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Sodium Restriction in Heart Failure: Benefit or Harm?

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Abstract

Opinion Statement

Current guidelines vary in the recommended amount of dietary sodium intake for heart failure (HF) patients. Observational studies and the hypertension literature support the concept that sodium restriction improves HF outcomes. In contrast, several randomized controlled trials imply that dietary sodium restriction can cause harm through hypovolemia and increased neurohormonal activation. Data from hypertensive animal models and humans suggest that dietary sodium intake may need to be individually tailored based on HF severity and the physiologic response to sodium loading. Future studies must assess interactions between sodium intake, fluid intake, and diuretics to match clinical practice and improve safety. More information is needed in multiple areas, including accurate measurement of sodium intake, implementation of dietary changes in HF patients, and establishment of biomarkers that predict response to changes in sodium intake. Additional research is urgently needed to determine the true impact of the most commonly recommended self-care strategy in HF.

Keywords

Sodium Restriction; Heart Failure; Hypovolemia; Biomarkers; Neurohormonal Activation

Introduction

According to nationally representative survey data, over five million Americans currently are living with heart failure (HF). As the U.S. population ages, the prevalence of HF is expected to increase by 25% in the coming decades.¹ In 2012, an estimated \$32 billion was spent on HF-related care in the U.S., with much of this expenditure related to hospitalizations for HF decompensation.¹ The Center for Medicare and Medicaid Services now financially penalizes hospitals for excessive 30-day readmission rates in older HF patients. Reducing the incidence of HF and its associated morbidity, in particular hospitalizations, has become a major goal for insurance payers and public health authorities.

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Compliance with Ethics Guidelines

Conflict of Interest

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Human and Animal Rights and Informed Consent

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Dietary sodium ‘indiscretion’ is viewed as a common and potentially modifiable precipitant of HF admissions.²⁻⁵ Dietary sodium restriction is considered the most frequent self-care behavior recommended to patients with HF,⁶ and dietary recommendations are a mandated component of HF hospital discharge instructions.^{7, 8} However, current guidelines vary widely in their recommended degree of sodium restriction. On average, Americans consume between 3,400-3,700 mg per day of sodium.⁹ Based primarily on data from cohort studies in hypertensives without HF, a recent American Heart Association task force called for a population-wide sodium restriction of < 1500 mg of sodium per day.¹⁰ This proposal places several HF guidelines in the interesting position of recommending a higher sodium intake for HF patients than the general population. The 2013 American Heart Association/American College of Cardiology guidelines suggest 3 grams or less per day in symptomatic HF patients.¹¹ The Heart Failure Society of America recommends 2-3 grams per day in all HF patients with further restriction to less than 2 grams per day in patients with “moderate to severe HF.”¹² The 2012 European Society of Cardiology HF Guidelines omit completely any recommendations regarding sodium intake for the management of chronic HF.¹³

The variability in these guidelines is not surprising, given the paucity of data on sodium restriction in HF. Much of the rationale for sodium restriction stems from studies in hypertension, a major HF risk factor, but it is unclear how these lessons translate to patients with prevalent HF. Most observational studies support the concept that low sodium intake improves HF outcomes. However, the few controlled trials that have been performed, though challenging to interpret, suggest that strict sodium restriction can be harmful in some HF patients. In light of this apparent contradiction, it is worthwhile to review the evidence arguing for and against sodium restriction in HF.

The Arguments in Favor of Sodium Restriction

Systemic hypertension accounts for over 40% of the population-attributable risk for HF, and precedes the development of HF in up to 91% of cases.¹⁴ The lifetime risk for HF doubles with blood pressure 160/100 versus < 140/90 mmHg,¹⁵ and treatment of systolic hypertension markedly reduces incident HF even in very elderly adults.¹⁶ High sodium consumption has long been considered one of the main modifiable factors promoting hypertension within populations.¹⁷ Data from a meta-analysis of 34 trials including 3,230 participants support a dose-response relationship between salt (sodium chloride) intake and blood pressure across a range of 3 to 12 grams per day.¹⁸ Several interventions achieving moderate sodium restriction within communities have also successfully reduced population blood pressure.¹⁹

