Quantitative Esophageal Scintigraphy: How Reproducible Is This Test?

TO THE EDITOR: We read with interest the article by Tatsch et al (*1*). This article reports the diagnostic performance of optimized esophageal scintigraphy using the multiple swallow technique, which was shown to be close to that of manometry, and supports previous findings of this group (*2,3*). The method clearly discriminates between normal and pathologic function with a sensitivity of 95% and a specificity of 98%.

Unfortunately, in all reports concerning this method, no data are provided on the reproducibility of the test, either in patients or healthy individuals. As long as these data are not available, this technique cannot be recommended to be used in clinical practice, especially not for monitoring progression of or therapeutic effects on esophageal dysmotility. We therefore kindly ask Tatsch and colleagues to provide us with data on reproducibility of this test.

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The Therapeutic Approach in Subacute (de Quervain's) Thyroiditis

TO THE EDITOR: In a recent article, Meier and Nagle (*1*) reported three interesting cases drawing attention to the differential diagnosis of a painful thyroid. The therapeutic approach in subacute thyroiditis may be somewhat misleading to the clinicians. Indeed, Meier and Nagle (*1*) used corticosteroids to relieve symptoms of subacute (de Quervain's) thyroiditis as there is no specific therapy for the subacute thyroiditis. Almost every review of this subject has recommended employment of corticosteroids in relieving symptoms of disorder (*2*). Corticosteroids, however, should not be routinely used.

We performed a retrospective review of the clinical course of 318 patients (284 women, 34 men; range 24–76 yr; mean age 44.9 ± 8.9 yr) who had had subacute thyroiditis diagnosed between 1970 and 1990. Our purpose was to validate and compare the efficiency of corticosteroid and nonsteroidal treatment of subacute thyroiditis. To be included in the study, a patient had to have a complete set of scintigrams and thyroid function tests made at the time of presentation and follow-up. Diagnostic criteria for subacute thyroiditis were generalized somatic symptoms, pain and tenderness of the thyroid, nonvisualization of the thyroid on scan, increased erythrocyte sedimentation rate and absence of antimicrosomal antibodies. Fine-needle aspiration biopsy was available in 262 patients, and in 213 (81.3%) of them typical cytopathologic finding was found. Complete restauration (restitutio ad integrum) of the thyroid was recognized and defined when the thyroid was clearly visualized on the scan, preceded by normalization of thyroid function tests and erythrocyte sedimentation rate. We identified 237 of the patients who had received nonsteroidal anti-inflammatory drugs (mostly ibuprofen and acetylsalicylic acid), and 49 patients who had received corticosteroids (mostly prednisone, initially with 40–60 mg daily, and gradually discontinued). The response after corticosteroids therapy was prompt and excellent, but with withdrawal of therapy, even very gradually, exacerbation of disease with all signs and somatic symptoms was often observed. Thus, corticosteroids had to be given once again and the treatment of subacute thyroiditis was significantlly prolonged. The mean time for achieving complete restitution of the thyroid was 3.6 ± 1.0 mo in patients on nonsteroidal therapy versus 6.4 ± 2.7 mo in patients on corticosteroids.

Treatment of subacute thyroiditis should be nonsteroidal analgesics anti-inflammatory drugs, while corticosteroids should not be recommended routinely and should be reserved only for the most seriously ill patients.

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Feasibility of Estimating Glomerular Filtration Rate on Children Using Single-Sample Adult Technique

TO THE EDITOR: We read with interest the recent article by Ham and Piepsz (*1*) on the feasibility of estimating glomerular filtration rate on children using single-sample adult techniques. The authors concluded that the single-sample adult technique, using plasma concentration prescaled for 1.73 m^2 body surface area, cannot be used in place of a specific pediatric single-sample method to estimate ^{51}Cr-EDTA renal clearance in children. The authors also reported that they were not aware of a validation of the technique for a glomerular agent. We would like to comment on both these issues.

The idea of scaling plasma concentrations using body surface area had been introduced by our group (*2*) somewhat earlier than Bubeck et al. (*3*), which is cited by the authors as being the first description of the principle. This was applied to the assessment of GFR using ^{99m}Tc-DTPA. We pointed out that this was not only useful in dealing with adults of different size, but also children, and demonstrated its use in this situation in a small number (n = 7) of pediatric patients for 180-min samples.

