Calculation of Ejection Fraction in Gated SPECT

TO THE EDITOR: In a recent article (*1*), my friend and colleague Grant Gullberg presented a method for the calculation of ejection fraction in gated myocardial perfusion SPECT studies. The crucial point is the avoidance of edge detection. In their method, the authors used the maximal activity plane as the ventricular delineator. The originality of the method resides in the latter, not in the former, since avoidance of edge detection for ventricular delimitation has been described before. Several studies (*2–5*) have used a method in which the delineator was the first moment of the count density distribution across the myocardial wall. I will admit that the Japanese reference could easily have been missed.

REFERENCES

1. Feng B, Sitek A, Gullberg GT. Calculation of the left ventricular ejection fraction without edge detection: application to small hearts. *J Nucl Med.* 2002;43:786–794.
2. Goris ML, Thompson CJ, Malone LJ, Franken PR. Modeling the integration of myocardial perfusion and function. *Nucl Med Commun.* 1994;15:9–20.
3. Everaert H, Franken PR, Flamen P, Goris M, Momen A, Bossuyt A. Left ventricular ejection fraction from gated-SPET myocardial perfusion studies: a method based on the radial distribution of count rate density across the myocardial wall. *Eur J Nucl Med.* 1996;23:1628–1633.
4. Goris ML, Malone LJ, Franken PR, Thompson CJ. Myocardial wall thickening rather than motion is a predictor of fixed perfusion defects in integrated myocardial perfusion and kinetic studies [abstract]. *Eur J Nucl Med.* 1993;20:910.
5. Goris ML. Evaluation of myocardial status by the integration of perfusion and kinetic measurements [abstract]. *Kaku Igaku.* 1993;30:838.

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REPLY: We truly regret having overlooked the work of Michael Goris. As is mentioned in his letter, he also proposed a method for estimating left ventricular ejection fraction (LVEF) without having to measure the edge of the intraventricular cavity. Our work was aimed at improving calculation of the LVEF for small hearts by developing a method that was less sensitive to partial-volume effects, whereas his work was aimed at developing a method that would improve the calculation of the LVEF in the case of perfusion defects. Because both methods do not detect edges, they should both work better in the case of perfusion defects since no interpolation is required for missing data.

The Goris method (*1*) processes the 3-dimensional gated nuclear tomographic images to eliminate nonmyocardial structures and to locate the center of the left ventricular cavity in the end-systolic time bin. The position of the centroid of the counting rate distribution along all radii emanating from this center is estimated for each time bin. All of the centroid distances at end-systole and end-diastole are used to estimate the corresponding volumes for calculating the LVEF (*2*). On the other hand, our method transforms the 3-dimensional image in Cartesian coordinates into an image in prolate spheroid coordinates. In this coordinate system, the wall of the left ventricle appears as a plane. The maximum activity along each radius can then easily be determined. We present a mathematic derivation that shows that the position of this maximum value can be used to accurately estimate the LVEF for large and smaller hearts. As Michael Goris correctly points out, this is the innovation in our method.

LVEF calculated using the Goris method of calculation correlates well with LVEF calculated using conventional planar equilibrium radionuclide angiocardiography, even in the case of perfusion defects. Our method gave results that correlated well with the quantitative gated SPECT method (*3,4*) for large hearts and was shown to be more accurate for smaller hearts. However, our work was not evaluated for perfusion defects, but the method may do well for the same reason that the Goris method does well in the presence of severe perfusion defects (*2*).

We thank Michael Goris for bringing his excellent work to our attention. Both his method and our method have significant merit for improving the calculation of LVEF from nuclear scintigraphic images. Further work is needed to evaluate these techniques for different sizes of hearts with various abnormalities.

REFERENCES

1. Goris ML, Thompson C, Malone LJ, Franken PR. Modelling the integration of myocardial regional perfusion and function. *Nucl Med Commun.* 1994;15:9–20.
2. Everaert H, Franken PR, Flamen P, Goris M, Momen A, Bossuyt A. Left ventricular ejection fraction from gated SPET myocardial perfusion studies: a method based on the radial distribution of count rate density across the myocardial wall. *Eur J Nucl Med.* 1996;23:1628–1633.
3. Germano G, Kiat H, Kavanagh PB, et al. Automatic quantification of ejection fraction from gated myocardial perfusion SPECT. *J Nucl Med.* 1995;36:2138–2147.
4. Germano G, Kavanagh PB, Kavanagh JT, et al. Repeatability of automatic left ventricular cavity volume measurements from myocardial perfusion SPECT. *J Nucl Cardiol.* 1998;5:477–483.