Dietary sodium intake specifically impacts populations at risk for and mechanisms implicated in the development of HF.^{14, 20} In the DASH (Dietary Approaches to Stop Hypertension)-Sodium study, blood pressure lowering with sodium restriction to 50 mmol/day was most significant in older adults, the demographic most at risk for developing HF.^{1, 21} A follow-up study of over 10,000 patients from the first National Health and Nutrition Examination Survey (NHANES) associated lower sodium intake with decreased risk of HF in overweight/obese participants.²² Cohort studies of 36,000 Swedish post-menopausal women and 38,000 middle-aged to older men found that subjects adhering to components of the low-sodium DASH diet experienced lower long-term rates of incident HF.^{23, 24} In hypertensives, left ventricular mass, diastolic function, and large-arterial vascular stiffness are proportional to 24-hour urinary sodium excretion,²⁵⁻²⁷ and long-term reduction of sodium intake is associated with regression of left ventricular hypertrophy.²⁸ Seals and colleagues have performed several carefully controlled dietary modification studies in older hypertensive adults. They found that restriction of sodium intake to 50-70

mmol/day reduced large-arterial stiffness²⁹ and improved conduit-artery and microvascular endothelial function.³⁰

For patients already diagnosed with HF, many argue that the pathophysiology of volume retention mandates strict sodium restriction. HF is characterized by a state of reduced renal perfusion leading to sympathetic and renin-angiotensin-aldosterone system activation,^{31, 32} promoting sodium reabsorption and concurrent water retention at the proximal and distal nephron. In this “salt-avid” state, excess sodium intake in the setting of neurohormonal activation promotes volume retention and the development of congestive symptoms in HF. In hospitalized HF patients, insufficient clinical decongestion at hospital discharge predicts HF readmission and all-cause mortality.³³ Emerging data indicate that vascular overfilling in HF activates pro-oxidant and pro-inflammatory gene programs in endothelial cells,³⁴ and may be an important contributor to cardiorenal dysfunction.^{35, 36}

Some studies suggest that disturbed sodium handling is already evident early in the course of HF. Volpe et al. (1993) studied the hemodynamic response to a high-sodium diet in 12 patients with NYHA Class I-II HF. In contrast to healthy controls, HF patients displayed elevated end-systolic and end-diastolic left ventricular volumes without a compensatory increase in stroke volume in response to sodium loading. As a result, HF patients experienced increased sodium retention and weight gain in comparison to controls.³⁷ Even patients with structural heart disease who have never had HF symptoms have evidence of impaired natriuresis. McKie et al. (2011) studied the response to fluid overload in two groups of 20 patients with asymptomatic systolic or at least moderate diastolic left ventricular dysfunction. In comparison to controls, these patients did not increase the rate of urinary sodium excretion in response to volume expansion with normal saline and released decreased levels of urine cGMP, a downstream effector of natriuretic peptides.³⁸

Several observational studies of HF patients have demonstrated associations between lower dietary sodium intake and improved HF status. In a prospective study of 232 NYHA Class III-IV HFREF patients, Son et al. found that patients with a 24-hour urine sodium excretion of > 3 grams exhibited a greater symptom burden and shorter cardiac event-free interval over a 12 month period.³⁹ Arcand and colleagues measured 24-hour urinary sodium excretion in 123 medically stable, ambulatory HFREF patients followed for 3 years. The highest tertile of sodium intake was associated with increased episodes of decompensated HF, increased HF hospitalizations, and increased mortality.⁴⁰ In HFREF patients with advanced disease, frequent intake of salty foods has been associated with the need for high-urgency transplantation.⁴¹

In summary, in part through its blood-pressure lowering effects, sodium restriction has the potential to reduce the incidence of HF. It may also be associated with physiologic changes that delay the onset or slow the progression of HF. Observational data suggest that sodium restriction can improve HF outcomes.

The Arguments Against Sodium Restriction

While low dietary sodium knowledge has been identified as an independent risk factor for HF admission,⁴² conflicting data exist regarding the benefit of dietary education on HF outcomes. In the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF), Fonarow et al. (2007) noted no impact of discharge instructions (which included all types of diet recommendations), on 60-90 day hospitalization or mortality rates in hospitalized HF patients.⁷ In contrast, Hummel and colleagues observed that a specific discharge recommendation to restrict dietary sodium predicted a lower risk of 30-day readmission in heart failure with preserved ejection fraction (HFPEF) patients, who were also less likely than HFREF patients to receive this advice.⁸ In

a large prospective study, Koelling and colleagues randomized 223 HFREF inpatients to standard care or one hour of comprehensive self-care instruction by a trained nurse educator just prior to hospital discharge. Patients in the education group were significantly more likely to report dietary sodium restriction and other self-care behaviors at 30 days post-discharge, and were 51% less likely to be readmitted for HF exacerbation over six months of follow-up.⁴³ Further highlighting the difference between discharge recommendations and education, the EuroHeart Failure Survey found that 42% of patients did not recall advice to restrict dietary sodium 12 weeks post-hospital discharge.⁴⁴

