsening diastolic function. Beyond a certain threshold, the system may decompensate and cause fluid overload followed by pulmonary congestion and peripheral edema. Another cause is excessive fluid intake is another cause, which, with inappropriate diuretics use, is a part of poor fluid management. Tachycardia and poorly controlled hypertension may be responsible for CHF exacerbation as well, although they may be a consequence of over-activation of the catecholamine system as a part of decompensated CHF. Less commonly, myocardial ischemia is another cause.

Chronic use of diuretics is often prescribed to prevent CHF symptoms, which may disturb auto-regulating mechanisms although a new balance of the system may be established. However, when the fluid intake decreases for one reason or another such as decrease in oral intake or diahrrea, diuretics may inadvertently exacerbate CHF by reducing intravascular volume and triggering a compensatory catecholamine release. This response increases blood pressure, heart rate and wall tension of the left ventricle, inducing further diastolic dysfunction and perpetuating the CHF cycle, leading to worsening of symptoms. In this situation, increasing doses of diuretics will further disturb the system and not relieve the symptoms, instead of being followed by admission due to further depletion of intravascular volume. This is a fairly common scenario in everyday outpatient practice. In this situation, the fluid overload is due to a disturbance of the self-regulation of the cardiovascular-renal system and diastolic dysfunction of the left ventricle. This is due to dysfunctional cardiovascular and renal systems not being able to handle the small and continuous fluid through the renal secretion, and this fluid will leak into the third space, resulting in worsening of the lower extremity and pulmonary edema, which will create a clinical picture of fluid overload followed by an increase in diuretics and admission. Therefore, most outpatients should not be on diuretics daily but on PRN for fluid overload based on body weight to avoid excessive fluid accumulation caused by depleting the intravascular volume. Every patient should be on fluid restriction based on their tolerance to fluid. The beta-blocker should be the center for avoiding diastolic dysfunction associated with CHF exacerbation. Blood pressure and heart rate control are also important. This will significantly decrease admission and readmission rates. It has been observed clinically with promising results [1]. It needs to mention the 62 reported cases. They were seen and treated as inpatients at the first encounter and discharged with clinical follow-

up. In 14-year follow-up, there was only one readmission.

Intravenous diuretics are frequently and aggressively administered to patients hospitalized with CHF exacerbations as the first-line treatment, which has been used to achieve euvolemic status. Some patients respond favorably, achieving euvolemia and symptomatic relief before discharge. However, patients with lower cardiovascular reserve may experience a poor response to diuretics, leading to worsening symptoms and kidney function or even dialysis due to the exact mechanism as above. This pattern of diuretic treatment without addressing the underlying cardiac dysfunction due to overreaction catecholamine-associated tachycardia and increased blood pressure often results in prolonged hospitalizations.

The treatment of acute CHF exacerbation will focus on restoring the function of the cardiovascular system and relieving symptoms. The goal of restoring the function of the cardiovascular system is to control the heart rate to about 60 BPM and systolic blood pressure to about 120 mmHg, with urine output more than 600 cc/day with strict fluid restriction. In patients with HFpEF, the diuretics have limited effects. One or two doses of diuretics may be given if patients do not respond to heart rate and blood pressure control. In patients with HFrEF, more diuretics may be indicated since fluid overload may cause further diastolic dysfunction by stretching the LV wall with an increase in wall tension in the combination of rapid heart rate and increase in blood pressure. In HFpEF, the dysfunction of the cardiovascular system is due to the worsened left ventricular diastolic pressure caused by the overreaction of the catecholamine system. Diuretics may further deplete intravascular volume and further activate the catecholamine system. In HFrEF cases, volume overload in the cardiovascular system may also contribute to increased LV diastolic pressure. Diuretics may provide more symptom relief and restore cardiovascular function. All inpatients with CHF should be on fluid restriction and a low-sodium diet. When shortness of breath resolves and urine output is adequate, the patients should be discharged. The lower extremity usually is not an indication to keep patients in the hospital unless it is severe with complications, such as cellulitis.

Euvolemia is frequently used to assess the patient's fluid status in treating CHF. However, euvolemia needs to be further defined. It can be defined as no lower extremity edema, no shortness of breath, and no JVD. It can also be defined as no shortness of breath and restoration of urine output with adequately controlled heart rate and blood pressure, even though the patient still has lower extremity edema which may be called euvolemia of the intravascular space. From a clinical standpoint, the latter could be better used for the assessment of the treatment of CHF. The further removal of the excessive fluid should be achieved by the cardiovascular system. At this point of time, diuresis may disturb the system and cause worsening of CHF symptoms.

