Long-Term Effects of Dietary Sodium Intake on Cytokines and Neurohormonal Activation in Patients With Recently Compensated Congestive Heart Failure

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ABSTRACT

Background: A growing body of evidence suggests that the fluid accumulation plays a key role in the pathophysiology of heart failure (HF) and that the inflammatory and neurohormonal activation contribute strongly to the progression of this disorder.

Methods and Results: The study evaluated the long-term effects of 2 different sodium diets on cytokines neurohormones, body hydration and clinical outcome in compensated HF outpatients (New York Heart Association Class II). A total of 173 patients (105 males, mean age 72.5 ± 7) recently hospitalized for worsening advanced HF and discharged in normal hydration and in clinical compensation were randomized in 2 groups (double blind). In Group 1, 86 patients received a moderate restriction in sodium (120 mmol to 2.8 g/day) plus oral furosemide (125 to 250 mg bid); in Group 2, 87 patients: received a low-sodium diet (80 mmol to 1.8 g/day) plus oral furosemide (125 to 250 mg bid). Both groups were followed for 12 months and the treatment was associated with a drink intake of 1000 mL daily. Neurohormonal (brain natriuretic peptide, aldosterone, plasma rennin activity) and cytokines values (tumor necrosis factor-α, interleukin-6) were significantly reduced with a significant increase of the anti-inflammatory cytokine interleukin-10 at 12 months in normal, $P < .0001$) than low-sodium group. The low-sodium diet showed a significant activation of neurohormones and cytokines and worsening the body hydration, whereas moderate sodium restriction maintained dry weigh and improved outcome in the long term.

Conclusions: Our results appear to suggest a surprising efficacy of a new strategy to improve the chronic diuretic response by increasing Na intake and limiting fluid intake. This counterintuitive approach underlines the need for a better understanding of factors that regulate sodium and water handling in chronic congestive HF. A larger sample of patients and further studies are required to evaluate whether this is due to the high dose of diuretic used or the low-sodium diet. (*J Cardiac Fail 2009;15:864–873*)

Key Words: Aldosterone, BNP, bioelectrical impedance, congestive heart failure, cytokines, furosemide, moderate sodium restriction, plasma renin activity.

Previously we showed that in relatively small patient populations with heart failure (HF) treated with hypertonic saline solution (HSS) and high intravenous furosemide dose combined with a moderate Na restriction during hospitalization reached a significantly faster reduction in brain natriuretic peptide (BNP) levels, and a dry weight more rapidly and had shorter hospitalization stays and readmissions.[1–7] In addition, the patients receiving, after discharge, the combination of high diuretic dose, moderate Na restriction (120 mmol/day), and water intake restriction (1000 mL/day) were less likely to have required further hospitalizations and more likely to be alive than patients receiving low Na diet (80 mmol/day).[6] This combination was also effective in reducing neurohormonal activation (BNP, plasma renin activity [PRA], and aldosterone (ALDO)].[8–10]

Since the original observation that circulating levels of tumor necrosis factor (TNF) were elevated in patients with HF, several studies have demonstrated that congestive HF patients are characterized by persistent immune activation. The activation of this systemic inflammation,

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demonstrated by the raised circulating levels of several inflammatory cytokines (TNF-α, interleukin [IL]-1β and IL-6) and chemokines (monocyte chemoattractant protein-1 and IL-8), as well as enhanced expression of various adhesion molecules, is independent of the cause of congestive HF (11) and correlates with the severity degree of disease. Thus far, prior studies have shown that circulating levels of TNF and IL-6 are elevated in direct relation to deteriorating functional class of HF.[12−14] The study was designed to evaluate the effects of a moderate sodium restriction (120 mmol to 2.8 g/day) versus a low-sodium diet (80 mmol to 1.8 g/day),on neurohormonal and cytokines activation and on clinical outcome and the maintenance of the dry weight in patients compensated after recently decompensated congestive HF, during 12 months of follow-up.

Methods

Patient Population

Between September 2005 and August 2007, 192 patients were consecutively admitted to Biomedical Department of Internal and Specialist Medicine of the University Hospital of Palermo and to department of Cardiology of G.F. Ingrassia Hospital (Palermo) with worsening HF.

