Reconfirmation of Clinical Unpredictability of Lymphatic Drainage in Cutaneous Melanoma and New Developments in Sentinel Lymph Node Diagnostics

TO THE EDITOR: I read with interest the continuing education article by Uren et al. (*1*) stating that clinical prediction of lymphatic drainage from the skin is not possible and that the old clinical guidelines based on Sappey's lines therefore should be abandoned. To the best of my knowledge, my former group at the Hospital of the Frankfurt Goethe University was the first ever to standardize scintigraphic mapping of lymphatic drainage in cutaneous tumors, particularly malignant melanoma, in the late 1970s and early 1980s (*2–4*). We were able to clearly document that not only tumors located inside but also outside lymphatic watersheds of the skin show an ambiguous lymphatic drainage, which is practically unpredictable by conventional anatomic guidelines in individual patients. We concluded that the anatomic thesis of lymphatic watersheds should be revised. In more than 90% of our patients with skin lesions on the trunk, one or both axillary lymph node groups were found to be involved in lymphatic drainage, either solely or combined with inguinal, supraclavicular, posterior cervical, parasternal, or other node-bearing areas or in-transit lymph nodes; hence, the axillary lymph node groups as the "center in lymphatic drainage from the truncal skin in man" should attract our greatest attention in melanomas or other cutaneous tumors of the trunk independent of their topographic position (*3*). Our data on the lymphatic drainage patterns in skin tumors of trunk, head and neck, and upper and lower limbs published some 20 y ago were proven to be true (*1*,*5*).

Detection and localization of "true" sentinel lymph nodes, permitting correct staging of regional lymph nodes, is essential for management and prognostic assessment in malignant melanoma. In 43 of the 100 melanoma patients examined prospectively, additional information was obtained by simple temporary lead shielding of hot spots in lymphatic drainage areas, applied in combination with dynamic acquisition in various views: In 7 patients, the exact course of lymph vessels could be mapped only after shielding; in 3 patients, hot spots in the drainage area proved to be lymph vessels, lymph vessel intersections, or lymph vessel ectasias; in 33 patients, 1 or 2 additional sentinel lymph nodes that showed less tracer accumulation or were smaller ($<$1.5 cm) were detected after shielding by visualization of their own lymph vessels (7% sentinel lymph node metastases) (*6*). Preliminary data from another prospective study on 276 melanoma patients indicated that the time of scintigraphic appearance of sentinel lymph nodes is a clinically relevant factor for prediction of metastatic spread to sentinel lymph nodes, provided the time of appearance is assessed under standardized conditions (*7*). However, larger numbers of patients need to be examined to truly evaluate the benefit of the time of scintigraphic appearance compared with other predictors of sentinel lymph node tumor positivity.

Finally, we have created a classification of the lymphatic drainage status of primary tumors that preferably metastasize via their draining lymph vessels (*8*). The classification is based on the number of sentinel lymph nodes and their locations (node group or in-transit node) and comprises 4 classes (D-class I–IV) and distinct subclasses (A–E): For example, D-IA means 1 draining node location (NL) and 1 sentinel lymph node (SN); D-IIA means 2 NL, 2 $\times$ 1 SN; D-IIIB means 3 NL, 1 $\times$ $>$1 SN; and D-IVE means $\geq$4 NL, $\geq$4 $\times$ 1 SN. The classification is easy to learn and reliably reproducible using various approaches (e.g., γ-camera imaging, γ-probe detection, or dye mapping). We are currently testing its diagnostic, prognostic, and therapeutic value in prospective studies on melanoma and breast cancer patients and encourage others to join us.