Even though adherence to dietary sodium restriction has been described as “a cornerstone of HF disease management,”² HF patients have difficulty complying with a low-sodium diet. After reviewing food diaries, Friediani et al. concluded that only a third of NYHA Class II-III HF patients consumed less than 2,000 mg of sodium daily.⁴⁵ Several barriers exist that decrease adherence to a sodium restricted diet. Bentley et al. (2005) identified the following three themes: lack of knowledge, interference with socialization (e.g. family member preferences, eating out often), and lack of access to appropriate food selections.⁴⁶ In addition, 42% of HF patients in one study were unable to quantify sodium content by reading food labels.⁴⁷ Many HF patients have an increased taste preference for salt, making it more difficult to resist high-sodium foods.⁴⁸

Leaving aside implementation challenges, dietary sodium restriction has physiologic consequences that could contribute to adverse outcomes in HF. Especially in the setting of diuretic therapy and fluid restriction, sodium restriction may increase sympathetic and reninangiotensin-aldosterone system activation by contributing to intravascular volume depletion.⁴⁹⁻⁵² A recent Cochrane group meta-analysis including 167 studies of patients with and without hypertension associated a sodium-restricted diet with increased plasma levels of renin, aldosterone, epinephrine, and norepinephrine.⁵² Similarly, in a study of 24 patients with stable, mild-moderate HFREF, sodium restriction was associated with elevated aldosterone, epinephrine, and norepinephrine levels.⁵⁰ Neurohormonal blockade is the foundation of HF medical management, particularly in HFREF patients, and could ameliorate adverse effects of these changes.¹¹ However, in a retrospective analysis of 4,291 symptomatic HFREF patients from the Val-HeFT trial, elevated renin-angiotensin-aldosterone system activity was associated with high symptom burden, worsened cardiac remodeling, and increased mortality regardless of ACE inhibitor or beta-blocker use.⁵³ Even though these agents may not fully block neurohormonal activation induced by sodium restriction, optimally treated and compensated HF patients may handle sodium loading similar to controls. Damgaard et al. (2006) performed a randomized crossover trial of low (70 mmol/day) and high (250 mmol/day) sodium intake for 7 days each in 12 Class II-III HFREF patients, all of whom were taking beta-blockers and ACE inhibitors. In contrast to earlier studies,³⁷ they found that optimally managed HFREF patients receiving a high-sodium diet displayed the same degree of sodium excretion, volume expansion, weight gain, and neuroendocrine response as controls.⁵⁴

While hospitals often limit dietary sodium in hospitalized HF patients,⁵⁵ surprisingly few studies have formally assessed the value of sodium restriction in the inpatient setting. Aliti et al. (2013) recently randomized 75 patients in acute decompensated HFREF (mean EF 26%) to strict sodium (800 mg/24h) and fluid (800 mL/24h) restriction or liberal sodium and fluid intake. After three days, there were no significant differences in weight loss, urine output, clinical improvement, amount of diuretic used, or time to discharge. Readmission rates at 30 days were similar between the two groups.⁵⁶ While the study could not separate the impact of fluid restriction from sodium restriction, the results do imply that more intensive sodium restriction than the standard 2,000 mg/day used by many hospitals does not expedite clinical improvement or decrease length of stay.

The few controlled studies addressing sodium restriction in chronic HF management come from a single Italian research group. Paterna et al. (2008) enrolled 232 HFREF patients with class II symptoms thirty days after admission for class IV symptoms and diuretic resistance. Enrolled patients were required to have an EF < 35%, creatinine < 2.0, blood urea nitrogen < 60, urine output < 500 mL/hr, and natriuresis of < 60 mmol/day at the time of hospital admission. At thirty days after discharge, patients were randomized to a diet of 1.8 or 2.8 grams of sodium per day. All patients received furosemide at doses between 250-500 mg twice daily and a 1 liter fluid restriction. Sodium intake was assessed by phone interview. After 180 days of follow-up, a moderate-sodium diet was associated with a significant reduction in readmissions and a trend toward lower mortality.⁵⁷ The low-sodium diet increased aldosterone and renin levels and was associated with worsened renal function. In addition to these studies, in an effort to define the ideal combination of sodium restriction, fluid restriction, and diuretic dosing, the same group randomized 410 HFREF patients (selected by identical inclusion criteria listed above) using a 2 × 2 × 2 factorial design to the following: 1.8 or 2.8 grams of sodium daily, 1 or 2 liters of fluid daily, and 125 or 250 mg furosemide twice daily. The group receiving 2.8 grams of sodium daily, 1 liter of fluid daily, and 250 mg furosemide twice daily experienced a reduction in readmissions and a trend toward lower mortality at 180 days of follow-up.⁵⁸