Inclusion Criteria

We included into the study only compensated patients who previously were hospitalized (previous 30 days) for recently decompensated congestive HF with the following characteristics: patients had to have, according to the definition of refractory congestive HF[15] and according to Framingham criteria and New York Heart Association (NYHA) functional classification for congestive HF,[9] uncompensated congestive HF (dyspnea, weakness, lower limbs edema, or anasarca), NYHA functional Class IV that was unresponsive to treatment with oral high doses of furosemide up to 250 to 500 mg/day and/or combinations of diuretics (thiazide, loop diuretic, and spironolactone), angiotensin-converting enzyme inhibitors (captopril 75 to 150 mg/day), digitalis, β-blockers, and nitrates and to be under this therapy at least 2 weeks before hospitalization. The patients were judged unresponsive when they showed, during the above treatment, a reduction of urine volume and constant increase of body weight (BW) and impairment of clinical signs of congestive HF as previously reported, in spite the increase of furosemide and the combination of other diuretics (including thiazide). Additionally, they had to have a left ventricular ejection fraction $<35\%$, serum creatinine <2 mg/dL, blood urea nitrogen (BUN) ≤ 60 mg/dL, a reduced urinary volume (<500 mL/24 hours), and a low natriuresis (<60 mEq/24 hours) despite receiving the established treatments. None of the patients had to take nonsteroidal anti-inflammatory drugs. All patients received intravenous high-dose furosemide (250 mg bid), hypertonic saline solution, a moderate restriction of sodium (120 mmol to 2.8 g), and a reduced drink fluid intake (1000 mL/day) during hospitalization. When compensated state was achieved (NYHA Class II), patients received oral furosemide (125 to 250 mg/bid), moderate restriction of sodium (120 mmol to 2.8 g), and a drink fluid intake of 1000 mL daily according to our previous reports,[2-8,10] and the treatment was continued after discharge. The tailored therapy (angiotensin-converting enzyme inhibitors, digitalis, antialdosterone, β-blockers, and nitrates) obtained during hospitalization was continued also after discharge. Patients were considered clinically compensated when they reached a change in NYHA functional class to at least Class II and the accomplishment of an ideal BW, calculated by the Lorenz formula (lean body weight (men) = ((weight-((height-150)/4))*0.25)+(height-100)-(height-150)/4. Lean body weight (women) = ((weight-((height-150)/2.5))*0.25)+(height-100)-(height-150)/2.5).[16] In addition, the compensation fluid balance was detected by a tetrapolar impedance plethysmography (BIA-101, Akern, Firenze, Italy). The bioelectrical parameters of resistance and reactance were measured using an electric alternating current flux of 800 _A and an operating frequency of 50 kHz. The accuracy was checked with a calibration circuit of known impedance (R = 380 μ, Xc = 47 Ω, 1% error; where R = resistance and Xc = reactance). Whole-body impedance measurements were taken by using a standard position of outer and inner electrodes on the right hand and foot. The entire procedure was performed according to the indications of the National Institutes of Health technology assessment conference statements.[17] For each patient, a database was created that included anthropometric data (height, weight, and body mass index). Bioelectrical impedance analysis (BIA) evaluates some basic properties of the body by measuring resistance, reactance (reactance is a form of opposition that electronic components exhibit to the passage of alternating current because of capacitance or inductance; in some respects, reactance is like an alternating current counterpart of direct current and indicates an absolute amount of body cell mass), and phasic angle (phase angle is an indicator of cellular health and integrity; a low-phase angle is consistent with an inability of cells to store energy and an indication of breakdown in the selective permeability of cellular membranes; a high-phase angle is consistent with large quantities of intact cell membranes and body cell mass; phase angle is proportional to the ratio of reactance and resistance; the range of phase angle in the human body is 1° to 20°). In healthy and ill individuals, total body water and fat-free mass can be estimated using formulas that include BIA variables and often also individual's general characteristics. As an alternative, BIA values are evaluated, as such, in comparison to reference values obtained in the general population (as resistance and reactance percentiles, or bivariate resistance-reactance confidence limits). It is well-known that BIA reflects variation in total body water and the ratio between extracellular water and total body water; BIA is used to estimate the volumes of body fluid compartments. Electrical current is conducted by body water and impeded by other body components. The opposition to flow of electrical current is called impedance. Impedance is proportional to the length of the conductor, and inversely proportional to the cross-sectional area. Because volume is simply length multiplied by area, impedance is directly related to the volume of the body fluid. Fluid compartment volume measures are a useful part of body composition assessment for several reasons. Estimates of extracellular fluid volume together with total body water volume allow calculation of intracellular fluid volume. Intracellular fluid volume correlates strongly with body cell mass.[7,18] At discharge, all the patients underwent a complete physical and laboratory examination, Doppler echocardiography, and ultrasound abdominal examination. Diuretic doses were 125 to 250 mg bid because these doses allowed maintenance of BW and water balance, during hospitalization and after discharge. Only patients in NYHA Class II and with a dry profile at 30 days after discharge were included in the study and randomized.

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