REFERENCES

1. Uren RF, Howman-Giles R, Thompson JF. Patterns of lymphatic drainage from the skin in patients with melanoma. *J Nucl Med.* 2003;44:570–582.
2. Munz DL, Hör G. Utility of lymphoscintigraphy in management of cutaneous malignant melanoma [abstract]. *J Nucl Med.* 1982;23(suppl):P97.
3. Munz DL, Altmeyer P, Sessler MJ, Hör G. Axillary lymph node groups: the center in lymphatic drainage from the truncal skin in man—clinical significance for management of malignant melanoma. *Lymphology.* 1982;15:143–147.
4. Munz DL. *Experimentelle und klinische Untersuchungen über die regionäre Lymphdrainage der Haut mit ^{99m}Tc-markiertem Antimontrisulfid-Kolloid: Bedeutung für das maligne Hautmelanom* [habilitation thesis]. Frankfurt, Germany: University of Frankfurt/Main; 1983.
5. Statius Muller MG, Hennipman FA, van Leeuwen PAM, Pijpers R, Vuylsteke RJCLM, Meijer S. Unpredictability of lymphatic drainage patterns in melanoma patients. *Eur J Nucl Med.* 2002;29:255–261.
6. Maza S, Valencia R, Geworski L, et al. Temporary shielding of hot spots in the drainage areas of cutaneous melanoma improves accuracy of lymphoscintigraphic sentinel lymph node diagnostics. *Eur J Nucl Med Mol Imaging.* 2002; 29:1399–1402.
7. Maza S, Valencia R, Geworski L, et al. Influence of fast lymphatic drainage on metastatic spread in cutaneous malignant melanoma: a prospective feasibility study. *Eur J Nucl Med Mol Imaging.* 2003;30:538–544.
8. Munz DL, Maza S, Ivancevic V, Geworski L. Classification of the lymphatic drainage status of a primary tumor: a proposal. *Nuklearmedizin.* 2000;39:88–91.

Dieter L. Munz, MD
Humboldt University of Berlin
Berlin, Germany

REPLY: The group from the Goethe University in Frankfurt have reported what many who have studied the lymphatic drainage of the skin have found, and that is the variability of drainage from one person to another. In the late 1700s Mascagni (*1*) observed lymph drainage across the midline of the body, and in 1903 Delamere et al. (*2*) described "accessory channels" draining the trunk to supraclavicular nodes from the anterior trunk and drainage from the upper back over the shoulders to neck nodes.

After the development of lymphoscintigraphy by Sherman and Ter-Pogossian (*3*) in 1953, this physiologic approach to lymphatic mapping was applied to individual patients with melanoma. Fee et al. (*4*) in 1978 and Meyer et al. (*5*) in 1979 described lymphatic mapping using lymphoscintigraphy in melanoma patients to determine the pattern of drainage in individual patients and thus to determine which lymph node field to dissect. Many others over the years, including Munz and Hör (*6*) from Frankfurt, have continued this work. More recently, completely new lymphatic drainage pathways from the skin have been discovered (*7*).

The challenge today is to apply the techniques carefully in individual patients so that all true sentinel nodes are located for

surgical removal and careful histologic examination. An understanding of the possible drainage pathways from each area of skin will make this more likely.

It is interesting that the Frankfurt group has published data (*8*) that suggest that the speed of lymph flow through lymphatic collecting vessels influences the likelihood that metastases will be found in the draining sentinel nodes (SNs). We have measured the speed of lymph flow, in centimeters per minute, on dynamic imaging in 198 patients with melanoma (*9*), and though we found that lymph flow rates vary systematically throughout the body, we did not find this variance to have any influence on the incidence of metastasis in the draining SNs. The fastest flow occurred from the foot and leg, with an average flow rate of 10.2 cm/min in our study, yet the incidence of metastasis in groin SNs is the same as in other node fields.

We agree that the best method of identifying a true SN on lymphoscintigraphy is to visualize the lymphatic vessel passing directly to the SN on dynamic imaging. Some find star artifacts a problem when the injection site is in the field of view, and this problem can be overcome by shielding; however, we find this cumbersome because we perform many studies every day. We have found that using a super-high-resolution collimator with a septal penetration of less than 1% at 140 keV solves the problem. Lymphatic vessels can clearly be visualized without the need to shield the injection site.

Finally, we have found that all SNs, regardless of their location, can contain metastatic disease and that the incidence varies with the thickness of the primary melanoma and presence or absence of ulceration. We have not found that the number of sentinel nodes at each site or their exact location has any effect on this incidence. We therefore suspect that use of a rather complex classification system based on SN numbers and location will not provide useful prognostic or therapeutic information.

