^{123}I -mIBG scintigraphy: Clinical tool for assessing renal sympathetic activity?

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Among patients with treatment-resistant hypertension, transcatheter renal denervation has been shown to reduce blood pressure (BP) in a number of uncontrolled, unblinded clinical trials.¹ However, in a prospective, single-blind, randomized trial that compared transcatheter renal denervation to a sham procedure, there was no significant difference in systolic BP between the two treatment arms at 6 months follow-up.² Proposed reasons for the lack of benefit include a substantial placebo effect related to the procedure, differences in medication adherence such that the sham-treated control group may have taken more antihypertensive medications, operator inexperience with transcatheter renal denervation, and performance of an inadequate number of ablations in each renal artery.³ It has been postulated that operator inexperience and performance of too few ablations may have led to incomplete denervation and therefore an inadequate BP response to the procedure. The absence of a readily available methodology to define completeness of transcatheter renal denervation in humans remains as an unmet need in defining the potential role of the procedure in clinical practice.

The contribution of increased renal sympathetic tone to the pathophysiology of hypertension has been known for decades. Surgical renal denervation in hypertensive animal models has been shown to cause significant decreases in BP compared to sham controls.⁴ A commonly employed method of surgical denervation

involves stripping the adventitia from the renal artery of hypertensive rats and exposing the artery to phenol, a compound that irreversibly blocks neural conduction.⁵ Renal norepinephrine (NE) content measured at specified time points after surgical denervation in hypertensive rats has been shown to decrease dramatically (94% reduction compared to sham-controlled rats at 1 week; $P < 0.001$), suggesting complete ablation of the renal nerves. A positive correlation was also shown between absolute change in BP after denervation and renal NE content in denervated animals ($r = 0.80$, $P < 0.001$).⁴

In the clinical research setting, a number of methods have been utilized to assess the completeness of renal denervation in hypertensive humans. The most promising and best characterized are the measurements of muscle sympathetic nerve activity (MSNA), renal NE spillover rate, and assessment of sympathetically mediated responses to electrical stimulation of the renal artery before and after denervation.^{6–8} Assessment of MSNA is minimally invasive and entails percutaneous insertion of a recording electrode into a superficial nerve (peroneal or radial), allowing direct recording of post-ganglionic sympathetic neural bursts. MSNA reflects moment-to-moment sympathetic outflow from the central nervous system to either skeletal muscle or skin, but does not provide direct information on sympathetic outflow to the kidney or heart.⁹

Renal NE spillover is assessed by infusing small doses of radiolabeled NE intravenously and measuring its level in the renal vein compared to the systemic arterial concentration.^{10,11} Renal NE spillover has been shown to be positively correlated with MSNA¹² but since sympathetic regulation differs regionally, renal NE spillover is superior to MSNA in its ability to selectively quantify sympathetic drive to the kidney.⁹

Electrical stimulation of the renal artery before and after transcatheter denervation has been explored as a rapid method of determining the completeness of

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denervation at the same sitting as the procedure. Electrical stimulation of the renal artery triggers afferent renal sensory nerves, leading to increased central sympathetic outflow from the brainstem and an increase in BP.⁶ Attempts have been made, with some success, to exploit differential responses in BP, heart rate, heart rate variability, and plasma epinephrine and NE concentrations to renal artery stimulation before and after transcatheter renal denervation in order to assess the completeness of the procedure.^{6,13,14} However, none of these methods is currently being used in clinical practice.

Noninvasive imaging with ¹²³I-metaiodobenzylguanidine (¹²³I-mIBG) evaluates the anatomy and function of the sympathetic nervous system.^{15,16} mIBG is a synthetic analogue of NE that is radiolabeled with ¹²³iodine (¹²³I-mIBG) and is taken up by sympathetic presynaptic vesicles. The major mechanism of ¹²³I-mIBG uptake is via the NE transporter (NET), a transmembrane protein located in presynaptic sympathetic nerve terminals that transports NE and dopamine from the synapse back into presynaptic cytosol.¹⁵