Cardiovascular renal syndrome is another term used for CHF patients when they present with CHF and renal dysfunction or worsening of the renal function during the treatment of CHF exacerbation. In most cases, it is due to intravascular

volume depletion, especially when patients do not have adequate fluid intake lose of fluid such as diarrhea with continuous diuresis. The urine output is auto regulated by the cardiovascular system's control of perfusion to the kidney. When the fluid intake decreases, the perfusion to the kidney decreases, resulting in less urine output and keeping the euvolemic status and vice versa. It happens in our everyday life. For example, when a person has diarrhea or/and a decrease in oral fluid intake, the cardiovascular system will decrease the perfusion, decreasing urine output to preserve fluid and maintain normal intravascular volume. At certain point it will cause increasing creatinine. It is not a malfunction of cardiovascular and renal system. When the body increases the fluid intake, the situation will be corrected. This happens in everyday life. In CHF patients receiving diuretics without adequate fluid intake, this will cause further volume depletion, trigger an overreaction of the catecholamine system, and further decrease perfusion to the kidney, increasing creatinine. This may be a reason for the exacerbation of CHF in the outpatient setting and poor response to diuretics. This is a general principle of the cardiovascular and renal system. Different patients may be at a variable stage of system dysfunction. The treatment plan needs to be tailored based on each patient's specific condition. Some patients may respond to diuretics well.

In this paper, inpatient treatment is for patients with significantly worsening symptoms, increased blood pressure, and heart rate, which includes most CHF inpatients. A small percentage of CHF inpatients may present with cardiogenic shock. The treatment for these patients is not discussed in the paper. This paper is not a hypothesis. It is an understanding of the pathophysiology of CFH based on the knowledge from medical school, which guided CHF treatment in the author's more than 20 years of practice as a general cardiologist with promising results [1], which need verification systemically and scientifically. It will provide a basis for further study in CHF treatments and pathogenesis.

It is also essential that patients and their families are educated about their treatment plan, including a low-sodium diet and fluid restriction, and what and why medication they use. This is equally important since it increases patients' compliance with treatment. The author's observation is that significant percentages of patients do not follow treatment, especially those with fluid restriction and a low-sodium diet. This will require developing an education system for patients and their families, not only telling them what to do but also making them understand why they need to do it. It is the author's experience that will result in much better compliance of the patients to the treatment plan. We also need to give patients practical expectations for everyday life based on their clinical conditions. Most of the patients should be able to live a normal life.

In conclusion, while diuretics are effective for managing CHF symptoms, they do not correct the fundamental dysfunction of the cardiovascular system. Understanding cardiovascular physiology, pathophysiology, and cause of CHF should guide CHF treatment. Diuretics should be used to restore cardiovascular function rather than to achieve euvolemia. This may offer improved long-term outcomes

for CHF patients. The treatment plan should be based on each patient's needs. The most important treatment principle is restoring the cardiovascular system by blocking and downregulating the catecholamine system. Hopefully, with the priority use of beta-blockers, appropriate use of diuretics, and adequate fluid management in combination with other guideline-recommended medications for CHF, we can decrease the admission and readmission rate and the cost of CHF.

NIH started the Precision Medicine Initiative, which required an approach that considers individual variability in genes, environment, and lifestyle for disease treatment and prevention. The treatment strategy proposed in this paper details how to use beta-blockers and diuretics, which aligns with Precision Medicine. Clinicians should tailor their treatment plan based on the patient's response and adjust as indicated. In addition, precision medicine may need to include the treatment directly focusing on the cause of the illness, such as restoration of the function of the cardiovascular system, instead of restoration or maintenance of euvolemia in treating CHF, which may be a new direction for CHF.

Author's Note

This opinion letter is based on a previous paper "Congestive Heart Failure: Treatment of Symptoms or Causes". The data in that paper was not complete from a research standpoint. It has a historical reason for it. The author was trained as any cardiology fellow in treating CHF, attempting to correct fluid overload in the acute phase of CHF and maintain euvolemic status using diuretics. After a few years of practice, the strategy did not seem good enough to control the patient's symptoms, resulting in readmission. The author gradually realized that our strategy of correcting the volume status using diuretics was inadequate. Based on the knowledge of physiology and pathophysiology learned in medical school, it seemed that the worsening of diastolic function and vessel restriction resulted in cardiovascular and renal systems dysfunction. This led to a change in the author's practice in the following 14 years when the author practiced in a community hospital. The number of cases was kept without details for professional and personal interest. It was never meant to be a research project until the author left the hospital and started a locum tenant position, which allowed him to see the practice of others in treating CHF patients. The author realized that his experience might help to improve our treatment of CHF patients. The author started to work on the paper (Congestive Heart Failure: Treatment of Symptoms or Causes). However, the author cannot access detailed patient data after leaving the hospital. That paper was based on the author's experience. It gives us a clue for possible improvement in the treatment of CHF. Well-designed research is needed to verify the results, especially those with significant clinical and socioeconomic meanings.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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Abbreviations

CHF, Congestive Heart Failure

LV, Left Ventricle