Cardiac sympathetic imaging in heart failure: Is revival possible?

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Received Feb 21, 2019; accepted Feb 22, 2019
doi:10.1007/s12350-019-01682-3

See related article, pp. 72–85

Heart failure (HF) is a clinical syndrome that is a consequence of activation of compensatory neurohormonal systems in response to myocardial injury. The sympathetic nervous system, renin-angiotensin-aldosterone system, and natriuretic peptides are compensatory neurohormonal pathways activated in systolic heart failure. Activation of neurohormonal systems results in adverse cardiac remodeling and progression of myocardial dysfunction with increased mortality due to pump failure and sudden cardiac death. Insights into the pathophysiology of progression of systolic heart failure have led to the introduction of medical regimens targeting different neurohormonal pathways, thereby improving survival.[1] Annual mortality in heart failure can range from 10% in Stage C HF with New York heart association (NYHA) functional class II-III symptoms to 75% in Stage D HF patients.[2,3]

Sympathetic activation of the heart results in release of norepinephrine from cardiac sympathetic nerve endings and epinephrine from the adrenal medulla. Norepinephrine (NE) is the predominant neurotransmitter that binds to adrenergic receptors in the heart with resultant increase in positive inotropic (increased contractility) and chronotropic (increased heart rate) effects.[4] The released NE is recycled into the presynaptic nerve terminals by the uptake-1 transporter system.[5]

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J Nucl Cardiol 2021;28;86–9.
1071-3581/$34.00

The heightened activity of sympathetic nervous system in systolic HF was demonstrated by increase in plasma norepinephrine (NE) levels from increased cardiac NE spillover.[6] The increased NE release due to chronic sympathetic activation and impairment in the NE uptake transporter system results in depletion of cardiac norepinephrine stores.[7] Evidence suggests chronic exposure to increased NE levels at the synaptic cleft results in beta-adrenoreceptor downregulation with downstream effects on second messenger signaling (adenylate cyclase) and decreased contractile function in systolic HF.[8] The plasma norepinephrine levels correlated with severity of left ventricular systolic dysfunction and predictor of mortality from progressive heart failure.[9,10]

MEASUREMENT OF SYMPATHETIC ACTIVATION IN HEART FAILURE

Clinical assessment of sympathetic nervous system activity can be performed by measuring plasma norepinephrine levels, heart rate variability using spectral analysis, cardiac NE spill over using radiolabeled technique, and muscle sympathetic nerve activity using microneurography. However, these techniques have limitations in qualitatively and quantitatively measuring selective cardiac sympathetic activation.[11]

I-123 MIBG IN SYSTOLIC HEART FAILURE

I-123 meta-iodobenzylguanidine (I-123MIBG) was developed as a radioiodinated analog of guanethedine, a false neurotransmitter that competes with NE for uptake into presynaptic nerve terminal via the uptake 1 transporter.[12] The affinity of I-123 MIBG to concentrate in tissues with sympathetic innervation was seen as a prospect to use this radiotracer to image the cardiac sympathetic innervation. Early and late planar imaging using I-123 MIBG provides information on the integrity

of presynaptic sympathetic terminals and function of uptake-1 transporter system. Myocardial washout rate of I-123 MIBG reflects the intensity of sympathetic activation with higher washout rates indicating heightened sympathetic activation. The protocol for standardized planar I-123 MIBG imaging in patients with systolic HF has been detailed by Agostini et al[13]

