¹²³I-MIBG cardiac sympathetic imaging provides further insight into cardiorenal interactions in systolic heart failure patients

Thomas H. Schindler, MD, PhD,^{a,b} and Sudhir Jain, MD^b

^a Division of Nuclear Medicine, Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, MO

^b Cardiovascular Division, John T. Milliken Department of Internal Medicine, Washington University School of Medicine, St. Louis, MO

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Systolic heart failure is predominantly related to coronary artery disease followed by idiopathic cardiomyopathy, valvular disease, and hypertensive heart disease.¹ The left ventricular remodeling process owing to permanent increases in volume load plays a critical role in the clinical manifestation and outcome in systolic heart failure patients. This also leads to the systemic and local activation of the renin-angiotensin-system (RAS) associated with some hypertrophic growth, change in the phenotype of the cardiac myocyte due to reappearance of fetal gene program, increasing degeneration of contractile protein, malfunctioning excitation-contracting coupling, interstitial fibrosis, and a decrease in contractile response to beta-adrenergic stimulation.² In this respect, numerous clinical investigations have unraveled beneficial effects of RAS blockade with angiotensin-converting enzyme inhibitors, angiotensin II type 1 receptor blockers, and aldosterone antagonists leading to a distinct improvement in symptoms and clinical outcome in systolic heart failure patients.^{1,2} Yet, RAS blockade treatment may not necessarily lead to a beneficial treatment response as a variety in individual responses may exist.^{3,4} The reported inter-individual variability in treatment response to RAS blockade in

systolic heart failure patients remains obscure that may be related, at least in part, to differences in race, ethnicity, comorbid conditions, concomitant use of other medications, and certain genetic predispositions.^{1,2} Given the reported variability in myocardial response to medical RAS blockade, apart from suboptimal medical RAS blockade in the myocardium, differences in myocardial contractile responsiveness to sympathetic activation and its interaction with decreased renal function may, at least in part, account for observed variability in treatment responses in heart failure patients.^{5,6}

In this issue of the Journal of Nuclear Cardiology, Marsico et al.⁷ report of novel and important findings in that patients with renal dysfunction and systolic heart failure have a worse impairment of cardiac sympathetic activity than in those systolic heart failure patients with preserved renal function. The study consisted of 263 patients with mild-to-severe heart failure (NYHA II-III) of ischemic and non-ischemic origin (27% vs. 73%) undergoing ¹²³I-meta-iodobenzylguanidine (¹²³I-MIBG) myocardial scintigraphy assessing cardiac sympathetic activation. The heart-to-mediastinal (H/M) ratio was derived from early and late activities and the wash out rate was calculated.^{8,9} As it was observed, the GFR positively correlated with late H/M ratio ($r = 0.215$; $p < 0.001$), signifying some interaction among reductions in kidney function and an impairment of cardiac sympathetic activity. When the study population was sub-grouped into moderate-to-severe and normal-to-mild GFR reduction, a decrease in late H/M ratio was noted in patients with renal dysfunction compared to those without (1.49 ± 0.21 vs. 1.56 ± 0.26 , $p = 0.03$). Importantly, a reduction in glomerular filtration rate (GFR) was indeed an independent predictor of reduced cardiac sympathetic activity, implying indeed a direct

Reprint requests: Thomas H. Schindler, MD, PhD, Division of Nuclear Medicine, Mallinckrodt Institute of Radiology, Washington University School of Medicine, 510 S. Kingshighway, St. Louis, MO 63110; thomas.h.schindler@gmail.com, thschindler@wustl.edu
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role of worsened kidney function in altering cardiac sympathetic activity in systolic heart failure patients, while this was not observed for the early H/M ratio and the wash out rate. When analyzing the positive association among GFR and late H/M ratio or cardiac sympathetic activity (Figure 1) in four quadrants applying the median of both parameters, however, someone could realize that the proportion of individuals did differ only mildly among the four quadrant groups. Interestingly, the group with reduced GFR and late H/M ratio (group 1; lower-left quadrant) was similar in numbers to those with reduced GFR but normal late H/M ratio (group 2; upper-left quadrant) or with normal GFR but reduced late H/M ratio (group 3; lower-right quadrant). In addition, despite the presence of heart failure, there was an equally distributed group with normal values for kidney function and cardiac sympathetic activity (group 4; upper-right quadrant). Such variability in characteristics of the HF patients related to kidney function and cardiac sympathetic activity emphasizes the complexity or multifactorial etiology of cardiac-renal axis disturbance,^{5,6} contributing to progressive cardiac dysfunction in heart failure patients. Thus, it appears indeed that renal dysfunction contributes, at least in part, to the observed impairment of cardiac sympathetic activity that carries important information on the outcome of these heart failure patients.^{10,11} Thus, despite optimal medical heart failure treatment a significant portion of these patients still had a severe impairment of cardiac sympathetic activity associated with renal dysfunction (group 1). The study also demonstrated that in a substantial portion of these patients treated for heart failure, reductions in left ventricular ejection fraction were accompanied by a progressive impairment of cardiac sympathetic activation reflecting an increase cardiac risk.¹² When systolic function progressively decreases then the increase in circulating epinephrine and norepinephrine levels strive to prevent a further decline in cardiac stroke volume by stimulating β 1-mediated myocyte contraction.¹³ This compensatory mechanism to maintain myocardial contractility and thus cardiac output, however, may be detrimental in the further course and the myocardium commences protecting itself from permanent adrenergic overstimulation by a downregulation of myocardial β 1-receptors. Such downregulation of myocardial β 1-receptors also results in a decrease in myocardial ¹²³I-MIBG uptake reflecting impaired cardiac sympathetic activity.^{14,15}

The study conducted by Marsico et al.⁷ adds further important information that a worsening of kidney function may not only be seen as a consequence of heart failure-related low cardiac output leading to low arterial blood pressures and relative hypoperfusion of the

kidneys¹³ but also as a source causing a further impairment of cardiac sympathetic activity associated with a further worsening of cardiac function. The exact kidney-related mechanism mediating a further decrease of cardiac sympathetic activity remain uncertain but it may offer a new and critical target of systolic heart failure therapy as current observations suggest.⁷ This appears of utmost importance, as the manifestation of a cardiorenal syndrome commonly leads to a further worsening of clinical outcome in systolic heart failure patients.

Disclosure

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