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Why Are Physicians So Confused about Acute Heart Failure?

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For most of the past 3000 years, physicians believed that all patients with heart failure had acute heart failure. Heart failure was viewed as an episodic disorder — that is, patients were considered to have heart failure when they presented with fluid retention, and they no longer had heart failure after diuresis.[1] The chronicity of heart failure was recognized only when invasive and noninvasive measurements showed severe ongoing structural and functional abnormalities between episodes.[2]

To develop approaches to preventing hospitalizations and minimizing the functional and prognostic consequences of heart failure, clinical investigators needed to focus on the underlying disease process. Extensive research beginning in the 1980s established that combination therapy with neurohormonal antagonists reverses ventricular remodeling, improves functional capacity, and reduces the risk of disease progression and death. However, use of these drugs in primary care has been distinctly suboptimal, possibly because physicians have been inclined to discount the importance of intensive treatment for a disease whose progression is typically clinically silent.[3]

Instead, practitioners have focused on the treatment of worsening episodes that require hospitalization. Forty years ago, in an era when rheumatic heart disease was common, these events were often dramatic and life-threatening. When patients presented with acute pulmonary edema, physicians took swift steps to abruptly redistribute blood volume away from the pulmonary circulation, with the use not only of diuretics but also of nitrates to increase systemic venous capacitance. The response in patients was dramatic, and it often occurred within minutes; therapy was immediately lifesaving.[1]

Acute pulmonary edema still occurs in clinical practice, and it is often related to a drug-induced or endogenous catecholamine surge. However, most patients who are hospitalized with worsening heart failure do not have a new, acute disorder. Instead, they present with decompensation of chronic underlying ventricular dysfunction as a consequence of gradual but progressive increases in cardiac filling pressures in the preceding weeks.[4] Sometimes the deterioration is triggered by cardiac arrhythmia or pulmonary infection, but typically the deterioration is not sudden or immediately life-threatening.

Are these episodes of worsening heart failure a medical emergency akin to acute pulmonary edema decades ago? Most patients recover within a few days after intensification of medical therapy. However, these events are often accompanied by the early release of troponin, indicating a small degree of myocardial injury[5] that is possibly related to acute ventricular distention. Could emergency interventions to reduce volume overload salvage a few cardiomyocytes, which might (in turn) have benefits for long-term prognosis? We know that each hospitalization accelerates the rate of progression of heart failure.[6] So, is decompensated heart failure similar to an acute coronary syndrome, for which it is critical to perform an emergency intervention to minimize irreversible cardiac injury?

The hypothesis that exceptionally early short-term therapy during a hospitalization for heart failure might yield long-term benefits was sup-

ported by the findings of the Relaxin in Acute Heart Failure (RELAX-AHF) trial.[7] In that trial, a 48-hour infusion of the vasodilator serelaxin decreased the release of troponin and resulted in a remarkable 37% lower risk of death during the subsequent 6 months than placebo.[8] However, because the benefit with respect to mortality was based on a sparse number of deaths, it was greeted with great skepticism. Outsized mortality benefits that have been observed in underpowered phase 2 trials in patients with heart failure often have not been subsequently confirmed in definitive phase 3 trials.[9]

The dramatic reduction in mortality that was seen with early vasodilator therapy in patients with acute decompensated heart failure in the RELAX-AHF trial was shown to be spurious in two subsequent large-scale, definitive trials. In TRUE-AHF (Trial of Ularitide Efficacy and Safety in Acute Heart Failure),[10] a 48-hour intravenous infusion of the natriuretic peptide ularitide did not result in lower all-cause mortality in the long term than placebo, even though the drug caused an immediate reduction in cardiac-wall stress, as evidenced by a reduction in levels of N-terminal pro–brain natriuretic peptide. Similarly, in the RELAX-AHF-2 trial, the results of which are reported in this issue of the *Journal*, the risks of death from any cause and from cardiovascular causes at 180 days were not lower in patients who had received intravenous serelaxin for 48 hours than in patients who had received placebo.[11]

Hospitalization for worsening symptoms is an important event in chronic heart failure; it identifies patients with particularly rapid advancement of the underlying disorder.[6] However, decompensation is not an acute illness or an indicator of subclinical myocardial injury that requires emergency intervention with a novel treatment; the acute elevation of troponin level may subside, but the troponin level remains elevated after hospital discharge. Although it is important to achieve clinical stabilization, it is more critical to ensure that patients are treated vigorously between hospitalizations to decrease the risk of readmission and death.[2] A focus on intensive outpatient care (rather than an obsession with inpatient therapy) is needed to reduce the burden of heart failure.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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