In systolic HF, decreased uptake of I-123 MIBG due to impairment of the uptake -1 transporter system and increased sympathetic activity results in increased clearance of the radiotracer from the synaptic junction.[14] A proof of concept study by Henderson et al using I-123 MIBG tomographic imaging in 14 healthy controls and 16 patients with dilated cardiomyopathy showed significant differences in the myocardial kinetics of I-123 MIBG between the two groups with increased myocardial washout rate in the dilated cardiomyopathy group.[15] Schofer et al used I-123 MIBG scintigraphy to correlate myocardial radiotracer activity (I-123 MIBG uptake and myocardial/mediastinum activity ratio) to myocardial NE concentrations, left ventricular ejection fraction (LVEF), and functional capacity in patients with dilated cardiomyopathy. The investigators demonstrated a positive correlation between scintigraphic imaging variables and left ventricular ejection fraction and myocardial NE concentrations.[16] Merlet et al evaluated the prognostic significance of I-123MIBG planar imaging in 90 patients with ischemic or nonischemic cardiomyopathy and demonstrated that heart/mediastinum (H/M) I-123MIBG activity ratio < 1.2 predicted poor survival.[17] A large-scale multicenter study to validate the prognostic significance of cardiac sympathetic imaging using I-123 MIBG planar imaging to predict cardiac events in systolic HF led to design of ADMIRE-HF (Adre View Myocardial imaging for risk evaluation in heart failure). ADMIRE-HF was a multicenter study designed to prospectively evaluate the prognostic significance of I-123 MIBG scanning in 961 patients with systolic heart failure with LVEF $< 35\%$ and NYHA functional class II or III on optimal guideline-based medical therapy. The composite primary endpoint was the time to occurrence of heart failure progression, life-threatening arrhythmias, or cardiac death (cardiac events) in relation to late heart/mediastinum (H/M) ratio. Using a H/M ratio cutoff of 1.6 based on prior studies, late H/M ratio $>$ 1.6 had a significantly lower cardiac event rate compared to ratio of H/M ratio < 1.6 (15% vs 38% $p < 0.0001$). Arrhythmic events (ICD discharges, resuscitated cardiac arrest, and ventricular tachycardia) were reported more frequently in patients with H/M < 1.6 (10.4% vs 3.5%). Multivariate analysis yielded late (H/M) ratio, brain natriuretic peptide (BNP), LVEF, and NYHA class as significant predictors of cardiac events. Late H/M ratio provided additional risk stratification for cardiac events in patients with elevated BNP ($>$ 140 ng/L) and LVEF $< 30\%$. Late H/M ratio < 1.2 identified a high-risk group with cardiac mortality of 9.6%/year compared to less than 1% annual mortality rate with H/M ratio > 1.6.[18] Heart/Mediastinum ratio showed high degree of reproducibility in stable NYHA class II-III systolic heart failure patients with LVEF $< 35\%$.[19]

The present study by Silverio and colleagues investigated the role of combined myocardial and lung 123-I MIBG imaging to prognosticate newly diagnosed systolic HF patients and LVEF $< 40\%$ by echocardiogram. Patients hospitalized with first episode of decompensated heart failure and LVEF $< 40\%$ underwent 123-MIBG scanning after 3 months, if they had persistent LV systolic dysfunction with echocardiographic evidence of LVEF$< 40\%$ and NYHA II or III functional class despite optimal medical therapy. During a mean follow-up of 40 months, there were 33 cases (39.3%) of rehospitalization and 24 deaths (28.6%). Late lung/heart ratio (L/H), systolic pulmonary artery pressure, and left ventricular end-systolic volumes (LVESV) estimated by echocardiogram predicted HF rehospitalizations, cardiac death, and all-cause mortality. A ratio cutoff of late L/H ratio $>$1.1 was able to further discriminate patients who are at risk for cardiac events (HF rehospitalization and cardiac death) based on their baseline estimated pulmonary artery pressures and improved risk prediction for cardiac and all-cause mortality with high LVESV. This study contrasted the conclusions from ADMIRE-HF study in that H/M ratio, LVEF, and natriuretic peptide measurements did not predict cardiac events or all-cause mortality. Kamiyoshi et al identified a high-risk cohort for cardiac events (hospitalization, sustained ventricular tachycardia, and cardiac death) based on delayed L/H ratio cutoff > 1.1. Other imaging variables like late H/M ratio and late L/M ratio were not identified as significant predictors of cardiac events. It is noteworthy that delayed L/H ratio correlated with mean pulmonary artery pressures, pulmonary vascular resistance, and pulmonary capillary wedge pressures.[20] Silverio and colleagues did not have data on invasive hemodynamics but echocardiographic estimation of systolic pulmonary artery pressure was predictive of cardiac events. Both studies identified a high-risk patient cohort who may need close surveillance, identification of comorbidities, and triggers for decompensation, medication adjustment, and referral for advanced therapies.

I-123 MIBG scan parameters have been used to assess treatment response to beta-blockers, angiotensin-converting enzyme inhibitors, and aldosterone blockers. Lack of improvement in myocardial washout rate on serial imaging has shown to predict cardiac events in

patients started on optimal medical therapy after first episode of decompensated heart failure.[12]

I-123 MIBG scanning was approved by the Food and Drug Administration (FDA) for cardiac sympathetic nerve imaging in 2013 after the results of ADMIRE-HF trial were published. The Japanese Circulation society guidelines approved the use of I-123 MIBG scanning for assessment of severity of HF, effects of treatment, and prognostication.[21] Despite its discriminatory power to predict cardiac events irrespective of LVEF, application of cardiac sympathetic imaging has not found a role in daily clinical practice in the United States due to lack of standardization of imaging protocols. The absence of reference values based on age, medication interference with MIBG uptake, cost constraints if serial imaging is opted, and the long wait time(4 hrs) to complete scan may prevent the widespread application of this technology.