In clinical practice, ¹²³I-mIBG is mainly used to localize neuroendocrine tumors such as pheochromocytomas, neuroblastomas, and paragangliomas and for imaging myocardial sympathetic innervation, while in research its applications go beyond and include tissue-specific, functional assessment of sympathetic activity in various disease states. This functional assessment has been best studied in the heart, with image analysis and quantification of myocardial uptake and washout rate of ¹²³I-mIBG. Cardiac ¹²³I-mIBG uptake is thought to reflect the density of sympathetic innervation.¹⁷ The timing of mIBG uptake is tissue-specific.¹⁵ Most cardiac ¹²³I-mIBG studies image early and late uptake at approximately 15 min and 3–4 h after injection, respectively, whereas oncologic studies typically image at roughly 24 h.¹⁸ Washout rate is determined as the rate of decrease in myocardial uptake between early and delayed imaging and reflects sympathetic activity and tone. In the heart, a high washout rate indicates increased sympathetic activity,¹⁶ and unlike uptake, is independent of the number of neurons in the tissue.¹⁷

In heart failure, variations in cardiac ¹²³I-mIBG uptake and washout correlate with the risk of future adverse cardiac events¹⁹ and therapeutic interventions in heart failure patients have been shown to lead to increases in uptake.^{20–22} These findings suggest that ¹²³I-mIBG scintigraphy can reflect dynamic changes in adrenergic function in the heart.

In the current issue of the *Journal*, Takamura et al tested the hypothesis that renal ¹²³I-mIBG imaging is associated with MSNA in patients with primary hypertension. As discussed previously, MSNA is a measure of generalized sympathetic outflow and has been shown to

be elevated in patients with essential hypertension.²³ Further, some studies have found positive correlations between MSNA and the severity of BP elevation,²³ and between decreases in MSNA and BP reduction after renal denervation.²⁴

In the Takamura et al study, 31 patients with primary hypertension (27 of whom were well controlled with antihypertensive medication) received injection of ¹²³I-mIBG, with uptake into the kidney and heart measured via planar, 2D imaging at 20 min (early) and 3 h (delayed) relative to the mediastinum. Cardiac and renal washout rates were calculated based on the uptake values. Significant positive associations of renal ($r = 0.68$, $P < 0.001$) and cardiac ($r = 0.45$, $P = 0.0035$) washout rates with MSNA were demonstrated. In contrast, neither early nor delayed kidney and heart uptake was associated with MSNA. The authors concluded that in patients with primary hypertension, renal ¹²³I-mIBG washout rate reflects the activity and function of the renal sympathetic nerves. Further, Takamura et al postulated that renal ¹²³I-mIBG imaging offers a noninvasive clinical technique to evaluate the completeness of transcatheter renal denervation.²⁵

A number of barriers may limit the application of renal ¹²³I-mIBG scanning in clinical practice. First, design features of the Takamura et al study confound the applicability of the results to the general population of hypertensive patients. The cohort was small ($n = 31$), and the majority (87%) had BP controlled with medications: 58% were on beta blockers; 45% were on calcium antagonists, and 71% were on angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. A variety of medications, including the classes of antihypertensive drugs, e.g., calcium antagonists¹⁸ and beta blockers^{18,26} that were taken by participants in the Takamura et al study, are known to interfere with mIBG imaging. It is recommended that these medications be discontinued 24–72 h prior to radiotracer injection, creating safety concerns for patients with resistant hypertension, a population that would be likely candidates for the renal denervation procedure were it to be incorporated into clinical practice.

Takamura et al reported 2D planar data only, without including 3D SPECT/CT imaging. In general, for tumor imaging, 3D SPECT/CT imaging is recommended in order to improve diagnostic accuracy.¹⁸ In Figure 1 of Takamura et al, a clear delineation between the right kidney and the liver (an area of high physiologic uptake) cannot be made reliably. Whether this contributed to the difference in uptake and washout between the right and left kidney was not evaluated. The potential role of SPECT or SPECT/CT for more accurate quantification of renal uptake and washout rate by avoiding overlapping liver activity remains unknown.

