Efficacy of Thyroid Blockade on Thyroid Radioiodine Uptake in ^{123}I-*m*IBG Imaging

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Although iodinated radiopharmaceuticals usually contain a small quantity of unbound iodine, it is difficult to establish the degree to which thyroid activity on scintigraphic images reflects uptake of free radioiodine. The objective of the present study was to examine the effectiveness of thyroid blockade in subjects undergoing ^{123}I-*meta*-iodobenzylguanidine (*m*IBG) imaging and to estimate the relative contribution of bound and unbound radioiodine to imaging findings. **Methods:** All subjects were participants in prospective trials of ^{123}I-*m*IBG cardiac imaging in which pretreatment with thyroid blockade was optional unless locally required. In a pilot project, 15 subjects (6 blocked) had thyroid uptake measured at 4 h using a probe system. Fifteen-minute (early) and 4-h (late) anterior planar chest images that included the thyroid region were visually scored for thyroid uptake (scale of 0–4) in another group of 152 subjects (98 blocked). Quantitative analysis based on thyroid regions of interest was performed on anterior planar images from a further sample of 669 subjects (442 blocked). For all 3 investigations, quantitative comparisons of thyroid uptake were made between the blocked and nonblocked subjects. **Results:** There was no statistical difference between probe uptake of the 6 blocked and 9 nonblocked subjects. However, in the second series, mean visual score on the late images was significantly lower for blocked than nonblocked subjects ($P < 0.001$). In the region-of-interest analyses, net thyroid counts were significantly higher on the late images of nonblocked subjects ($P < 0.0001$), and compared with early images, 87% of subjects who received blockade showed decreased or unchanged counts whereas 75% of nonblocked subjects had increased net thyroid activity. In nonblocked subjects, an estimated 79% of thyroid counts on late images could be attributed to unbound ^{123}I. **Conclusion:** On the basis of 3 different methods for assessing thyroid uptake of ^{123}I, use of thyroid blockade pretreatment in ^{123}I-*m*IBG imaging prevents increase of thyroid activity over time because of uptake of unbound ^{123}I. In most subjects, there is a low level of ^{123}I-*m*IBG thyroid activity that probably represents specific uptake in sympathetic nerve terminals.

Key Words: thyroid; blockade; ^{123}I; *m*IBG

J Nucl Med 2014; 55:211–215
DOI: 10.2967/jnumed.113.124826

In the late 1970s, ^{131}I-*meta*-iodobenzylguanidine (*m*IBG), an analog of norepinephrine, was developed by Wieland et al. at the University of Michigan for the purpose of functional imaging of the adrenal glands (*1,2*). This agent subsequently became used for diagnostic imaging of neural crest and neuroendocrine tumors (*3,4*). However, because of the superior dosimetric and imaging properties of ^{123}I (*5,6*), most diagnostic imaging with *m*IBG is now performed using the ^{123}I-labeled compound.

Routine clinical practice for *m*IBG imaging (as is the case for most radioiodine-labeled radiopharmaceuticals) includes pretreatment of patients with nonradioactive iodine to reduce radioactive free iodide uptake by the thyroid (*5,6*). Thyroid protection occurs via inhibition of the Na/I symporter and inhibition of thyroid hormone production via the Wolff–Chaikoff effect (*7–9*).

Free radioactive iodine is available either by metabolism of *m*IBG to release free iodide or by free iodine present in the preparation (*10*). As a result of the high radiation dosimetry associated with ^{131}I, as well as the long-term harmful effects of radiation to the thyroid gland, particularly to younger patients, aggressive measures to reduce thyroid dose are required. The recommended thyroprotective regimen for diagnostic studies includes administration of saturated solution of potassium iodide (SSKI) or Lugol solution starting 1 d before administration of *m*IBG and continuing for up to 7 d after injection (*5,6*). Even using such a regimen, thyroid uptake was identified in 21% of diagnostic and posttherapy *m*IBG studies in children with neuroblastoma (*11*). Significant numbers of children treated with therapeutic quantities of ^{131}I-*m*IBG have also developed hypothyroidism despite aggressive thyroid blockade regimens (*11,12*).