REFERENCES

1. Mascagni P. *Vasorum Lymphaticorum Corporis Humani Historia et Ichnographia.* Sienna, Italy: P. Carli; 1787.
2. Delamere G, Poirier P, Cuneo B. The lymphatics. In: Charpy PP, ed. *A Treatise of Human Anatomy.* Westminster, U.K.: Archibald Constable and Co. Ltd.; 1903.
3. Sherman A, Ter-Pogossian M. Lymph node concentration of radioactive colloidal gold following interstitial injection. *Cancer.* 1953;6:1238–1240.
4. Fee HJ, Robinson DS, Sample WF, et al. The determination of lymph shed by colloidal gold scanning in patients with malignant melanoma: a preliminary study. *Surgery.* 1978;84:626–632.
5. Meyer CM, Lecklitner ML, Logic JR, et al. Technetium 99m sulfur-colloid cutaneous lymphoscintigraphy in the management of truncal melanoma. *Radiology.* 1979;131:205–209.
6. Munz DL, Hör G. Utility of lymphoscintigraphy in management of cutaneous malignant melanoma [abstract]. *J Nucl Med.* 1982;23(suppl):P97.
7. Uren RF, Thompson JF, Howman-Giles RB. *Lymphatic Drainage of the Skin and Breast: Locating the Sentinel Nodes.* Amsterdam, The Netherlands: Harwood Academic Publishers; 1999.
8. Maza S, Valencia R, Geworski L, et al. Influence of fast lymphatic drainage on metastatic spread in cutaneous malignant melanoma: a prospective feasibility study. *Eur J Nucl Med Mol Imaging.* 2003;30:538–544.
9. Uren RF, Howman-Giles RB, Thompson JF, Roberts J, Bernard E. Variability of cutaneous lymphatic flow rates. *Melanoma Res.* 1998;8:279–282.

Roger F. Uren, MD
Robert Howman-Giles, MD
John F. Thompson, MD
University of Sydney
Sydney, New South Wales, Australia

Absolute Quantitation of Myocardial Blood Flow After Nitroglycerin and Ischemic Cardiomyopathy with a Low Ejection Fraction

TO THE EDITOR: Tamadura et al. (*1*) and Sciagrà (*2*) have advanced our knowledge with original research and original thought.

With an accepted method to quantify regional blood flow using ^{15}O-water and correction for water in the blood pool, Tamadura et al. (*1*) reported that nitroglycerin did not increase myocardial blood flow in ischemic segments. The authors rather demonstrated that the effect of the nitrate is to selectively decrease coronary vascular resistance in either ischemic or viable myocardium. At the present time, there is no other way to address these scientific questions.

As Americans age, the demographic implications of ischemic cardiomyopathy with a low ejection fraction become ever so important. As Sciagrà pointed out (*2*), an increased body of evidence indicates that in chronic coronary heart disease and after myocardial infarction, reversible myocardial dysfunction is caused by repeated stunning in the presence of a severe reduction in coronary blood flow reserve but may be accompanied by preserved resting perfusion (*3*). Hibernation, then, may be due to repeated stunning, and Braunwald and Kloner anticipated such a chronic stunning state (*4*).

One fascinating aspect of ischemic cardiomyopathy with a low ejection fraction is the response of dysfunctional but recoverable myocardium to low-dose dobutamine as monitored by echocardiography (*5*). In fact, Bax et al. (*6*) used resting perfusion, as determined by an extractable ^{99m}Tc-agent and low-dose dobutamine echocardiography, to assess myocardial segments for the likelihood of recovery of function after revascularization, and they studied a true population of patients with ischemic cardiomyopathy with a low ejection fraction. It is unclear how the regional thickening of myocardial segments with severely reduced coronary blood flow reserve can be made to improve in response to low-dose dobutamine.

In patients with contractile dysfunction, moderately reduced baseline coronary arterial blood flow with associated increased ^{18}F-FDG uptake, and maintained wall-thickness inotropic responsiveness to dobutamine, a head-to-head comparison after nitroglycerin and during low-dose dobutamine will clearly offer new knowledge (*7*). This may lead to better segment selection for revascularization.