Another limitation of the Takamura et al study is the failure to stratify patients based on obesity and age. In comparison with lean patients, studies have shown that obese patients have increased baseline sympathetic activity, manifested by elevations in MSNA and in renal NE spillover. These elevations appear to be somewhat independent of BP, with elevations in MSNA and renal NE spillover present in obese patients with and without hypertension.⁹

Renal NE spillover in hypertensive patients is also a function of age.²⁷ Compared to age-matched normotensive controls, hypertensive patients <40 years old have been shown to have a significantly higher rate of renal NE spillover, and this difference diminished with increasing age.¹⁰ Similar findings have been reported in animal studies, suggesting that the renal sympathetic nerves may have a greater effect on the development (younger patients) than on the maintenance (older patients) of hypertension.⁴ These findings raise important questions about the confounding effects of age in the Takamura et al cohort, and more broadly, about the age group of patients that may have the best BP response to renal denervation.

Takamura et al's finding of an association between renal ¹²³I-mIBG washout rate and MSNA in hypertensive patients, combined with the observations of Grassi et al and Hering et al that MSNA increases with severity of BP elevation²³ and decreases with BP reduction after renal denervation,²⁴ suggests that renal ¹²³I-mIBG scintigraphy correlates with the severity of hypertension and with BP response to renal denervation. However, MSNA is not selective for the kidney, and it is premature to conclude that a correlation between renal ¹²³I-mIBG scintigraphy and MSNA indicates that renal ¹²³I-mIBG scintigraphy can predict the success or failure of transcatheter renal denervation.

In contrast, renal NE spillover is selective for the kidney, and elevations in renal NE spillover in hypertensive patients,²⁷ as well as reductions in renal NE spillover after renal artery denervation, have been demonstrated.^{7,28} Future studies designed to determine whether there is a relationship between renal ¹²³I-mIBG scintigraphy and renal NE spillover, rather than MSNA, would provide a more direct evaluation of renal sympathetic nerve function in patients with uncontrolled hypertension. Establishment of such a relationship could potentially lead to the use of renal ¹²³I-mIBG imaging as a tool to identify patients likely to respond to transcatheter renal denervation. Studies investigating a relationship between renal ¹²³I-mIBG imaging and renal NE spillover should include patients with uncontrolled hypertension, and be stratified for age and obesity.

Available data on renal ¹²³I-mIBG scintigraphy in general and in conjunction with renal denervation in

particular are sparse, and the potential application of renal ¹²³I-mIBG in assessing the completeness of transcatheter renal nerve ablation has been limited by the lack of a "gold standard" for completeness of denervation.²⁹ Renal ¹²³I-mIBG scintigraphy before and after surgical renal denervation can provide such a gold standard, since renal denervation is complete in this setting. A pioneering study of use of ¹²³I-mIBG scintigraphy before and after surgical renal denervation was recently reported by Dobrowolski et al. Renal ¹²³I-mIBG scintigraphy was performed on a patient with hypertension secondary to fibromuscular dysplasia of the right renal artery whose BP had been unresponsive to antihypertensive medication, angioplasty, and renal artery stenting. The patient underwent autotransplantation of the right kidney, with renal ¹²³I-mIBG scintigraphy performed before and two weeks after the procedure.³⁰ Since the renal artery was ligated and reanastomosed during the procedure, denervation was complete. After the procedure, the patient's ambulatory BP normalized (119/74 mmHg) without need for antihypertensive agents, and early and late uptake and washout rate decreased in the right (transplanted) kidney, whereas these variables increased in the left (control) kidney. Compared to pre-transplantation values in the transplanted kidney, post-transplantation right renal early uptake decreased by 21%, late uptake decreased by 29%, and washout rate decreased by 7%. Conversely, compared to pre-transplantation values in the control kidney, post-transplantation left renal early uptake increased by 5%, late uptake increased by 4%, and washout rate increased by 4%. To our knowledge, this is the only published demonstration of reduced renal ¹²³I-mIBG uptake and washout following complete surgical renal denervation. Of note, even in the setting of complete denervation, the reductions in renal ¹²³I-mIBG uptake were much less than the reductions in total NE stores following denervation of the rat kidney.⁴ Correlating renal ¹²³I-mIBG scintigraphy with renal NE spillover before and after surgical renal artery denervation may possibly be a novel method of assessing the completeness of transcatheter renal denervation.