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White Blood Cell Labeling with ^{99m}Tc-HMPAO

TO THE EDITOR: We were interested to read the contribution of Dr. Ak and collaborators dealing with the chromosomal consequences induced by white blood cell labeling with ^{99m}Tc-hexamethylpropyleneamine oxime (HMPAO) (*1*). The authors considered that their experimental conditions mimicked routine conditions. However, the final radioactive concentration they obtained was 325.6 MBq for 4.2–7 million mononuclear cells, that is, about 150-fold higher than the radioactive concentration on mononuclear cells we have under routine conditions (325 kBq per million mononuclear cells (*2*)). The authors said that they use "mixed leukocyte labeling," whereas they have, in fact, labeled isolated mononuclear cells without reducing radioactive concentration in order to correct for the absence of granulocytes in their preparation. Mononuclear cells are only a fraction of white blood cells, less abundant than granulocytes, and their affinity for HMPAO is lower than granulocyte affinity (*3*).

In our opinion, it is therefore not surprising that the authors, having worked under such conditions, noted a high frequency of unstable chromosomal aberrations that led them to conclude that all the aberrant cells would be unable to clone after in vivo injection and would be eliminated.

In contrast to the observation made by Ak et al., we have previously shown that some lymphocytes, after being labeled under conditions mimicking routine nuclear medicine practice, had chromosomal aberrations and that a fraction of labeled cells was still able to clone in vitro.

We think that it is safer and therefore advisable to exclude lymphocytes before labeling in order to avoid the injection of damaged lymphocytes.

REFERENCES

1. Ak İ, Vardereli E, Durak B, et al. Labeling of mixed leukocytes with ⁹⁹ᵐTc-HMPAO causes severe chromosomal aberrations in lymphocytes. *J Nucl Med.* 2002;43:203–206.
2. de Labriolle-Vaylet C, Colas-Linhart N, Sala-Trepat M, Petiet A, Voisin P, Bok B. Biological consequences of the heterogeneous irradiation of lymphocytes during technetium-99m hexamethylpropylene amine oxime white blood cell labelling. *Eur J Nucl Med.* 1998;25:1423–1428.
3. Peters AM, Osman S, Henderson BL, et al. Clinical experience with ⁹⁹ᵐTc-hexamethylpropylene amineoxime for labeling leucocytes and imaging inflammation. *Lancet.* 1986;2(8513):946–949.

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REPLY: As indicated in our publication (*1*), all cultured, labeled lymphocytes carried heavy chromosomal damage. However, judging from the letter to the editor of de Labriolle Vaylet et al., in their study (*2*) only some lymphocytes had chromosomal aberrations and some were even able to form clones in vitro. It thus seems that the lymphocytes in their study contained much less radioactivity, so that we assume their labeling procedure must have been different from ours. With our methodology, we feel confident that reinjection of heavily damaged lymphocytes in the patient will not have adverse clinical consequences.

REFERENCES

1. Ak İ, Vardereli E, Durak B, et al. Labeling of mixed leukocytes with ⁹⁹ᵐTc-HMPAO causes severe chromosomal aberrations in lymphocytes. *J Nucl Med.* 2002;43:203–206.
2. de Labriolle-Vaylet C, Colas-Linhart N, Sala-Trepat M, Petiet A, Voisin P, Bok B. Biological consequences of the heterogeneous irradiation of lymphocytes during technetium-99m hexamethylpropylene amine oxime white blood cell labelling. *Eur J Nucl Med.* 1998;25:1423–1428.

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Influence of Renal Function on Renal Output Efficiency

TO THE EDITOR: The investigation by Kuyvenhoven et al. reported in the June 2002 issue of *The Journal of Nuclear Medicine* (*1*) purported to study quantitatively the influence of renal function on the parameter of renal output efficiency (OE) and to evaluate factors that may modify this effect. This aim of the study is welcome. However, we would like to comment on several points affecting the simulations, and at least one important modifying factor seems to have been overlooked.

