In the now classic 1985 fantasy-comedy film Back to the Future, teenage 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.

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±vasodilators and their usual medications for heart failure, including β-adrenergic antagonists and renin–angiotensin system blockers. In some cases, chlorthalidone 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, (54%), 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, (54%), and New York Heart Association functional class III (54%).

As an example of this elaborate renal response, bumetanide acts by increasing the activity of the NaCl cotransporter,13,14 increase mitochondria volume, and trigger epithelial cell hypertrophy and hyperplasia.15 All of these adaptations enhance the reabsorptive capacity for NaCl in the distal convoluted tubule.
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 al5 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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Urine Electrolyte Composition and Diuretic Therapy in Heart Failure: Back to the Future?

Alan C. Pao and Glenn M. Chertow

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