Expanding the clinical potential of cardiac radionuclide adrenergic imaging

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The autonomic nervous system, divided into sympathetic and parasympathetic components, plays an essential role in sustaining body functions. In particular, direct cardiac autonomic innervation working in conjunction with circulating neurohormones (epinephrine, norepinephrine (NE), renin-angiotensin-aldosterone system (RAAS) hormones, cytokines) controls cardiac function (heart rate, contractility) and adjusts vascular tone for maintenance of proper perfusion to organs and tissues.¹

There is a long history of exploring methods to assess human autonomic nervous system activity. These include efforts to measure the sympathetic component through determination of systemic plasma concentration, organ-specific amounts, and regional spillover of the chemical mediator norepinephrine (NE).² One can also perform direct measurements of systemic post-ganglionic sympathetic activity via microneurography that records pulses in a peripheral nerve,³ commonly the peroneal. Alternatively, for focused assessment of cardiac sympathetic activity, one can directly visualize and quantitate cardiac uptake and washout of catecholamines using radionuclide tracer analogues of NE, such as SPECT iodine-123 *meta*-iodobenzylguanidine (¹²³I-*m*IBG)⁴ and various positron emission tomographic (PET) agents,⁵ which are taken up and concentrated in cardiac innervating sympathetic nerves. Most clinical

focus has been on ¹²³I-*m*IBG, with studies showing convincing evidence that such imaging is effective in risk stratifying patients with advanced heart failure (HF) independently of, and often better than, conventional techniques including measurement of plasma NE levels,⁶ and is also potentially useful in evaluating other cardiac conditions such as arrhythmias and ischemic heart disease.⁴

Of course, a crucial objective of cardiac risk stratification with ¹²³I-*m*IBG and analogous PET adrenergic tracers is to effectively guide therapies that can reduce mortality and improve the quality of life. While there is a strong logical basis and robust observational data demonstrating that adrenergic imaging can, beyond and arguably better than commonly used methods, help guide the use of invasive expensive cardiac electronic devices and procedures, no one has yet been able to undertake and complete the necessary prospective randomized clinical studies needed for inclusion of such imaging into societal guidelines and use in routine clinical practice. Consequently, and also because of financial constraints, after decades of investigation and discussions about this relatively easy, noninvasive technique that assesses a crucial component of cardiovascular function in health and disease, it is not being used.⁷

POTENTIAL TO BROADEN THE POTENTIAL USE OF CARDIAC ADRENERGIC IMAGING BY CONSIDERING ASSOCIATION OF CARDIAC DISEASE WITH OTHER ORGAN SYSTEMS

As sympathetic innervation involves the whole body, clinical use of sympathetic cardiac imaging could be encouraged by finding utility in performing it in conjunction with diseases related to other systems and organs. For example, there is currently much interest in cardiac ¹²³I-*m*IBG imaging to more accurately distinguish Parkinson's disease and dementia with Lewy

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bodies from other similar appearing neurologic conditions.⁷

However, a key organ that interacts closely with the heart, and that is highly controlled by autonomic innervation, is the kidney. Renal sympathetic efferent and afferent neurons innervate the kidneys via their course within and just adjacent to the renal artery wall, proceeding to renal vasculature, tubules, and the juxtaglomerular apparatus, serving to regulate volume retention through sodium reabsorption, control renal blood flow via neutrally mediated effects on local vascular tone, and stimulate renin release that directs the renin-angiotensin-aldosterone system (RAAS), while also sending afferent signals to the brain that in turn sends out efferent signals adjusting cardiac function and systemic vascular tone.⁸ Under normal physiologic conditions, this interplay between the heart and kidney acts in concert to maintain proper homeostasis at rest and during various physiologic “stresses.” However, in pathologic conditions such as hypertension, systemic, renal, and cardiac sympathetic tone is abnormal. The abnormality is manifest systemically as increased muscle sympathetic nerve activity (MSNA), increased plasma NE levels, and higher NE plasma spillover from activated sympathetic fibers,¹ while locally at the kidney there is increased NE regional spillover and an increase of renal sympathetic nerve firing.⁹ Augmented cardiac and vascular sympathetic nerve activity is demonstrated by increased cardiac NE spillover, a higher rate of left ventricular ejection, reduced aortic compliance, and arteriolar vasoconstriction.^{2,8}

In response to the aforementioned understanding of the role of renal sympathetic innervation in the pathophysiology of hypertension, as early as the 1950s surgical disruption of renal sympathetic innervation has been undertaken in an attempt to treat resistant disease, but this approach has been associated with prohibitively high morbidity, mortality, and long-term complications.¹⁰ A major breakthrough was the development of a percutaneous approach in which a catheter is threaded into the renal arteries, with subsequent ablation of the nearby sympathetic nerves using radiofrequency energy or more recently ultrasound.¹¹ Among the first to demonstrate the efficacy of catheter-based renal sympathetic denervation (RDN) was Krum et al.,¹⁰ who reported a substantial and sustained reduction in blood pressure (BP) without serious adverse events. Subsequent work has shown that catheter-based RDN not only reduces renal NE spillover, a manifestation of blockage of renal efferent sympathetic activity that leads to turning-off of the renin-angiotensin-aldosterone system, but also produces a sustained reduction in muscle sympathetic nerve pulses not directly related to the BP reduction,¹² and therefore likely to involve

alterations in afferent signals from the kidney that are relayed to integrative structures in the brainstem and hypothalamus with resultant suppression of central sympathetic outflow.⁸

