What Happens to Stable Heart Failure Patients When They Don’t Take Their Medicines?

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The bedrock on which existing knowledge in cardiology rests comprises of studies involving only a handful of patients– what was central to this research was the uniqueness of the research question rather than the size of the cohort. In contemporary times, however, we assume that the “low hanging fruit” of cardiovascular knowledge has already been gathered, and any additional advancements in our understanding of disease pathophysiology will come from investigations on a substantial scale. It is therefore quite refreshing when researchers rely on creativity rather than brute force and perform studies like the one presented by Dr. Cleland’s group in this issue of the European Journal of Heart Failure that challenge our basic assumptions about heart failure, all with less than two dozen patients.

In hindsight, the question they sought to answer was surprisingly simple, and yet previously unanswered: what are the effects of not taking heart failure medications on key disease parameters in patients with stable disease? For this, they recruited 20 outpatients with stable systolic heart failure who were on guideline recommended therapies, including sufficient doses of loop diuretic, and had NT-proBNP levels of >200ng/L. Using a randomized crossover design, they subjected the patients to 48 hours of medication continuation and omission. A host of parameters relevant to heart failure pathophysiology were collected, specifically: weight, blood pressure, heart rate, NT-proBNP, creatinine, detailed echocardiographic data, and bioimpedance information. They found medication omission to be associated with an increase in systolic blood pressure, almost doubling in NT-proBNP levels, and a decrease in creatinine. There was significant worsening in echocardiographically determined left atrium and left ventricle volumes and increases in both transthoracic and total body impedance. Of note, there was no significant increase in body weight with medication omission.

Most unexpected among these findings was the lack of change in weight with medication discontinuation despite obvious evidence of increasing clinical instability. At first glance, heart failure clinicians might find this odd as weight gain is ubiquitous among disease-management programs as a fundamental marker of decompensation. On digging deeper, however, it becomes quite apparent that there is but little high-quality data that quantifies the relationship between weight change and disease pathophysiology. In fact, if weight were

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a biomarker of heart failure introduced today, it would likely never meet the criteria required for clinical use.\(^4\)

That said, some key principles of human physiology can go a long way to explain the findings presented here. If we assume that the subjects were compliant and on a 2gram (low sodium) diet, their intake of sodium would be \(\sim 86\) mmol/day. If they retained 50\% of their dietary sodium load, it would translate to the retention of \(86\) mmol of sodium over the 2-day intervention. This would induce a 0.6 kg weight gain (since extracellular fluid has a sodium concentration of \(\sim 140\) mmol/L), consistent with the observed weight gain of in the study of 0.5 kg that missed significance with a \(P\) value of 0.09. Furthermore, assuming a total body water of these subjects of be about 45 L, a 0.6 L addition of fluid would equate to a 1.3\% increase in total body water; similar to the bio-impedance derived total body water increase of 2\%, which was highly statistically significant.

Is it possible for a mere 0.6L of fluid gain to result in the increases in ventricular filling pressures, as suggested by the changes in cardiac chamber volumes and doubling in NT-proBNP? The clear-cut answer is no: even if 100\% of the 0.6L of fluid gain stayed in the extracellular space, this would equate to a \(\sim 40\) cc increase in blood volume, which would be incapable of causing the above mentioned findings. The accurate answer to these results pertains to the known—yet underappreciated—disconnect between volume and vascular tone.\(^5\) Rather than excessive volume, the marked increased distension of the cardiac chambers likely occurred due to withdrawal of neurohormonal blockade causing vasoconstriction—particularly in the venous circulation—leading to redistribution of fluid from capacitance vessels such as the splanchnic vessels that hold up to \(1/4\text{th}\) of all intravascular volume into the central circulation increasing intracardiac filling pressures.

Another unanticipated finding was the decrease in serum creatinine with a hiatus in heart failure therapy despite clear evidence of worsening cardiac distension and removal of evidenced based medications. This highlights the shortcomings of simply using directionality of creatinine trend as the measure of cardiorenal health. In fact, our team has repeatedly shown that an improvement in creatinine can be associated with worsened survival and, depending on the clinical context, sometimes a worsening in creatinine can result in improved outcomes.\(^6–8\) The bottom line, while often unappreciated, is that the underlying mechanisms behind changes in GFR trump the directionality of laboratory values.\(^9,10\)

Implicit in the above observations are a few key take home messages. First, the current methods by which we gauge clinical stability of heart failure need a complete reboot; away from using macroscopic measures of heart failure such as daily weights and trends in creatinine that are too displaced from mechanism of disease to provide anything other than a blunt assessment of clinical status. Second, a substantial body of literature shows us that changes in natriuretic peptide levels are among the most sensitive and potent predictors of adverse outcomes in heart failure.\(^11\) We need to enrich our assessment tools with additional objective and easily assessable measures of heart failure that report directly on upstream pathophysiological derangements. Finally, we must appreciate the sizable biological perturbations that can occur with interventions as minor as discontinuation of medications
for 2 days in what we must assume to be a highly contentious cohort of patients; this shows that a considerable amount of damage can be present “under the hood” without any outward signs of worsening heart failure in patients who are not putting additional stressors on their cardiovascular systems (e.g. via consumption of a very high salt meal).

Whereas novel in its approach, the current study has methodologic limitations such as size and unblinded design that prohibit any direct clinical application of the findings. The possible exception might be that we need to watch patients closely while holding ACE-inhibition for 36 hours in order to transition a patient to sucubatril/valsartan. That said, the study goes a long way to reinforce the notion that heart failure is a state of dysregulation within multiple biological pathways, that guideline recommended therapies can negate some of this homeostatic disruption, and that the most commonly used tools to assess clinical state—weight and creatinine—may not serve us well for clinical decision making. What is needed now is for us to better measure and quantify instability, and to react to these prior to outward clinical decompensation. This is likely to occur at the rapidly evolving interface between technology, precision medicine, and patient engagement. With that, heart failure patients might ward off clinical instability for as long as possible.

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References