In their largest study to date, the same group randomized 1,771 hospitalized HFREF patients with class III symptoms unresponsive to outpatient treatment. The intervention group received hypertonic saline with loop diuretics while consuming a moderate-sodium diet (2.8 g/day); the control group received diuresis without hypertonic saline while consuming a low-sodium diet (1.8 g/day). All patients received furosemide 250 mg IV twice daily with a 1 liter fluid restriction during the 4-6 day treatment period. Patients receiving hypertonic saline and a moderate-sodium diet achieved greater diuresis and natriuresis, a lower NYHA class, and lower B-type natriuretic peptide level during shorter hospital stays. At discharge, all patients received furosemide 50-125 mg twice daily (dosed based on inpatient requirements) and their originally assigned diet was continued. Over 57 months of follow-up, patients in the intervention group were readmitted less frequently and had lower mortality.⁵⁹

In summary, these provocative findings suggest that avoiding sodium restriction may enhance response to diuresis, lead to more rapid compensation, and predispose patients to more favorable long term outcomes. However, as highlighted in a recent Institute of Medicine review, these trials have several weaknesses.⁶⁰ First, generalizability is limited by the fact that these studies enrolled only HFREF patients hospitalized with refractory class III-IV heart failure from a single geographic region. In addition, very high doses of diuretics were used, often in conjunction with strict fluid restrictions. Diuretic dosing and fluid restriction were not modified during follow-up, and adverse events could have been related to intravascular volume depletion. Many participants were not receiving optimal neurohormonal blockade for HFREF (e.g. depending on group assignment, 7-70% of participants in these studies were treated with beta-blockers, in comparison with 84% in the U.S. OPTIMIZE-HF registry⁷). Lastly, a meta-analysis of these studies was recently retracted over concern that they included duplicate data.⁶¹ For these reasons, further randomized trials are needed to elucidate the impact of sodium restriction on outcomes in HF patients.

The Arguments for Moderation or Individualized Targets

Some investigators argue that there is a “J-shaped” relationship between sodium intake and cardiovascular outcomes. After reviewing 9 randomized-controlled trials and 23 observational trials (most of which included subjects from the general US population rather

than HF patients), Alderman & Cohen contend that sodium intakes above and below the range of 2.5 to 6.0 grams/day are associated with increased cardiovascular risk.⁶² O'Donnell et al. (2011) performed an observational analysis of 28,880 patients with established cardiovascular disease or diabetes utilizing a fasting morning urine sample to estimate 24-hour urine sodium excretion. After a median follow-up of 56 months, both a sodium excretion of greater than 7 g/day and a sodium excretion of less than 3 g/day were associated with a significantly increased risk of hospitalization for HF.⁶³

Observational data suggest that sodium restriction may need to be tailored to a patient's HF severity. Lennie et al. (2011) prospectively studied 302 NYHA Class I-IV HF patients using a single 24-hour urinary sodium excretion measurement to stratify baseline sodium intake. Prior to enrollment, medication regimens (including diuretics) had to be stable for at least three months. Patients were followed over 12 months for the composite outcome of emergency department visits for worsening HF, HF hospitalizations, and death. A baseline urine sodium > 3 grams/24h was associated with significantly longer event-free survival in NYHA Class I-II patients. In contrast, urine sodium > 3 grams/24h more than doubled the hazard for the primary outcome in NYHA Class III-IV patients. This suggests that sodium restriction may preferentially benefit patients with advanced HF and supports the hypothesis that neurohormonal activation in previously compensated HF patients may eliminate or decrease the benefits of dietary sodium restriction.⁶⁴