Interesting insights into the potential for RDN to affect cardiac pathophysiology were reported in a study by Brandt et al.¹³ in which patients with medication-resistant hypertension underwent RDN. Six months after the procedure, not only was there a significant reduction in BP, but also reductions in intraventricular septal thickness and left ventricular mass index, improved diastolic function with increased diastolic relaxation velocity and decreased filling pressures, and a significant increase in ejection fraction. A key finding was that left ventricular hypertrophy regression was not exclusively associated with BP reduction, raising speculation that decreases in systemic sympathetic tone, with reduced RAAS activity, facilitated regression of myocardial fibrosis beyond that from the BP decrease.

HOW MIGHT MIBG IMAGE FINDINGS RELATE TO ALTERATIONS IN SYSTEMIC SYMPATHETIC ALTERATIONS?

Given these demonstrated effects of RDN on the heart, one would expect that cardiac ¹²³I-*m*IBG imaging could be an effective way to assess the results of the procedure. Nevertheless, one must consider that the relationship of image findings to RDN is likely to be complex. For example, not only would changes in systemic sympathetic input to the heart influence cardiac ¹²³I-*m*IBG uptake, but pathologic structural and functional changes to the myocardium and innervating sympathetic neurons would also affect ¹²³I-*m*IBG images.

Cardiac sympathetic innervation is most commonly assessed by global tracer uptake on a planar image in relation to mediastinal background, i.e., the heart-to-mediastinum ratio (HMR), found most useful in delayed images that reflect tracer retention. While there is robust evidence that a reduced HMR is associated with a variety of worsened cardiac outcomes, there are several mechanisms that can result in this image finding. As described by Fallavollita and Canty,¹⁴ a reduced HMR can indicate either “denervation” from anatomic loss of sympathetic nerves, or “dysinnervation” in which an insult results in sympathetic nerve dysfunction that can be reversible with recovery from injury. The dysfunction can involve abnormalities in any of several components of tracer uptake and storage in the pre-synaptic sympathetic terminal, including disruption or downregulation of the NET uptake-1 transporter, problems with the vesicular monoamine transport (VMAT) of tracer into protective vesicles, issues related to the degradative

monoamine oxidase (MAO) enzyme, and perhaps also increased extraneuronal uptake (uptake 2).¹⁵

Another matter to consider is that the relation of cardiac MIBG uptake to the systemic sympathetic state is unclear. While a correlation between the HMR and myocardial NE content has been shown, in a study of patients with cardiomyopathy, both Schofer et al.¹⁶ and Tamaki et al.¹⁷ did not find significant correlations between HMR and plasma catecholamine levels.

Another commonly measured parameter in cardiac ¹²³I-*m*IBG imaging is tracer decrease between early (about 15 minutes after tracer administration) and delayed (approximately 4 hour later) images, i.e., myocardial washout (WO). An abnormally increased ¹²³I-*m*IBG WO has been associated with worsened patient outcome.⁴ While the exact mechanism of increased cardiac ¹²³I-*m*IBG WO is not completely understood, Tamaki et al.¹⁷ did observe a significant correlation between WO and plasma NE concentration. This finding would be in accord with the concept that a potential mechanism of elevated WO is excessive local release of endogenous NE, a reflection of increased sympathetic tone to the heart, competing with radio-tracer for uptake sites,¹⁶ although other factors likely also contribute.^{4,15}

Another issue to consider is that RDN, by altering efferent innervation of the kidney, impedes output of renin, thus decreasing the production of RAAS neuro-hormones. Many studies have shown that medications directed at RAAS components, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blocking agents, and mineralocorticoid blockers, can increase HMR and decrease WO.⁴ It is unclear how much of the image changes brought on by these medications is related to cardiac structural changes that impact local sympathetic nerve function versus hemodynamic improvements mediating changes to cardiac sympathetic drive.

Thus, numerous factors can contribute to observations and measurements from cardiac ¹²³I-*m*IBG imaging, making it difficult to predict how such images would be affected by RDN. In the first reported study assessing the effect of RDN on cardiac ¹²³I-*m*IBG imaging, Donazzan et al.¹⁸ assessed eleven patients with resistant hypertension just before and 6 months following RDN. Delayed HMR that was normal at baseline (2.52 ± 0.47) was essentially unchanged by the RDN. However, the mean baseline WO of $24.1 \pm 12.7\%$ decreased to $7.9 \pm 25.5\%$ ($P = 0.047$). While RDN succeeded in improving BP, the change in BP did not correlate with WO improvement.