REFERENCES

1. Tadamura E, Mamede M, Kubo S, et al. The effect of nitroglycerin on myocardial blood flow in various segments characterized by rest-redistribution thallium SPECT. *J Nucl Med.* 2003;44:745–751.
2. Sciagrà R. Nitrates and viability: a durable affair. *J Nucl Med.* 2003;44:752–755.
3. Camici P, Rimoldi OE. Myocardial blood flow in patients with hibernating myocardium. *Cardiovasc Res.* 2003;57:302–311.
4. Braunwald E, Kloner R. The stunned myocardium: prolonged, postischemic ventricular dysfunction. *Circulation.* 982;66:1146–1149.
5. Pierard LA, Lancelloti P, Benoit T. Myocardial viability: stress echocardiography vs nuclear medicine. *Eur Heart J.* 1997;18(suppl D):D117–D123.
6. Bax J, Poldermans D, Schinkel AF, et al. Perfusion and contractile reserve in chronic dysfunctional myocardium: relation to functional outcome after surgical revascularization. *Circulation.* 2002;106(suppl 1): I14–I18.

7. Heusch G, Schulz R. Perfusion-contraction match and mismatch. *Basic Res Cardiol.* 2001;96:1–10.

Jesus A. Bianco, MD
University of Wisconsin Medical School
Madison, Wisconsin

REPLY: We appreciate the comments on our article (*1*) and the article by Sciagra (*2*). As Dr. Bianco mentions, viability assessment is of paramount clinical importance, especially in patients with severe left ventricular dysfunction in whom the outcome without intervention is poor but the risk of revascularization is high. It is interesting that the regional thickening of myocardial segments with severely reduced coronary blood flow reserve can improve in response to low-dose dobutamine. Lee et al., using PET, reported that myocardial blood flow increased more in contractile reserve–positive segments than in contractile reserve–negative segments in patients with left ventricular dysfunction (*3*). Thus, low-dose dobutamine is considered able to improve myocardial blood flow and contractile function, even in segments with impaired flow reserve of severe left ventricular dysfunction.

In our study (*1*), nitroglycerin preferentially reduced coronary vascular resistance (CVR) without significantly changing it in the nonischemic or nonviable myocardium. The reduction in CVR in viable myocardium with ischemia could be caused by dilatation of epicardial coronary stenosis and collateral vessels. The lack of reduction in CVR in nonviable myocardium may be because of damage in the myocardium itself or in the microcirculation, despite the dilatation of these vessels. CVR in nonischemic myocardium may be determined by the small microvessels, on which nitroglycerin has little effect. This change in CVR apparently makes coronary blood flow redistribute from the nonischemic to the ischemic myocardium with viability. From the teleologic point of view, apparent redistribution of flow from the nonischemic to the ischemic myocardium with viability effectively relieves regional ischemia and anginal pain, if present. Further studies are needed to evaluate myocardial perfusion induced by nitroglycerin and by low-dose dobutamine in the various myocardial segments. Studies of coronary circulation have demonstrated that the control of CVR is interesting but complex. Mechanisms responsible for these heterogeneous responses need further examination. The difference in flow responsiveness to nitrate and dobutamine will offer new insights into the pathophysiology of dysfunctional myocardium and may be useful for better tissue characterization.

REFERENCES

1. Tadamura E, Mamede M, Kubo S, et al. The effect of nitroglycerin on myocardial blood flow in various segments characterized by rest-redistribution thallium SPECT. *J Nucl Med.* 2003;44:745–751.
2. Sciagrà R. Nitrates and viability: a durable affair. *J Nucl Med.* 2003;44:752–755.
3. Lee HH, Davila-Roman VG, Ludbrook PA, et al. Dependency of contractile reserve on myocardial blood flow: implications for the assessment of myocardial viability with dobutamine stress echocardiography. *Circulation.* 1997;96:2884–2891.

Eiji Tadamura, MD
Masaki Yamamuro, MD
Shigeto Kubo, MD
Marcelo Mamede, MD
Kyoto University Graduate School of Medicine
Kyoto, Japan