Despite the more favorable dosimetric characteristics of ^{123}I, with 100 times lower estimated radiation dose per megabecquerel than for ^{131}I (*5*), recommendations for multiday thyroid blockade regimens in association with ^{123}I radiopharmaceuticals are still relatively common (*3,6*). With the use of ^{123}I-*m*IBG manufactured with low free iodine content (typically 1%–3%) and considering the 13.2-h half-life of the radioisotope, such extended blockade is probably unnecessary. However, the clinical effectiveness of limited thyroid blockade (such as via a single-dose procedure) for reducing ^{123}I dose to the thyroid has not been assessed in detail.

Patients evaluated with ^{123}I-*m*IBG imaging for cardiac disease are different from those studied for neuroendocrine tumors, with ages typically over 60 y, thus decreasing concerns about the long-term effects of low-level thyroid exposure to ionizing radiation. The studies presented in this report were drawn from the ^{123}I-*m*IBG clinical trial called AdreView (GE Healthcare) Myocardial Imaging for Risk Evaluation in Heart Failure (ADMIRE-HF). In ADMIRE-HF, physicians and patients were allowed to choose whether to receive thyroid cytoprotection, consisting of a single dose of blocking agent 1 h before ^{123}I-*m*IBG administration. The objectives of the current study, including data from the entire trial population and selected subsets, were to assess the effectiveness of the single-blockade-dose

Received Apr. 15, 2013; revision accepted Sep. 12, 2013.
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Published online Jan. 2 2014.

regimen and provide estimates of the relative radiation doses to the thyroid contributed by ^{123}I-*m*IBG and free ^{123}I.

MATERIALS AND METHODS

ADMIRE-HF (Clinicaltrials.gov identifier numbers NCT00126425 and NCT00126438) studied 961 New York Heart Association II–III heart failure subjects with impaired systolic function (left ventricular ejection fraction ≤ 35%) and 94 age-matched control subjects without heart disease (*13*). The study was approved by the Institutional Review Boards and Ethics Committees at each center, and all subjects gave written informed consent before performance of any procedures.

All subjects underwent 10-min anterior planar imaging of the thorax beginning at 15 min (early) and 3 h 50 min (late) after administration of 370 MBq (10 mCi) of ^{123}I-*m*IBG (AdreView). The anterior neck was included in most images, although for cameras with a smaller field of view, this region was sometimes truncated or completely excluded.

Thyroid Uptake Measurements

Fifteen subjects were recruited into the clinical trial at our site. We obtained approval from the sponsor and Human Studies Subcommittee to add a thyroid uptake measurement using a standard thyroid probe after the late image. Six subjects elected to undergo thyroid blockade (130 mg SSKI), and 9 elected not to receive this pretreatment.

Thyroid uptake measurements were performed using a Biodex Atomlab 950 thyroid probe using the standard neck uptake measurement protocol as well as a background measure of the thigh. Both regions were counted 4 h after injection for 1 min. The percentage thyroid uptake was calculated by conversion of net thyroid counts to percentage uptake by correction for detector efficiency and geometry as well as decay correction.

Visual Uptake Assessment

A first series of visual assessments of thyroid uptake was performed on images from a random selection of 114 subjects. Studies that did not include the lower neck region were excluded from the selection. Three board-certified nuclear medicine physicians who were masked to all clinical information, including whether thyroid blockade had been administered, reviewed the studies for visual scoring of thyroid uptake. Thyroid uptake was assessed semiquantitatively using the scoring system listed in Table 1.

A second series of visual assessments using the same scoring system was performed on images from 52 subjects who were taking thyroid hormone replacement at the time of ^{123}I-*m*IBG imaging. These reviews were performed by 2 readers.

TABLE 1
Scoring System for Semiquantitative Visual Assessment of Thyroid Uptake

Score	Characterization
0	No identifiable thyroid visualization
0.5	Faint uptake in neck, not definitively identifiable as thyroid gland
1	Subtle but distinct thyroid uptake, less than salivary glands if visualized
2	Moderate distinct thyroid uptake, equal to salivary glands if visualized
3	Significant thyroid uptake, greater than salivary glands if visualized and less than dome of liver
4	High thyroid uptake; maximum activity similar to dome of liver

Image Quantitation

All study images were visually reviewed by an experienced nuclear medicine technologist to determine whether the region of the thyroid gland was in the field of view. Images that did not include this region were not processed. For the remaining images, the following analysis procedures were used.