We have been using this technique clinically for the past 10 yr. Our own method of choice in children is to collect two blood samples at approximately 2 and 3 hr. If this is not logistically possible, then a single sample at about 3 hr is used. If we obtain both samples, then both the single sample and the two-sample GFR values can be calculated. In technically good studies, our experience shows that the 3-hr single sample and two-sample values agree within the errors specified previously i.e., a s.d. of 5.4 ml/min (*2*). For two sample measurements, this level of agreement can be used as a quality control measure of the study. Tissuing of the injection, for example, can lead to inconsistency between these values. An important practical aspect of using the single-sample technique is that the sample is not usually obtained at the exact times that the single-sample equations are defined. We have a set of equations defined at different times and clearance values at intermediate times are defined from these using linear extrapolation. It is also important to note that empirical equations are only valid over the range of values used in their derivation and should not be applied outside this range.

The equations quoted by Ham and Piepsz (*1*) have been compared with our own equations. Figure 1 shows the relationship between the apparent volume of distribution at 240 min for adult subjects, assuming a body surface area of 1.73 m^2. Our own equation, which was derived using ^{99m}Tc-DTPA, is almost identical to that of Morgan et al. (*4*) using

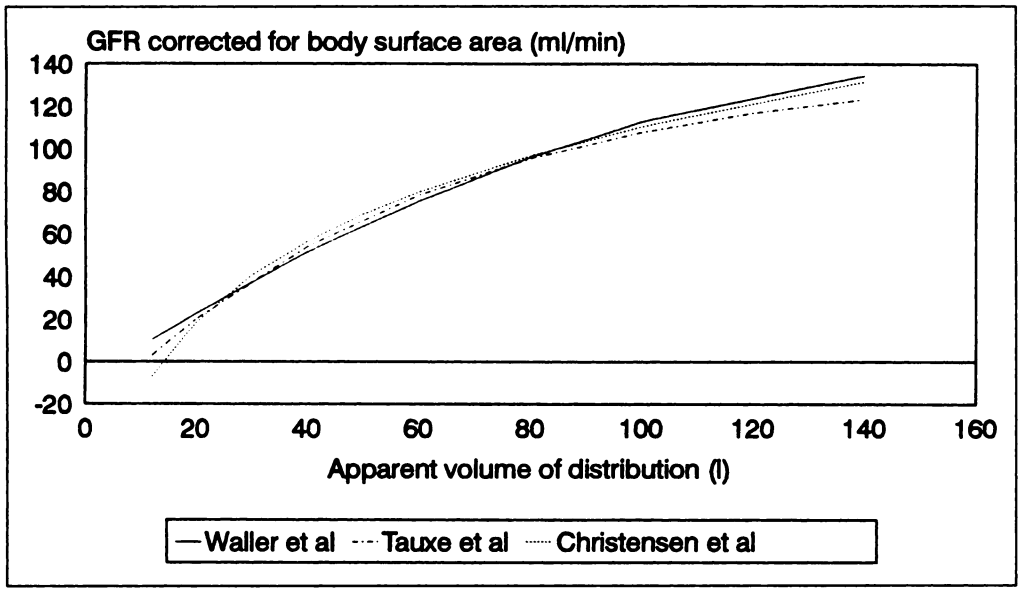

FIGURE 1. The relationship between body surface area corrected GFR and apparent volume of distribution obtained at 240 min postinjection in adults using three empirical equations.

^{51}Cr-EDTA; the latter is not displayed for clarity. The other equations illustrated of Tauxe (*5*) and Christensen and Groth (*6*), are very similar although there are slight differences notably at extreme values of GFR. In particular, for patients with renal failure, we obtain values of apparent volume distribution that would give a negative value for GFR using the Christensen and Groth (*6*) equation.