REPLY: I am grateful to Dr. Bianco for the kind attention to my commentary on the article by Tadamura et al. (*1*,*2*). In my opinion, the equation between hibernating myocardium and reduced resting blood flow is somewhat simplistic, and the concept that viable dysfunctional myocardium is always the result of repetitive stunning is oversimplified as well (*3*). As Bianco correctly remarks, it is difficult to explain the contractile response elicited by low-dose dobutamine in the absence of any change in coronary blood flow. Sun et al., measuring myocardial blood flow with PET and $^{13}NH_3$, observed a slightly reduced baseline flow in dysfunctional viable regions, and during low-dose dobutamine there was an increase that was more limited than in normal segments (*4*). In an experimental model of chronic regional dysfunction in dogs, Gerber et al., using PET and $^{13}NH_3$, demonstrated a preserved baseline myocardial blood flow with a reduced coronary reserve as compared with normally contracting segments (*5*). Thus, it could be concluded that a preserved although reduced coronary reserve must be present to support the contractile response to low-dose dobutamine stimulation, independently of the level of baseline blood flow (*6*). To return to the clinical issues raised by Bianco, it is important to remember, as for instance demonstrated by Bax et al. (*7*), that myocardial perfusion imaging is more sensitive (but less specific) than dobutamine echocardiography in detecting viable myocardium. The extent of ultrastructural damage in the dysfunctional region has been advocated to explain the discrepancy between preserved uptake of perfusion agents and maintained contractile reserve (*8*). To overcome the intrinsic limitation of each diagnostic modality and as correctly suggested by Bianco, the combined evaluation of different viability markers could be helpful to optimize the recognition of segments likely to recover after revascularization (*9*). This is most important in the current clinical scenario, in which population aging dramatically increases the number of patients with heart failure symptoms and consequently the need for methods able to identify at a reasonable cost the presence of reversible left ventricular dysfunction.

REFERENCES

1. Sciagrà R. Nitrates and viability: a durable affair. *J Nucl Med.* 2003;44:752–755.
2. Tadamura E, Mamede M, Kubo S, et al. The effect of nitroglycerin on myocardial blood flow in various segments characterized by rest-redistribution thallium SPECT. *J Nucl Med.* 2003;44:745–751.
3. Heusch G, Schulz R. Hibernating myocardium: new answers, still more questions! *Circ Res.* 2002;91:863–865.
4. Sun KT, Czernin J, Krivokapich J, et al. Effects of dobutamine stimulation on myocardial blood flow, glucose metabolism, and wall motion in normal and dysfunctional myocardium. *Circulation.* 1996;94:3146–3154.
5. Gerber BL, Laycock S, Melin JA, Borgers M, Flameng W, Vanoverschelde JL. Myocardial blood flow, metabolism, and inotropic reserve in dogs with dysfunctional noninfarcted collateral-dependent myocardium. *J Nucl Med.* 2002;43:556–565.
6. Rahimtoola SH. Hibernating myocardium has reduced blood flow at rest that increases with low-dose dobutamine. *Circulation.* 1996;94:3055–3061.
7. Bax JJ, Poldermans D, Schinkel AF, et al. Perfusion and contractile reserve in chronic dysfunctional myocardium: relation to functional outcome after surgical revascularization. *Circulation.* 2002;106(suppl 1):I14–I18.
8. Nagueh SF, Mikati I, Weilbaecher D, et al. Relation of the contractile reserve of hibernating myocardium to myocardial structure in humans. *Circulation.* 1999;100:490–496.
9. Leoncini M, Marcucci G, Sciagrà R, et al. Prediction of functional recovery in patients with chronic coronary artery disease and left ventricular dysfunction combining the evaluation of myocardial perfusion and contractile reserve using nitrate-enhanced technetium-99m sestamibi gated single-photon emission computed tomography and dobutamine stress. *Am J Cardiol.* 2001;87:1346–1350.

Roberto Sciagrà, MD
University of Florence
Florence, Italy

Blood Flow Heterogeneity Versus Cerebral Hypoperfusion Revealed by Fractal Analysis on ^{99m}Tc-HMPAO SPECT

TO THE EDITOR: A recent article published in *The Journal of Nuclear Medicine* reported findings on the "heterogeneity" of cerebral blood flow (CBF) in patients showing vascular dementia with small-vessel disease (*1*). The study applied 3-dimensional fractal analysis to images obtained with ^{99m}Tc-hexamethylpropyleneamine oxime (HMPAO) SPECT, using an intensity-cutoff algorithm previously documented for Alzheimer's disease (*2*). The results suggested that the CBF heterogeneity could readily be assessed by calculating the fractal dimension and that the fractal dimension was abnormally increased in vascular dementia patients, compared with age-matched healthy control subjects (*1*). In both articles (*1,2*), the fractal dimension derived from the image data was claimed to indicate the degree of CBF heterogeneity, with a larger fractal dimension standing for increased heterogeneity.