The main purpose of the development of OE was to aid the interpretation of the equivocal furosemide response in an F+18 diuresis study by compensating for the effect of reduced renal function and to give a validated single-number measurement at 30 min after injection of the radiopharmaceutical, provided the protocol was followed. In this it has succeeded, as evidenced both by the original study validating the use of OE (*2*) and by more recent work by Cosgriff and Morrish, who reported a reduction from 15% to about 2% for the equivocal rate in F+15 renography (*3*). Kuyvenhoven et al. (*1*) simulated a more general usage of OE with acquisition times of up to 2 h and reported expected SD values for OE measured at 20, 40, and 60 min after injection. The largest predicted SD values occurred for OE measured at 40 and 60 min after injection and correspond to mean transit times greater than 20 min. The authors did not explain the relevance of performing so many simulations with mean transit times in the range 40–60 min. We believe that many of these simulations associated with large SD values for OE are well outside the range encountered in routine clinical practice (*4*).

Second, the authors erred in suggesting that renal clearance should affect OE only in a 2-kidney model and not in a 1-kidney model. In a 1-kidney model, a decrease in renal uptake function automatically leads to changes in both the intercepts and the slopes of the exponential components of the plasma clearance curve in a way analogous to that of a 2-kidney model. The same input function could arise either from 1 kidney with a certain clearance value (in mL/min) or from 2 kidneys, each of which contributes different individual values of relative uptake that total that same clearance value.

Third, we would like to observe that the shape of the input function affects not only the parameter OE but also the parameter normalized residual activity (NORA) (*5*). The OE at a time t is defined for an individual kidney as the total output up to time t expressed as a percentage of the total input up to that time. From this simple definition it is clear that OE is normalized to, and thus numerically independent of, the total input at time t. The apparent residual dependence of OE on the total renal clearance arises from a difference in shape of the input function rather than from a difference in the total input up to time t. A difference in shape between the input function corresponding to a normal renal clearance and the input function corresponding to a poor renal clearance represents a difference in the time course of input, which leads to a difference in levels of occupancy of the individual transit time pathways through the system at the time that OE is measured. This difference in occupancy of the transit time pathways at the time of measurement will be apparent in the value of the background-subtracted renal curve at time t, R(t). The value of R(t) is used both in the calculation of OE and in the calculation of the parameter NORA. Thus, it is disappointing that the authors did not use their

simulation data to study, at the same time, the effect of the input function on the parameter NORA, and we would respectfully advise the authors to examine this possibility.

The fourth and perhaps most important point is that the authors completely overlooked the changes in OE consequent on the administration of furosemide. The effect of furosemide is to stimulate increased diuresis. When there is a nonzero response to furosemide, the subsequent transit time distribution is completely altered. Not only is the mean transit time decreased, but also the occupancy of the previously long transit time pathways may be eliminated, thus reducing the differences in OE arising from the input functions corresponding to normal and poor renal clearances. Therefore, for OE measured after furosemide, the input function will be less influential than was predicted by the authors' simulations, and when the response to furosemide is good, OE becomes effectively independent of total renal clearance. However, other sources of error are recognized, including the goodness of fit of the integral of the plasma clearance curve to the upstroke of the renal curve. This fit is improved by using a 10-s frame rate, as originally described.

The F+18 protocol that we published (2) has the advantage of a low equivocal rate for a value of between 70% and 78% for OE measured at 30 min after injection. This has been tested independently by Cosgriff, Morrish, and Turner, who presented their data at the Radionuclides in Nephrourology meeting in Monterey, CA, 2001. In only 2 of 100 patient studies of suspected outflow obstruction did the value fall between 70% and 78% for OE measured at 30 min after injection. In adult-urology practice, a yes-or-no decision about the presence of obstructing uropathy is what is required and what is expedited by the OE in our protocol designed for adults.

REFERENCES

1. Kuyvenhoven JD, Ham HR, Piepsz A. Influence of renal function on renal output efficiency. *J Nucl Med.* 2002;43:851–855.
2. Chaiwatanarat T, Padhy AK, Bomanji JB, Nimmon CC, Sonmezoglu K, Britton KE. Validation of renal output efficiency as an objective quantitative parameter in the evaluation of upper urinary tract obstruction. *J Nucl Med.* 1993;34:845–848.
3. Cosgriff PS, Morrish O. The value of output efficiency measurement in resolving equivocal frusemide responses [abstract]. *Nucl Med Commun.* 2000;21:390–391.
4. O'Reilly P, Aurell M, Britton K, Kletter K, Rosenthal, L, Testa T. Consensus on diuresis renography for investigating the dilated upper urinary tract. *J Nucl Med.* 1996;37:1872–1876.
5. Piepsz A, Kuyvenhoven JD, Tondeur M, Ham H. Normalized residual activity: usual values and robustness of the method. *J Nucl Med.* 2002;43:33–38.