IS THERE STILL A ROLE FOR CARDIAC SYMPATHETIC IMAGING TO RISK ASSESSMENT IN CARDIAC DISEASE?

2D echocardiogram is the most accessible modality for serial imaging to assess treatment response, disease progression, and implantable cardiac defibrillator implantation despite its limitations to accurately assess LVEF and prognostic capability. Cardiac magnetic resonance imaging provides comprehensive information of cardiac anatomy, accurate estimation of biventricular systolic function, myocardial viability in ischemic heart disease, etiology of restrictive cardiomyopathies, and risk prediction based on the presence of fibrosis by late gadolinium contrast.[22] The Seattle heart failure model was developed and validated to accurately prognosticate ambulatory HF patients up to 3 years using demographic characteristics, functional capacity, medication use, and laboratory parameters.[23] Despite the availability of imaging modalities and survival scores, individual short- and long-term risk assessment for worsening heart failure and sudden cardiac death is still imperfect.

Mortality in systolic heart failure is predominantly due to sudden cardiac death or pump failure. The introduction of neurohormonal antagonism with beta-blockers, angiotensin-converting enzyme inhibitors, and aldosterone blockers in management of systolic heart failure has resulted in significant reduction in all-cause mortality with major impact on reduction of sudden cardiac death or progressive heart failure.[24] In the Oregon registry of sudden cardiac death, severe left ventricular dysfunction (LVEF <35%) was seen in only one-third of cases of sudden cardiac death.[25] Some of the identified risk factors were younger age, women, and seizure disorder. DANISH study investigators concluded that defibrillator implantation in symptomatic patients (New York Heart Association functional class II or III) with nonischemic cardiomyopathy with LVEF <35% did not decrease all-cause mortality even though sudden cardiac death was decreased by 50%.[26] The findings of the VEST study showed no mortality benefit of the wearable cardioverter-defibrillator immediately after acute myocardial infarction and decreased left ventricular systolic function (LVEF <35%).[27] The improvement in medical and device therapy for systolic heart failure has seen a decrease in cardiac mortality with a parallel increase in noncardiovascular deaths due to comorbidities with competing risks.[24]

I-123 MIBG scanning may play role in identifying patients at risk for cardiac events with risk factors for ischemic heart disease and heart failure like diabetes mellitus, hypertension, and renal dysfunction. The risk of cardiovascular mortality is continuum in systolic heart failure and LVEF assessment alone should not be used for device therapy decision making and prognostication. Cardiac sympathetic imaging using I-123 MIBG should be explored further to provide risk assessment.

Personalized risk assessment using genetic sequencing, multimodality imaging approach targeting anatomical, functional, and cardiac autonomic function will be a futuristic approach to manage systolic HF. However, with the growing prevalence of heart failure and increasing costs of health care, clinicians will be left with a decision to use cost-effective methods to diagnose, manage, and prognosticate patients with systolic HF.

In conclusion, 123 MIBG scanning provides valuable data regarding cardiac sympathetic activation in heart failure but needs standardization of imaging protocols and parameters with clear indications and cost-effectiveness analysis before widespread adoption.

Disclosure

The authors have indicated that they have no financial conflict of interest.

References

1. Jessup M, Brozena S. Heart failure. NEJM 2003;348:2007-18.
2. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR et al; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371(11):993-1004
3. Rose EA, Gelijns AC, Moskowitz AJ, Heitjan DF, Stevenson LW, Dembitsky W et al; Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) Study Group. Long-term use of a left ventricular

