Urine Electrolyte Composition and Diuretic Therapy in Heart Failure
Back to the Future?

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In the now classic 1985 fantasy-comedy film *Back to the Future*, teenager Marty McFly travels back in time 30 years in a DeLorean sports car modified time machine and fortuitously befriends the younger version of his father. Marty finds his father to be a meek high school teenager and realizes that Biff Tannen, the bullying supervisor of the future version of his father, was also his father’s bully in high school. What was true then is true now.

Article see p 766

In this issue of *Circulation: Heart Failure*, Verbrugge et al bring an old concept back to the present by proposing the use of urine sodium (Na+) and chloride (Cl–) concentrations in guiding diuretic therapy for the treatment of heart failure. In this prospective cohort study, the investigators recruited patients with heart failure and worsening congestive symptoms, evidence of left ventricular ejection fraction <45% by echocardiogram, or clinical signs of volume overload. Study subjects were observed in an intensive care unit setting and placed on a low NaCl diet (<3 g per day) with restricted fluid intake (1.5 L). They received a bolus of intravenous bumetanide in 3 consecutive 24-hour intervals, typically in combination with spironolactone and diuretics, and their usual medications for heart failure, including β-adrenergic antagonists and renin–angiotensin system blockers. In some cases, chlorothalidone and acetazolamide were added. Echocardiograms were performed at baseline and after the 3-day period. Urine was collected for 3 consecutive 24-hour intervals.

Baseline characteristics of the 61 study subjects show that they were predominantly older (average age, 67 years), men (74%), and New York Heart Association functional class III (54%). The baseline mean serum Na+ concentration was 139 mmol/L; the baseline mean serum creatinine was 1.18 mg/dL, corresponding to an estimated glomerular filtration rate of 56 mL/min. Urine output diminished significantly for the 3 successive days. The decrease in urine output was partly driven by a parallel decrease in the diuretic dose such that the urine output remained roughly constant when corrected for diuretic dose. In contrast, the relative increase in urine Na+ and Cl– excretion observed on the first day diminished even after correction for the diuretic dose. Not surprisingly, subjects showed an improvement in diastolic function by echocardiogram after diuretic therapy. The investigators conclude that a progressive decline in urine Na+ and Cl– excretion after consecutive days of diuretic therapy reflects progressive decongestion.

Do these findings signal a role for urine electrolytes in guiding titration (or discontinuation) of diuretic therapy in heart failure, as the authors suggest? Perhaps. It is not possible to disentangle whether the observed decline in urine NaCl excretion actually indicates euvolemia or whether these findings simply reflect how the kidneys respond to daily diuretic therapy. Indeed, the decline in urine NaCl excretion after the first day of intravenous bumetanide reflects the beginning phases of diuretic resistance. In the face of ongoing diuretic therapy, the kidneys limit urine NaCl excretion by making adaptations during the period of diuretic-induced natriuresis (immediate), after the period of the diuretic-induced natriuresis (short-term), and after long-term diuretic administration (chronic). One feature of chronic adaptation is the braking phenomenon in which the peak natriuretic effect of a diuretic decreases with each successive dose. The proposed mechanisms underlying these different phases of adaptation are myriad, but a defining characteristic of diuretic resistance is that NaCl reabsorption increases in diuretic-insensitive nephron segments. When patients are treated with loop diuretics such as bumetanide, one segment that increases NaCl reabsorption is the distal convoluted tubule, where there is increased activity of the NaCl cotransporter. In these diuretic-insensitive nephron segments, numerous neurohormonal inputs, such as the renin–angiotensin–aldosterone system, prostaglandins, and sympathetic renal nerve activity, activate signaling programs that stimulate NaCl reabsorption and defend against volume depletion. Additionally, volume-independent pathways can stimulate NaCl reabsorption and limit urine NaCl excretion. As an example of this elaborate renal response, loop diuretics, by decreasing NaCl reabsorption in the loop of Henle, increase delivery of NaCl to the distal convoluted tubule, stimulate expression of the NaCl cotransporter, increase mitochondria volume, and trigger epithelial cell hypertrophy and hyperplasia. All of these adaptations enhance the reabsorptive capacity for NaCl in the distal convoluted tubule.

The Verbrugge et al study does not specifically examine the different phases of adaptation to bumetanide therapy, nor does it distinguish among subjects who have reached euvolemia.
and those who have not. Because renal adaptation to diuretic therapy can occur irrespective of the extracellular fluid volume status, a decline in urine NaCl excretion serves as a reflection of diuretic resistance—no more, no less. If urine electrolytes are to be used as a guide for the dosing of diuretics in heart failure, they must be applied in a manner that would identify patients who reach euvoolemia as opposed to those who simply develop diuretic resistance.

However, the study by Verbrugge et al serves as a keen reminder that knowledge of renal physiology from classic studies of the past can still be applied to current strategies for heart failure management. In the modern era, several medications that target neurohormonal pathways inhibiting NaCl reabsorption in the distal nephron, that is, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, aldosterone antagonists, and β-adrenergic antagonists, have proved effective at prolonging life and ameliorating symptoms in heart failure. The findings from the present study indicate that the urine response to diuretic therapy in these subjects is similar to those of past studies characterizing individuals with diuretic resistance. What was true then is true now.

Toward the end of Back to the Future, Marty returns back to the present but not before he inspires his father to stand up to Biff and rescue his future wife (Marty’s mother) in 1955. When Marty returns, he finds his father transformed into a self-confident and successful man. So it may be for diuretic agents in heart failure. Our collective challenge as physician-scientists is to build on what we have learned from the past and apply these lessons in the modern context. As designed, the Verbrugge et al study does not provide sufficient evidence to change clinical practice. Rather, this study should provide impetus for examining new ways by which the renal response to diuretics, including urine electrolyte composition, might inform and improve heart failure management. For instance, can a decline in urine NaCl excretion be used to identify patients who would benefit from specific inotropic agents or mechanical ultrafiltration? Does a decline in urine NaCl excretion serve as a harbinger for a decline in renal perfusion or the development of acute kidney injury (worsening renal function)? Is there a role for using the urine electrolyte composition in stratifying risk of acute kidney injury in patients who receive intravenous radiocontrast with coronary angiography or who undergo implantation of a left ventricular assist device or heart transplant? How exactly should diuretic resistance be defined, and can we develop new strategies to safely combat it? These are questions that should be addressed as our armamentarium for combating heart failure continues to expand.

Disclosures

None.

References


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