Initial processing was performed on the late image. The technologist noted when there was any distinct thyroid uptake and, in those images, whether the superior aspect of the gland was truncated. For images with any visualized thyroid activity, the smallest rectangular region of interest (ROI) that included such activity was drawn. If there was no visualized thyroid activity, an ROI in the expected location of the thyroid, above the sternal notch and below the submandibular salivary glands, was drawn. The number of pixels and counts per pixel in the thyroid ROI were then recorded. The technologist then drew a 7 × 7 pixel mediastinum (background) ROI in the midline upper chest directly below the thyroid ROI, adjusting the location and size of the background ROI as necessary to avoid including thyroid or high lung activity, and recorded the counts per pixel.

Using the late image as the template, the thyroid and mediastinum ROIs were reproduced in size and location on the early image and the counts and counts-per-pixel data were recorded.

Analysis and Statistics

Thyroid Uptake Measurements. Mean uptake values for subjects with and without thyroid blockade were compared using the Student *t* test. Differences at the $P < 0.05$ level were considered significant.

Visual Reads. Groups were classified in terms of thyroid blockade status. The mean scores for the readers were used in the analyses. Statistical comparisons were performed using *t* tests and 1-way ANOVA. Differences at the $P < 0.05$ level were considered significant.

Image Quantitation. The rectangular thyroid ROI was used because it was judged infeasible to draw an irregular ROI for the gland in many subjects. The net thyroid counts (A_t) were estimated by subtracting background activity from the total counts in the thyroid ROI:

$$A_t = \text{thyroid ROI counts} - (\text{thyroid ROI pixels} \times \text{mediastinum counts/pixel}),$$

where t = e for the early image and t = l for the late image.

These results were compared between subjects who did and did not receive thyroid blockade. In addition, for subjects with interpretable early and late images, change in total thyroid activity was determined as the difference between early and decay-corrected late counts in the thyroid ROI. Mean values were compared using *t* tests, with a *P* value of less than 0.05 considered significant.

RESULTS

Uptake Data

Thyroid uptake data acquired on the patients enrolled at our institution are summarized in Table 2. There was no statistical difference between the 6 subjects who were administered SSKI (blocked) and the 9 subjects who declined SSKI (nonblocked), although a tendency to higher uptake was noted in the latter group. Mean percentage uptake was 1.4% for nonblocked (range ± 2 SDs, 0.6%–2.2%) and 1.3% for blocked (range ± 2 SDs, 0.6%–1.9%).

Visual Analyses

Of the 114 randomly selected cases, 14 were deemed uninterpretable because the field of view did not include the entire lower neck. Of the remaining 100 cases, 64 had received thyroid blockade before injection of ^{123}I-*m*IBG and 36 had not received thyroid blockade.

For the group that received blockade, the mean visual semiquantitative score on the early images was 1.4 (±0.8) compared

TABLE 2
Probe-Measured Thyroid Uptake for 15 Subjects

Subject	Thyroid counts/min	Background counts/min	Background-corrected thyroid counts/min	Estimated μCi* in thyroid	Percentage uptake of injected dose
Nonblocked					
0002	652,783	117,756	535,027	150	1.8
0020	590,968	112,988	477,980	134	1.6
0004	377,888	101,925	275,963	78	0.9
0007	638,082	135,748	502,334	141	1.7
0009	543,946	89,304	454,642	128	1.5
0001	635,952	151,500	484,452	136	1.6
0005	331,940	178,212	153,728	43	0.5
0011	644,402	156,117	488,285	137	1.6
0019	543,283	107,075	436,208	123	1.4
Mean					1.4
Blocked					
0010	484,072	151,916	332,156	93	1.1
0003	420,677	137,013	283,664	80	0.9
0008	689,564	161,650	527,914	148	1.7
0013	556,816	134,898	421,918	119	1.4
0017	577,106	113,395	463,711	130	1.5
0018	436,055	101,902	334,153	94	1.1
Mean					1.3

*1 μCi = 37 kBq.

with 1.6 (±0.8) for the nonblocked group ($P = 0.15$). Comparable results on the late images were 0.5 (±0.6) for the blocked group, compared with 2.1 (±1.2) for the nonblocked group ($P < 0.0001$). The highest late image score in the blocked group was 2, whereas 15 subjects (37.5%) in the nonblocked group had scores of greater than 2. Representative images are presented in Figure 1.