assist device for end-stage heart failure. NEJM 2001;345(20):1435-43
4. Lymperopoulos A, Rengo G, Koch WJ. Adrenergic nervous system in heart failure. Pathophysiology and Therapy. Circ Res 2013;113:739-53.
5. Higuchi T, Schwaiger M. Imaging cardiac neuronal function and dysfunction. Curr Cardiol Rep 2006;8:131-8.
6. Hasking GJ, Esler MD, Jennings GL, Burton D, Johns JA, Korner PI. Norepinephrine spillover to plasma in patients with congestive heart failure: evidence of increased overall and cardiorenal sympathetic nervous activity. Circulation 1984;4:615-21.
7. Eisenhofer G, Friberg P, Rundqvist B, Quyyumi AA, Lambert G, Kaye DM, et al. Cardiac sympathetic nerve function in congestive heart failure. Circulation 1996;93:1667-76.
8. Bristow MR, Ginsburg R, Minobe W, Cubicciotti R, Sageman S, Lurie K, et al. Decreased catecholamine sensitivity and β-adrenergic—receptor density in failing human hearts. NEJM 1982;307:205-11.
9. Thomas JA, Marks BH. Plasma norepinephrine in congestive heart failure. Am J Cardiol 1978;41:233-43.
10. Cohn JN, Levine TB, Olivari MT, Garberg V, Lura D, Francis GS, et al. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. N Engl J Med 1984;311(13):819-23.
11. Esler M, Kaye D, Lambert G, Esler D, Jennings G. Adrenergic nervous system in heart failure. Am J Cardiol 1997;80:7L-14L.
12. Gupta S, Amanullah A. Radionuclide imaging of cardiac sympathetic innervation in heart failure:unlocking untapped potential. Heart Fail Rev 2015;20:215-26.
13. Agostini D, Carrio I, Verberne HJ. How to use myocardial 123I-MIBG scintigraphy in chronic heart failure. Eur J Nucl Med Mol Imaging 2009;36(4):555-9.
14. Rabinovitch MA, Rose CP, Rouleau JL, Chartrand C, Wieland DM, Lepanto L, et al. Metaiodobenzylguanidine [131I] scintigraphy detects impaired myocardial sympathetic neuronal transport function of canine mechanical-overload heart failure. Circ Res 1987;61(6):797-804.
15. Henderson EB, Kahn JK, Corbett JR, Jansen DE, Pippin JJ, Kulkarni P, et al. Abnormal I-123 metaiodobenzylguanidine myocardial washout and distribution may reflect myocardial adrenergic derangement in patients with congestive cardiomyopathy. Circulation 1988;78:1192-9.
16. Schofer J, Spielmann R, Schuchert A, Weber K, Schluter M. Iodine-123 meta-iodobenzylguanidine scintigraphy: A noninvasive method to demonstrate myocardial adrenergic nervous system disintegrity in patients with idiopathic dilated cardiomyopathy. J Am Coll Cardiol 1988;12(5):1252-8.
17. Merlet P, Valette H, Dubois-Randé JL, Moyse D, Duboc D, Dove P, et al. Prognostic value of cardiac metaiodobenzylguanidine imaging in patients with heart failure. J Nucl Med 1992;33(4):471-7.
18. Jacobson AF, Senior R, Cerqueira MD, Wong ND, Thomas GS, Lopez VA et al; ADMIRE-HF Investigators. Myocardial iodine-123 meta-iodobenzylguanidine imaging and cardiac events in heart failure. Results of the prospective ADMIRE-HF (AdreView myocardial imaging for risk evaluation in heart failure) study. J Am Coll Cardiol 2010;55(20):2212-2
19. Bateman TM, Ananthasubramaniam K, Berman DS, Gerson M, Gropler R, Henzlova M et al. Reliability of the ^{123}I-mIBG heart/mediastinum ratio: Results of a multicenter test-retest reproducibility study. J Nucl Cardiol 2018; https://doi.org/10.1007/s12350-017-1183-6
20. Kamiyoshi Y, Yazaki Y, Urushibata K, Koizumu T, Kasai H, Izawa A, et al. Risk stratification assessed by combined lung and heart iodine-123 metaiodobenzylguanidine uptake in patients with idiopathic dilated cardiomyopathy. Am J Cardiol 2008;101(10):1482-6.
21. JCS Joint Working Group. Guidelines for clinical use of cardiac nuclear medicine (JCS 2010)—digest version. Circ J 2012;76(3):761-7
22. Karamitsos TD, Francis JM, Myerson S, Selvanayagam JB, Neubauer S. The role of cardiovascular magnetic resonance imaging in heart failure. J Am Coll Cardiol 2009;54(15):1407-24.
23. Levy WC, Mozaffarian D, Linker DT, Sutradhar SC, Anker SD, Cropp AB, et al. The seattle heart failure model: prediction of survival in heart failure. Circulation 2006;113(11):1424-33.
24. Cubbon RM, Gale CP, Kearney LC, Schechter CB, Brooksby WP, Nolan J, et al. Changing characteristics and mode of death associated with chronic heart failure caused by left ventricular systolic dysfunction: a study across therapeutic eras. Circ Heart Fail 2011;4(4):396-403.
25. Stecker EC, Vickers C, Waltz J, Socoteanu C, John BT, Mariani R, et al. Population-based analysis of sudden cardiac death with and without left ventricular systolic dysfunction: two-year findings from the oregon sudden unexpected death study. J Am Coll Cardiol 2006;47(6):1161-6.
26. Køber L, Thune JJ, Nielsen JC, Haarbo J, Videbæk L, Korup E, et al. Defibrillator implantation in patients with nonischemic systolic heart failure. N Engl J Med 2016;375(13):1221-30.
27. Olgin JE, Pletcher MJ, Vittinghoff E, Wranicz J, Malik R, Morin DP, et al. Wearable cardioverter-defibrillator after myocardial infarction. N Engl J Med 2018;379(13):1205-15.