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REPLY: We thank Drs. Nimmon and Britton for their interest in our article and for the opportunity they offer us to debate about output efficiency (OE). The criticism they raise concerns 4 points. The first of these is that the introduction of OE has reduced the number of equivocal responses to furosemide. It is clear, from all studies done in children, that one can have poor renal emptying, even after micturition, in cases without "obstruction"—for in-

stance, in successfully operated patients with pelviureteral junction stenosis. It is well known that drainage is the result of 2 factors, volume and flow. Despite an acceptable flow, if the volume is large the drainage will be poor, whatever the parameter used for estimating it (furosemide curve, residual activity in percentage of the maximal activity, OE, or normalized residual activity [NORA]). This fact is now well recognized and was clearly underlined in the recent guidelines for standard and diuretic renography in children (1). We therefore think that the present controversy simply reflects population dependency: It may be that in adults with mainly acquired obstructive pathology, a clear-cut separation between obstructed and nonobstructed kidneys can be obtained without too many equivocal responses (2). This is not the case in children with prenatally detected congenital hydronephrosis. In this population, good drainage sends a favorable message to the surgeon, whereas equivocal or even poor drainage in no way indicates obstruction in cases of huge dilatation.

The second and third points that were raised concern the 1-kidney and the 2-kidney models and the shape of the input function in relation to OE and NORA. What we wanted to underline was that in the model of a single kidney, the overall function is, by definition, directly dependent on that unique kidney. In a 2-kidney model, the overall function may still be perfectly normal, even if 1 kidney has poor function. In both models, OE perfectly corrects for the function of the kidney for which it is calculated. (By definition, OE has been calculated on that basis (3).) However, if there is only 1 kidney, OE also corrects for the decrease in overall clearance; if there are 2 kidneys, OE is not able to correct perfectly for overall clearance. For the same "true" level of drainage, OE will vary depending on the function of the contralateral kidney. The same phenomenon will be observed whatever the parameter of drainage chosen, including, of course, NORA. The only parameter that, theoretically, does not depend on overall function is mean transit time (MTT). In practice, however, there are many other drawbacks related to its determination (4,5).

Finally, Nimmon and Britton consider that we have overlooked the fact that furosemide was given and that, therefore, because of higher diuresis, the effect of clearance is attenuated and less than what was predicted by the authors. Moreover, our choice of performing simulations with MTT in the range of 40–60 min is clinically irrelevant. Again, we disagree: An MTT in the range of 40–60 min is perfectly acceptable in cases of poor drainage, whether there is indeed an important impairment of flow or simply a huge dilatation such as is observed in congenital hydronephrosis. Moreover, even if MTT is significantly shortened after furosemide, the error due to impaired function is still important, as is obvious in Figure 3 of our article. The relevance of prolonging the simulation up to MTT values of 40–60 min is therefore obvious. We believe that the controversy concerning MTT is due to the fact that Nimmon and Britton measure only cortical transit. OE is measured on the whole kidney, and the MTT in a nondraining system can easily be estimated around these high 40- to 60-min transit values.

REFERENCES

1. Gordon I, Colarinha P, Fettich J, et al. Guidelines for standard and diuretic renography in children. *Eur J Nucl Med.* 2001;28:BP21–BP30.
2. Cosgriff PS, Morrish O. The value of output efficiency measurement in resolving equivocal frusemide responses [abstract]. *Nucl Med Commun.* 2000;21:390–391.
3. Chaiwatanarat T, Padhy AK, Bomanji JB, Nimmon CC, Sonmezoglu K, Britton KE. Validation of renal output efficiency as an objective quantitative parameter

in the evaluation of upper urinary tract obstruction. *J Nucl Med.* 1993;34:845–848.

4. Ham HR. Is renography suitable for deconvolution analysis [letter]? *J Nucl Med.* 1996;37:403–404.
5. Kuyvenhoven JD, Ham H, Piepsz A. Is deconvolution applicable to renography? *Nucl Med Commun.* 2001;22:1255–1260.

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