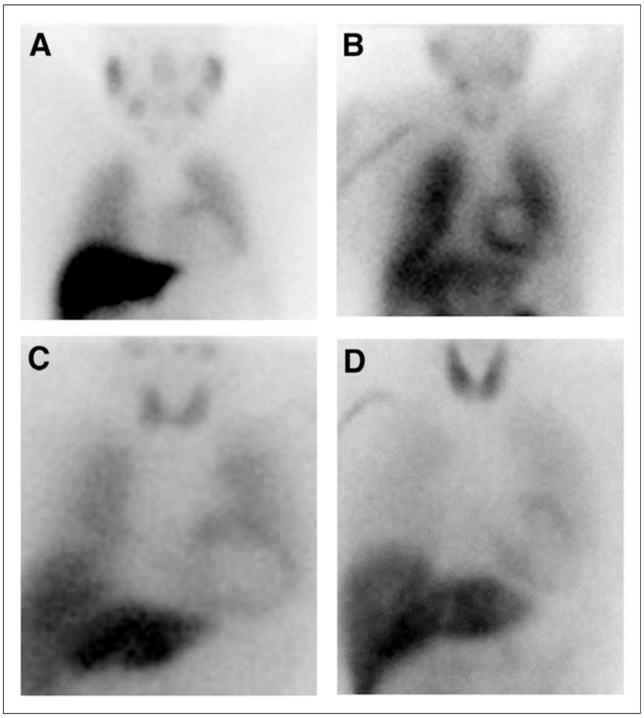

FIGURE 1. Representative thyroid visual analysis examples: score 0.5 (A), score 1 (B), score 3 (C), and score 4 (D).

Of the 52 thyroid-hormone replacement subjects, 34 had received thyroid blockade. There was no difference in the mean early and late image scores for the nonblocked subjects (0.9 vs. 0.9), whereas the score decreased over time in the blocked subjects (1.0 vs. 0.6, $P = 0.005$). However, the mean scores between blocked and nonblocked subjects were not different at either imaging time (early: $P = 0.66$; late: $P = 0.09$).

Image Quantitation

Images with any truncation of the upper pole of the thyroid were excluded from these analyses.

At least one anterior planar chest image from 840 subjects (77%) included the entire region of the thyroid gland. Both early and late images were assessable in 669 subjects (61%), whereas only 1 of the 2 images could be analyzed for 171 subjects (16%). To ensure consistency in results for the analyses, the following represent the findings for the 669 paired image analyses.

Thyroid uptake was visualized on both early and late images in 576 subjects. Thyroid uptake was seen on only 1 of the 2 images in 57 subjects, whereas in 36 subjects no uptake was identified on either image.

Of the 669 subjects with 2 assessable images, 442 (64%) had been pretreated with thyroid blockade (306 with potassium iodide preparations, 136 with perchlorate), whereas 227 (36%) had received no pretreatment. As another factor that could influence thyroid uptake of radioiodine, 65 subjects (10%) were taking thyroid hormone replacement, of whom 43 were also pretreated with thyroid blocking medication.

The ROI net thyroid count data (A_t) are summarized in Tables 3 and 4. On early images, there was no significant difference in A_e between subjects who had and had not received pretreatment with thyroid-blocking medications. There was a large difference in A_l on the late images, with most subjects who received blockade showing decreased or unchanged counts whereas most of nonblocked subjects had an increase in A_l. The largest difference between early and late images was seen in nonblocked subjects who were not receiving thyroid hormone replacement, whereas the smallest difference was

TABLE 3
Effect of Thyroid Blockade on Net Thyroid ROI Counts on Early and Late (Decay-Corrected) ^{123}I-*m*IBG Imaging

Parameter	Subjects (*n*)	Mean early thyroid counts	Mean late thyroid counts	Mean net count change (%)	No. with increased (late vs. early) thyroid counts (%)	No. with decreased or unchanged (late vs. early) thyroid counts (%)
Nonblocked	227	7,997 (SD, 6,927)	13,864 (SD, 10,423)	+5,867 (73.4%)	171 (75%)	56 (25%)
Blocked	442	9,033 (SD, 8,855)	5,440 (SD, 6,021)	−3,593 (−39%)	59 (13%)	383 (87%)
P		0.11	<0.0001	<0.0001		

Early = 15 min after administration; late = 3 h 50 min after administration.

in subjects with both thyroid blockade and hormone replacement. A_e in subjects on thyroid hormone therapy was more than 50% lower than in the other subjects.