In an effort to assess reinnervation of transplanted kidneys, Dobrowolski et al also carried out renal ¹²³I-mIBG scintigraphy at different time points after transplantation in 12 kidney transplant recipients (time after transplantation: median 7.4 years, range 0.1-34 years).³¹ Early uptake (15 min) and washout rates were positively correlated with time after transplantation, suggesting functional reinnervation of the kidneys (early uptake: $r = 0.720$, $P = 0.008$; washout: $r = 0.608$, $P = 0.04$). These results indicate that assessing the degree of reinnervation after transcatheter renal denervation (and the candidacy for repeat intervention) may be another

potential application of renal ¹²³I-mIBG imaging. Notably, late uptake (4 h) did not correlate with time since transplant. Dobrowolski et al noted that since washout of ¹²³I-mIBG from the kidney occurs earlier than washout from the heart, modifying the timing of imaging such that late imaging is performed earlier may provide more relevant results.

Although renal ¹²³I-mIBG washout rate was significantly associated with MSNA in the Takamura et al study, the lack of correlation of renal ¹²³I-mIBG uptake with MSNA warrants further investigation. The interpretation of ¹²³I-mIBG uptake and washout rates is specific to the tissue and disease of interest. As mentioned previously, NET is the transmembrane protein responsible for most of the ¹²³I-mIBG uptake into presynaptic sympathetic nerve terminals. ¹²³I-mIBG uptake is a measure of the density of sympathetic innervation in the tissue of interest, such that a higher number of sympathetic neurons leads to higher ¹²³I-mIBG uptake.¹⁷ In addition, the expression of NET on the presynaptic membrane also affects ¹²³I-mIBG uptake. Cardiac ¹²³I-mIBG has been more extensively studied than renal ¹²³I-mIBG, and the pathophysiology of cardiac NE reuptake is better understood. It has been shown that in some patients with heart failure, increased myocardial sympathetic tone exerts negative feedback on cardiac NET expression, leading to decreased cardiac ¹²³I-mIBG uptake.¹⁹ Primary hypertension is also a hypersympathetic state, but it is not known whether an analogous downregulation of NET on renal presynaptic sympathetic nerve terminals and a subsequent decline in renal ¹²³I-mIBG uptake occurs in hypertensive patients. If such a downregulation were present in some but not all hypertensive patients, this could explain the lack of correlation between renal ¹²³I-mIBG uptake and MSNA in the Takamura et al study. More research on the effects of hypertension on renal NET expression is needed to better understand its effect on renal ¹²³I-mIBG uptake.

As stated above, renal ¹²³I-mIBG uptake is a reflection of the density of sympathetic innervation on the renal artery, whereas ¹²³I-mIBG washout rate reflects central sympathetic outflow and is independent of the density of innervation. Thus, if hypertension is a function of increased sympathetic nerve traffic between the kidneys and the brain rather than a function of the density of renal sympathetic innervation, it follows that renal ¹²³I-mIBG uptake may be independent of hypertension, whereas renal ¹²³I-mIBG washout rate is not. This interpretation is consistent with the findings of Takamura et al

Sakakura et al addressed this issue, using immunohistochemistry to analyze peri-arterial renal nerve anatomy in an autopsy study of 20 patients with and without hypertension. The results showed no

significant difference in the mean number of nerves or the mean nerve size between patients with and without hypertension.³² The results of this small study suggest that hypertension does not cause increased renal nerve density, and thus renal ¹²³I-mIBG uptake may be independent of MSNA and hypertension.

Potential applications of renal ¹²³I-mIBG scintigraphy include assessing the candidacy for and the completeness of transcatheter renal denervation, as well as post-procedural reinnervation. Future studies should evaluate patients with uncontrolled hypertension, compare renal NE spillover directly to renal ¹²³I-mIBG, and control for the potentially confounding effects of anti-hypertensive medications, age, and obesity. Additionally, to study the effect of complete renal denervation on renal ¹²³I-mIBG uptake and washout rate, it would be useful to perform renal ¹²³I-mIBG scintigraphy on kidney transplant patients before and after transplantation. Longitudinal studies of renal ¹²³I-mIBG uptake and washout at intervals after transplant may be useful in assessing reinnervation of transplanted kidneys. Such data could also provide clues to the durability of renal denervation as a treatment for hypertension.

Disclosure

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

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