The situation in children is somewhat different. Figure 2 shows the relationship between body surface area scaled apparent volume of distribution at 120 min for patients with a body surface area of 0.8 m^2 and the body surface area corrected GFR for four different equations. The two pediatric-specific equations by Groth et al. (*7*) and Ham et al. (*8*) show good agreement for a small intermediate range of GFR, but there are differences at low and particularly high values. The equation by Tauxe et al. (*9*) is very similar to that of Ham et al. (*8*) and, therefore, has been omitted from the figure for clarity of display. It should be noted these curves have been derived using volumes of distribution that have not been scaled; they are plotted using scaled values of V_D for comparison with other equations. The 240-min equation by Morgan et al. (*4*) corrected to 120 min as described by Ham and Piepsz (*1*) and using body surface area scaled volume of distribution is also illustrated in Figure 2 and is seen to have a quite different relationship. This is entirely expected as the authors have assumed a single value for clearance rate constant k. This is clearly not appropriate for subjects with differing GFR who will have very different values of k. Figure 2 also shows the 120-min equation derived by Waller et al. (*2*) for the body scaled volume of distribution. This shows considerably closer agreement with the pediatric-specific equations although it produces smaller values at low GFR.

The poor agreement between the use of scaled adult models and specific pediatric equations described by Ham and Piepsz (*1*) is primarily caused by their inappropriate use of the 240 min equations at 120 min. However, even using equations derived at the appropriate time there are still differences. This may be due to the derivation of the gold standard GFR value. For example, the pediatric-specific equation by Tauxe et al. (*5*) has been derived using accurate GFR values produced from sampling up to only 2 hr. Our experience would suggest that this is insufficient for an accurate GFR leading to overestimated values. This could explain the difference between the specific pediatric equations and those of Waller et al. (*2*), in which the gold standard GFR was based on samples up to 4 hr in children and 5 hr in adults. The standard used in this study depends on the assumption that correction for the one pool approximation was similar in adults and children; this has been demonstrated to be the case by Brochner-Mortensen et al. (*10*). A further possible explanation of the differences in the equations is that it may not be valid to apply scaled adult equations in children using 120 min samples. At present, the technique has only been validated using 180 min samples.

The findings of Ham and Piepsz (*1*) are misleading. Appropriately defined adult equations can be scaled down for use in children using glomerular agents. There are, however, still disagreements between the use

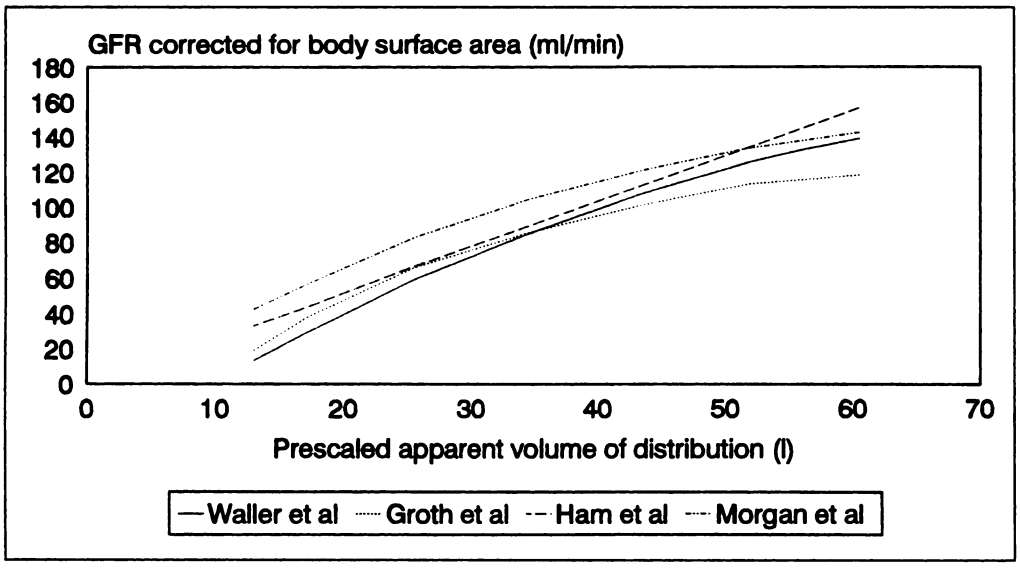

FIGURE 2. The relationship between body surface area corrected GFR and body surface area corrected apparent volume of distribution obtained at 120 min in subjects with a body surface area of 0.8 m^2 for four empirical equations.

of scaled equations and specific pediatric equations and between the different pediatric equations. Further work is required to resolve these differences and to move towards a universally agreed standard set of equations.

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Prognostic Value of Thallium-201 Re-Injection

TO THE EDITOR: The recent article by Petretta et al. (*1*) addresses an important issue regarding the possible incremental prognostic value of ^{201}Tl re-injection after standard stress-redistribution imaging. This is an interesting study with potentially important value. However, I feel that the current analysis leaves one with more questions than it answers.