Assuming that the 43 subjects with hormone replacement therapy and thyroid blockade were completely protected from uptake of free ^{123}I, it can be estimated that about 54% [(8,425–3,908)/8,425] of early and 79% [(14,733–3,069)/14,733] of late thyroid uptake in nonblocked subjects was due to unbound radioiodine. If the mean uptake for nonblocked subjects who had thyroid probe measurements (1.4%) is used as the basis for calculation of thyroid gland dosimetry (*5*), the following estimates are obtained: nonblocked: 70 mGy; blocked: 27.3 mGy; blocked and on thyroid hormone replacement: 14.6 mGy.

DISCUSSION

The present study used 3 different methods to estimate the effectiveness of thyroid-blocking medication for minimizing thyroid uptake of unbound radioiodine from ^{123}I-*m*IBG. Because the radiochemical purity of the ^{123}I-*m*IBG used in this study was greater than 98%, the maximum amount of free ^{123}I in the nominal administered activity of 370 MBq (10 mCi) was 7.4 MBq (0.2 mCi), similar to the quantity used for conventional thyroid scanning. The pilot study used probe measurements to quantify the effect of blockade. This sample of 15 subjects showed little difference between the measured 4-h thyroid uptake of subjects in the 2 groups, with uptake below 2% for all cases measured. There was a trend toward higher uptake in the nonblocked subjects, and this finding was supported by the results of the subsequent examination of visual uptake patterns in a sample of 100 subjects. The final quantitative analysis of 669 subjects with assessable early and late planar images confirmed the effectiveness of thyroid blockade for reducing progressive uptake of radioiodine over time, suggesting that only a small fraction of the thyroid activity seen on 4-h delayed images was likely due to specific uptake of ^{123}I-*m*IBG.

The reduction of thyroid uptake of radioiodine by pretreatment with agents such as SSKI and pertechnetate is well established (*7–9*). Although there remains considerable diversity of opinion about the regimen that should be used for administering blocking medication, both with regard to the number and the duration of administrations before and after exposure to radioiodine, the relevant published data suggest that for a short-lived isotope such as ^{123}I, an adequate dose of blocking medication administered within the 24 h before exposure will provide acceptable protection for up to 48 h. In a computer simulation performed by Wootton and Hammond, the optimum time for administration of blockade was 1 h before administration of radioiodine (*14*). This latter recommendation was the basis for the blocking procedure used in the present study.

Although the results of the visual and ROI-based analyses confirm the effectiveness of thyroid blockade for reducing radioiodine uptake in the gland, it is more difficult to precisely estimate the magnitude of the reduction in radiation dose. Effective blockade should result in visualization of only thyroid uptake of *m*IBG, but the observed differences in level of thyroid activity in blocked patients can be interpreted as reflecting variation in specific neuronal uptake, ineffectiveness of the blockade, or a combination of the two. Because published *m*IBG biodistribution studies have usually been performed with subjects blocked, the contribution of unbound iodine to thyroid dosimetry could be estimated only on the basis of the level of free iodine in the original injectate and sodium iodide dosimetry studies (*10*). There are sympathetic nerve fibers that reach the thyroid from the superior, middle, and inferior ganglia of the sympathetic trunk, and these small nerves enter the gland along with the blood vessels. It is therefore reasonable to presume that a low level of NET-mediated uptake of *m*IBG occurs in the presynaptic nerve terminals. The present study provides the first large body of data allowing comparison of the low level of thyroid activity in blocked patients (potentially reflecting specific *m*IBG uptake) to the higher uptake in the nonblocked cohort. In particular, the further uptake suppression produced by treatment with exogenous thyroid hormone suggests that there is a certain amount of uptake that cannot be prevented, presumably reflecting *m*IBG uptake in sympathetic nerve terminals in the gland. The slow decline in thyroid uptake between 15 min and 4 h in these fully suppressed subjects then likely represents normal physiologic turnover of norepinephrine and *m*IBG from the gland. On average, activity in the blocked and thyroid hormone–treated subjects was about 46% of that in untreated subjects at 15 min and 21% at 4 h, reflecting the progressive increase in thyroid uptake of unbound radioiodine over time in the latter subjects.