RDN AND ADRENERGIC IMAGING FOR CORONARY VASOSPASTIC ISCHEMIA

Cardiac ¹²³I-*m*IBG abnormalities have been reported in patients with vasospastic angina (VSA). Inobe et al.¹⁹ found regional tracer uptake reduction and abnormally high regional WO that were associated with more frequent anginal attacks and life-threatening ventricular arrhythmias. Watanabe et al.²⁰ also found focal ¹²³I-*m*IBG abnormalities in patients with VSA. However, it is unclear whether abnormal cardiac sympathetic image findings in VSA are caused by ischemic myocardial damage, versus abnormalities of the sympathetic innervation shown by the images being the primary problem and then causing the VSA. In contrast to other reports, Sakata et al.²¹ described reduced regional WO in VSA patients compared with normal controls. As another report by this group²² showed that administration of atropine increased WO, the authors attributed the reduced washout associated with coronary spasm to potentially reflect enhanced parasympathetic tone. On the contrary, Taki et al.²³ showed increased regional WO in patients with vasospastic angina, attributed to differences in disease severity and methods of analysis. Thus, for sure, the meaning of ¹²³I-*m*IBG abnormalities in the setting of VSA for which RDN is employed as a potential therapy is difficult to predict. Of note, the ¹²³I-*m*IBG abnormalities reported in these studies were focal, and thus tomographic imaging may be absolutely essential for proper evaluation of VSA using adrenergic imaging.

In the current issue of the Journal of the Nuclear Cardiology, Feyz and associates,²⁴ knowing that the autonomic nervous system—sympathetic and parasympathetic components—is a key etiologic factor in VSA, seek to explore the effect of RDN both in terms of subjective clinical response and objectively measured changes in cardiac ¹²³I-*m*IBG images. The authors cite a previous case report of theirs demonstrating resolution of dangerous ventricular arrhythmias following RDN, attributed to amelioration of hyperactive cardiac sympathetic activity in a patient with vasospastic angina.²⁵

In their study, 10 subjects with refractory VSA underwent RDN using ultrasound emissions. Cardiac planar ¹²³I-*m*IBG imaging (but no SPECT), was performed at baseline and 6 months post RDN, and clinical response was assessed based on changes in Canadian Cardiovascular Society grading, BP and heart rate changes, and quality of life using the Seattle Angina Questionnaire. The authors hypothesized that with clinical improvement from relief of the VSA, ¹²³I-*m*IBG

Figure 1. Schematic of selected components of cardiac, kidney, and systemic sympathetic innervation and tone, with potential effects on cardiac radionuclide adrenergic findings. (Note: the figure is a simplification of an extensively more complex system that also involves other organs, with some anatomic aspects not displayed in exact detail). *HF*, heart failure; *HMR*, heart-to-mediastinum ratio; *HTN*, hypertension; ^{123}I -mIBG, iodine-123 meta-iodobenzylguanidine; *NE*, norepinephrine; *RAAS*, renin-angiotensin-aldosterone system; *RDN*, renal denervation; *T*, thoracic; *VSA*, vasospastic angina; *WO*, washout.

parameters would improve as demonstrated by an increase in HMR and a decrease in washout.

As expected, the patients' clinical conditions improved with lower office BPs, fewer angina attacks, and less physical limitations, accompanied by better quality of life (although statistical power was limited by there being too few patients). ^{123}I -mIBG image changes, however, were less impressive and of less clear meaning. No significant change was observed in either the initial or delayed median HMRs, with 4 patients showing an increase in delayed HMR, and 6 patients showing a decrease. With only 10 subjects, one cannot make conclusions on this matter. For WO, the

number of patients (5 shown) was too underpowered for any meaningful conclusion, with 4 of the 5 patients increasing WO but the median value decreased from 15 to 13 because of one patient. It would have been helpful to have known if there were any changes in regional ^{123}I -mIBG uptake WO given prior reports using tomographic imaging. Also to be considered, despite the diagnosis of VSA, the subjects in this investigation had baseline ^{123}I -mIBG parameters within the normal range, making it difficult to show any image improvement with a therapy. As the authors propose, the investigation can be considered to be a pilot study that is hypothesis generating.

CONCLUDING THOUGHTS

The autonomic nervous system is extremely complex, with selected aspects of the discussed interaction of the sympathetic components among the heart, kidney, brain, and periphery displayed and summarized in the schematic Figure 1. Sympathetic innervation plays an integral role in cardiovascular health, while disruption of it from disease leads to morbidity and increased mortality. While there are many methods to assess the system, cardiac radionuclide adrenergic imaging with ^{123}I -mIBG and analogous PET tracers is a relatively simple, quick, and noninvasive method of assessment of the cardiac component, with robust literature proving its risk stratification value. Better understanding of how cardiac adrenergic imaging can help assess the utility of therapies directed at extracardiac organ systems, such as renal denervation, should provide better understanding of disease processes in order to direct therapies that can improve outcome and well-being.

Disclosure

The author has no conflicts of interest.

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