The resolution to the dilemma regarding whether and how much to restrict sodium to prevent HF-associated complications could relate to differences in individual response. Controlled feeding studies have identified subjects with a "salt-sensitive" blood pressure phenotype, i.e., those in whom blood pressure is higher during high sodium intake than during low sodium intake, and those with "salt-resistant" blood pressure, whose responses are minimal or even depressor.⁶⁵ The salt-sensitive phenotype consistently increases long-term overall mortality and cardiovascular morbidity independent of baseline blood pressure.^{66, 67} Salt-sensitive animal models develop ventricular diastolic dysfunction, left ventricular hypertrophy, increased arterial stiffness, and HF in the setting of high sodium intake.⁶⁸ The mechanisms of target organ damage, which include diet-induced oxidative stress and vascular inflammation, are shared by no fewer than 16 salt-sensitive experimental models.⁶⁸⁻⁷² Of note, emerging data suggest that oxidative stress and vascular inflammation are key contributors to HF incidence, progression, and acute decompensation in humans.^{34, 73-75}

As in animal models, salt-sensitive humans develop HF-associated cardiovascular abnormalities including higher left ventricular mass, larger left atrial size, ventricular diastolic dysfunction, and increased evidence of microvascular disease independent of baseline blood pressure.^{76, 77} While genetic factors have been linked to salt-sensitivity,^{78, 79} demographics and comorbidities may be even more important. Factors associated with the salt-sensitive phenotype such as advanced age, hypertension, central obesity, sleep apnea, insulin resistance, and chronic renal insufficiency are highly prevalent in HF cohorts.^{8, 80-82} Diurnal blood pressure 'non-dipping,' the failure of blood pressure to decline during sleep, is closely linked to salt-sensitivity.⁶⁵ Blood pressure non-dipping predicts incident HF,⁸³ and, in patients with prevalent HF, the combined outcome of HF hospitalization or death.⁸⁴

Dietary sodium restriction, particularly in concert with the Dietary Approaches to Stop Hypertension (DASH) eating plan, reduces blood pressure, decreases oxidative stress, and improves vascular function in salt-sensitive individuals.^{85, 86} In a recent interventional pilot study, Hummel et al. administered the low-sodium DASH diet for 21 days in 13 hypertensive HFPEF patients, with diuretic dose adjustment based on clinical status, renal function, and physical examination. The DASH/SRD was associated with reduced blood

pressure, oxidative stress, and arterial stiffness as well as improved diastolic function, contractility, arterial elastance, and ventricular-arterial coupling.^{82, 87} These findings remain to be confirmed in randomized controlled studies, and it is unknown whether hypertensive HFREF or nonhypertensive HF patients would display similar physiological changes.

Perspectives/conclusions

Many challenges remain for study design, implementation of dietary changes, and assessment of the benefits and harms of sodium restriction. Techniques to assess habitual sodium intake are imperfect; dietary recall methods often underestimate consumption,⁸⁸ and the gold standard of serial 24-hour urinary sodium measurements is too burdensome for many patients. Recent studies suggest that spot urinary sodium:creatinine ratio or dipstick urinary chloride testing are sufficient for general clinical use or large cohort studies.⁸⁹ Additional information is needed on the barriers to implementing dietary sodium restriction,^{46, 47} the educational methods that promote retention of dietary advice,⁴⁴ and the factors that predict long-term dietary adherence.⁹⁰ Research should continue to investigate biomarkers that can predict the physiologic impact of sodium restriction, with candidates including measures of oxidative stress,^{82, 85} 'local' activation of the renin-angiotensin-aldosterone axis (often in opposition to systemic effects),⁹¹⁻⁹³ and novel markers such as cardiotoxic steroids.⁹⁴ Future randomized studies should incorporate lessons from previous trials, in particular that maintaining an ideal intravascular volume in compensated HF patients in the setting of sodium restriction requires frequent assessment of volume status and adjustment of diuretic dosing. While addressing this issue complicates study design, it will more closely simulate real-life clinical practice and may increase safety. Surprisingly, controlled studies of dietary sodium restriction have yet not been performed in HF patients with persistent volume overload, in whom vascular overfilling likely exacerbates oxidative stress and vascular inflammation.⁹⁵

In summary, evidence supporting a specific recommendation for daily sodium intake in patients with HF is currently lacking. Observational studies support the conventional wisdom that dietary sodium restriction improves HF outcomes, particularly in patients with higher disease severity and symptom burden. In contrast, several randomized trials imply that dietary sodium restriction can cause harm, but may be confounded by non-standard treatment approaches. Data from hypertensive animal models and humans suggest that 'one size may not fit all,' and that dietary sodium restriction in HF may need to be individually tailored. Regardless of how this debate is viewed, previous studies make it abundantly clear that dietary sodium restriction can have profound effects on physiology and outcomes in HF. Further research is urgently needed to clarify the effects of this commonly recommended strategy.

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