In principle, reduction of any unnecessary radiation dose to a patient is desirable. In practice, the benefit of eliminating a small radiation dose to an older patient (such as the typical heart failure patient) whose lifetime risk of developing neoplasia from that dose is minimal might be questioned. The radiation burden to the thyroid from administration of 370 MBq (10 mCi) of high-purity ^{123}I-*m*IBG was estimated at 70 mGy in nonblocked subjects, similar to the dose received by clinical patients undergoing ^{123}I thyroid scans. The results of this study indicate that a single dose of SSKI (or equivalent) is effective in reducing thyroid dose by more than 50%. However, the clinician should still consider on an individual patient basis whether such blocking is necessary or worthwhile, particularly for elderly patients with multiple comorbidities or a possible iodine allergy.

This study had several limitations, the most significant of which were methodologic. The number of subjects who had probe measurements was small and likely resulted in the lack of significance

TABLE 4
Effect of Thyroid Hormone Replacement and Thyroid Blockade on Net Thyroid Counts on Early and Late ^{123}I-*m*IBG Imaging

Parameter	Thyroid hormone replacement	Number of subjects	Mean ROI net early thyroid counts	Mean ROI net decay-corrected late thyroid counts	Mean net count change	% count change
Nonblocked	No	205	8,425 (SD, 7,040)	14,733 (SD, 10,423)	+6,308	74.9
	Yes	22	4,012 (SD, 4,057)	5,754 (SD, 6,140)	+1,742	43.4
			$P = 0.0043$	$P = 0.0001$		
Blocked	No	399	9,585 (SD, 9,031)*	5,695 (SD, 6,176)†	−3,890	−40.6
	Yes	43	3,908 (SD, 4,547)	3,069 (SD, 3,573)	−839	−21.4
			$P = 0.0001$	$P = 0.0064$		

*$P = 0.11$ vs. no/no.
†$P < 0.0001$ vs. no/no.
Early = 15 min after administration; late = 3 h 50 min after administration.

between results for the nonblocked and blocked subjects and also limited the precision of the estimated thyroid dose calculations derived from these uptake determinations. Because the primary thyroid count data were derived from cardiac imaging studies rather than whole-body examinations, it was not possible to evaluate thyroid uptake in terms of quantitative parameters such as percentage of injected dose or MBq/g of tissue. In addition, limited visualization of the thyroid on many images precluded using a more precise or irregular ROI technique to define the organ boundaries. The method of drawing a larger thyroid ROI and then subtracting background was a practical compromise for obtaining net count estimates but one with definite limitations for achieving high accuracy. The position of the thyroid ROI at the edge of the image field of view in most cases also raises the possibility that field nonuniformities could have affected quantitative reliability. Finally, about 40% of subjects included in the original studies were excluded because the thyroid region was partially or completely absent from at least one image, thereby introducing a potential source of bias because sites that used small-field-of-view cardiac cameras were disproportionately affected. The numbers generated in this study provide a useful indication of the physiologic factors involved in thyroid blockade for adults undergoing ^{123}I-*m*IBG imaging, but more detailed quantitative application of these results should be approached with caution.

CONCLUSION

Use of single-dose thyroid blockade pretreatment in ^{123}I-*m*IBG imaging reduces thyroid radiation burden, preventing a progressive increase in thyroid activity over time due to uptake of unbound ^{123}I. Overall, only 13% of subjects who received thyroid blockade showed increased net thyroid activity between 15 min and 4 h after administration. Whether this finding reflected inadequate amounts of blockade medication or an effect of in vivo deiodination of ^{123}I-*m*IBG in these subjects is uncertain. Results for subjects who were taking thyroid hormone replacement at the time of receiving thyroid blockade suggest there is a low level of ^{123}I-*m*IBG thyroid activity that represents uptake in sympathetic nerve terminals. Overall, in nonblocked subjects the estimated thyroid dose from the preparation used in this clinical trial was similar to that received from a diagnostic thyroid scan.

DISCLOSURE

The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 USC section 1734. Arnold F. Jacobson is an employee of GE Healthcare, which manufactures ^{123}I-*m*IBG, and owns shares in the General Electric Company. The studies in which all imaging data were collected and quantitatively analyzed were sponsored by GE Healthcare. No financial support was provided for the probe or visual analyses of the imaging data. No other potential conflict of interest relevant to this article was reported.

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