It is now well-established that some fixed stress perfusion defects on standard redistribution imaging appear to be reversible with re-injection imaging. In addition, it has been demonstrated that myocardial segments corresponding to these defects have significant myocardial viability based on metabolic imaging and regional wall motion response to revascularization. However, the prognostic implications of such phenomenology has been unproven. While defects that show reversibility on standard redistribution imaging have clearly been shown to have important prognostic value (*2*), the vast majority of studies have demonstrated that defects which are fixed on standard redistribution imaging do not have significant prognostic implications (*2*). As the authors point out, prior studies have in fact suggested that defects that are fixed on standard redistribution imaging which become reversible with re-injection imaging also do not have significant prognostic value (*3,4*). Although the authors conclude in their current study (*1*) that the re-injection imaging has significant incremental prognostic value when added to standard stress-redistribution imaging, their methodology does not really address the issue of whether additional reversibility demonstrated by re-injection has significant prognostic value. In addition, their selection of variables to be tested is biased against standard stress-reduction imaging.

Petretta et al. (*1*) chose to use the following ^{201}Tl re-injection variables: (1) the sum of defects which are irreversible after redistribution that show reversibility with re-injection or that remained irreversible but are only moderate in severity; and (2) the number of severe fixed defects after re-injection. However, the standard ^{201}Tl stress-redistribution variables included only the number of reversible defects, persistent defects and lung-to-heart ratio. It did not include the sum of reversible defects plus moderate fixed defects (analogous to the re-injection variable). Thus, one cannot determine whether in fact the detection of reversibility with re-injection in defects that were otherwise fixed with standard stress-redistribution imaging has any significant prognostic value. In addition, if the presence of moderate fixed defects has any significant prognostic value, then the analysis is biased against standard stress-redistribution imaging which does not include this variable for analysis. One is curious as to why this component was lumped with new reversible defects with re-injection imaging, since although moderate fixed defects may have important implications regarding the presence of viable myocardium and improvement in regional wall motion following revascularization, they have not been demonstrated to have prognostic value for future cardiac deaths or myocardial infarction. One suspects that perhaps new reversible defects with re-injection did not have significant incremental prognostic value by itself.

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REPLY: We thank Dr. Brown for his interest in a recently published study in *The Journal of Nuclear Medicine* (*1*). This study addresses whether the detection of viable myocardium in patients with chronic coronary artery disease and left ventricular dysfunction, as assessed by thallium reinjection imaging, adds incremental prognostic information to the results of conventional stress-redistribution scintigraphy. We think that our results support this hypothesis.

We agree with Dr. Brown's observation that exercise defects showing reversibility on standard stress-redistribution thallium imaging have important prognostic value (*2*). Also in our study, the presence of redistribution on delayed images gives incremental prognostic information to clinical and exercise stress-test data (*1*). We do not agree with the concept that fixed thallium defects on standard exercise-redistribution imaging do not have significant prognostic implications. In fact, it has been recently demonstrated that the total extent of exercise thallium SPECT defects and the extent of irreversible thallium SPECT defects were significant predictors of major cardiac events and cardiac deaths in 217 patients with known or suspected coronary artery disease and a mean follow-up period of 70 ± 19 mo (*3*). These findings confirm the results of previous studies with shorter follow-up (*4,5*). Furthermore, Marie et al. (*3*) showed that the extent of reversible exercise defects is significantly related to the occurrence of major ischemic events, but not to cardiac death.

In response to the observation that preliminary previous studies suggested that fixed defects on standard stress-redistribution thallium imaging which became reversible after reinjection do not have significant prognostic value (*6,7*), there are some important points that should be highlighted. Zafrir et al. (*6*) included consecutive patients with coronary artery disease and not only patients with previous myocardial infarction and left ventricular dysfunction (i.e., those patients in whom thallium reinjection imaging is clinically relevant). Furthermore, in Pieri et al.'s (*7*) study the number of viable segments was not related to the outcome. Nevertheless, the number of fixed defects at stress-redistribution thallium scintigraphy that remained fixed after reinjection was the strongest predictor of hard events (*7*). This latter study, however, included patients with previous myocardial infarction but preserved left ventricular function. The criteria used for patient selection and the analysis performed (i.e., quantitative versus qualitative)