My colleagues and I have emphasized many times that *fractal dimension*, as defined using the intensity-cutoff approach, is an index representing solely the percentage volume of reduced radioactivity (*3–5*), independent of the anatomy examined and the imaging modality used. This point has been proven using more than a hundred sets of nuclear medicine image data, randomly chosen by combining SPECT images and projection scintigrams of the lungs, the livers, and the brains from 28 patients, to yield a Pearson correlation coefficient as high as 0.999 (*3*). The relationship between the intensity-cutoff fractal dimension and the percentage volume of low radioactivity was not only strong but almost a one-to-one association. As a natural consequence, it is not surprising that increased fractal dimensions were reported for diseases that are already known to exhibit impaired CBF, in particular vascular dementia (*1*) and Alzheimer's disease (*2*). In fact, if the scientific community were in favor of the intensity-cutoff fractal analysis approach, we would predict that all patients with physiologic and pathologic situations showing hypoperfusion on ^{99m}Tc-HMPAO SPECT, such as normal aging, cerebral ischemia, or cocaine abuse, would also exhibit significantly increased intensity-cutoff fractal dimensions. Likewise, for other diseases that manifest by focally reduced radioactivity in nuclear medicine examinations, such as impaired glucose uptake in epileptic seizure foci demonstrated on ^{18}F-FDG PET scans, an increase in the intensity-cutoff fractal dimension could also be anticipated. As long as the percentage volume of reduced radioactivity reaches statistical significance between patients and healthy control subjects, the intensity-cutoff fractal dimension will reach a similar level of statistical significance because of the modality-independent one-to-one association.

Fractal analysis is of contemporary interest to the scientific community, in that it may be an effective approach toward objective quantification of morphologically complex systems. But that is not to say that the fractal dimension can be arbitrarily defined. Parameters such as the fractal dimension defined in different manners will convey different physical meanings, even if named identically. The fractal dimension calculated from relative dispersion at different sizes of regions of interest indicates spatial heterogeneity of radioisotope distribution, whereas the fractal dimension computed by pixel counting at different cutoff intensities does not reveal equivalent information. In the case of the intensity-cutoff fractal dimension, whether *fractal dimension* is the appropriate term is not the most relevant issue. Rather, the essential point lies in the fact that, other than representing the percentage volume of low radioactivity (which can be obtained through simple, traditional methods of image analysis), the intensity-cutoff fractal dimension does not provide any new diagnostic or prognostic insights despite its methodologic origin.

We strongly suggest further nuclear medicine studies of the intensity-cutoff fractal analysis algorithm to include a scatter plot showing the fractal dimension versus the percentage volume of reduced radioactivity. Such a plot would provide direct evidence on whether the intensity-cutoff fractal dimension indeed offers additional information other than the existence of reduced radioactivity or, in the case of ^{99m}Tc-HMPAO SPECT, impaired CBF. Proof that the intensity-cutoff fractal dimension indicates "heterogeneity" requires at least that the variable of deterministic value in clinical diagnosis (i.e., the percentage volume of hypoperfusion) be controlled.

REFERENCES

1. Yoshikawa T, Murase K, Oku N, et al. Statistical image analysis of cerebral blood flow in vascular dementia with small-vessel disease. *J Nucl Med.* 2003;44:505–511.
2. Nagao M, Murase K, Kikuchi T, et al. Fractal analysis of cerebral blood flow distribution in Alzheimer's disease. *J Nucl Med.* 2001;42:1446–1450.
3. Chung HW, Huang YH. Fractal analysis of nuclear medicine images for the diagnosis of pulmonary emphysema: interpretations, implications, and limitations. *AJR.* 2000;174:1055–1059.
4. Chung HW. The severity of pulmonary emphysema investigated with fractal analysis: regional dependence. *J Nucl Med.* 2001;42:177–178.
5. Chung HW. Fractal analysis of nuclear medicine images again: validity and interpretation of results from new analysis methods. *J Nucl Med.* 2003;44:316–317.

Hsiao-Wen Chung, PhD
National Taiwan University
Taipei, Taiwan