Noninvasive Determination of the Regional Distribution of Cardiac Output: Effect of Pharmacological Agents on the Distribution of Tl-201

It has recently been suggested that Tl-201 distribution could reflect fractional distribution of cardiac output (*1*).

We have studied the effects of a variety of commonly employed therapeutic agents on the distribution of Tl-201 in mice, in order to evaluate the influence of secondary factors on the accuracy of regional perfusion measurements. The heart/liver fractional uptake ratio was significantly decreased after administration of propranolol, cardiac glycosides, and lidocaine (−25, −10, and −15%, respectively, $p < 0.05$). Dexamethasone produced a net increase in myocardial uptake (+55%, $p < 0.02$). Chronic administration of furosemide without K supplement produced an increased heart uptake and a decrease in liver uptake (+20% and −30%, $p < 0.02$). Similar observations have already been mentioned by other authors (*2*).

These findings strongly suggest that at the moment of scintigraphy the distribution of Tl-201 has already been influenced by factors affecting Na and K membrane permeability and by total-body potassium. We think that these introduce a severe limitation for the proposed use of Tl for the study of regional distribution of cardiac output, especially in pathologic conditions and where quantitative information is the goal.

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Reply

The arguments of Drs. Bossuyt and Jonckheer do not necessarily indicate that thallium will provide a faulty measurement of regional distribution of cardiac output under the circumstances cited. In fact, there may be changes in the regional distribution of cardiac output brought about by administration of these pharmaceuticals. It is certainly true that we are measuring tissue content of thallium with our imaging procedures and thus it is a tissue's balance between input and output of the radiopharmaceutical that is important. Only limited measurements have been made of regional loss rates of thallium from tissues and the effects of drugs on this phenomenon. It appears, however, that there will be only limited changes in the loss rate of thallium induced by these drugs.

The extraction of Tl-201 by the myocardium has been carefully measured by Weich and associates (*1*) and found to remain unchanged under the influence of increased heart rate, changes in acid-base balance, infusion of insulin, administration of propranolol, and infusion of acetyl strophanthin. Under all of these circumstances, the extraction remained between 85 and 90%. Under circumstances of severe hypoxia, or when myocardial blood flow increased in excess of myocardial oxygen demand, however, extraction of thallium from the coronary circulation decreased.

Thus, we are encouraged to see the use of this procedure by Drs. Bossuyt and Jonckheer. Their observations on the changes in myocardial uptake following propranolol, cardiac glycosides, and lidocaine administration suggest that there really are significant changes in coronary blood flow to account for their observations.

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Misuse of Statistics-Correlation Coefficient (r)—Thy Heart is Treacherous

Folland, Hamilton, Larson, et al. recently compared three radionuclide techniques with contrast angiography for determination of ejection fraction (*1*). After studying 30 patients, they concluded that the first-transit and blood-pool radionuclide techniques were equally accurate when the time-activity method of analysis was employed. As their standard they used ejection fractions measured by area-length analysis of x-ray contrast angiograms. Their results were subjected to a rather elegant analysis by linear regression and correlation coefficients ostensibly proving that significant correlation existed.

Correlation coefficients (r) of regression curves are an improper statistical test for evaluation of small-group comparisons. Although this method of analysis is complex and impressive, as used by Folland, it is an inappropriate test for significance. Clinical laboratory statisticians at the Norwalk Hospital do not accept r values of less than 0.95 as an indication of significance.

Reviewing Folland's data (*1*) we found an obvious discordance between the ejection fractions as measured by the various methods and, accordingly, we reanalyzed the data. We chose, in addition to regression-curve analysis, chi-square and simple Student's t-tests, and found that we cannot concur with their conclusions.

By simple t-test, the radionuclide first-transit and blood-pool ejection fractions are significantly different at the 1 percent level and, therefore, are from a population markedly different from those obtained by the x-ray contrast method.

By using a simple chi-square analysis and segregating the values into normal and abnormal ejection fractions, we find that the first-transit time-activity ejection fractions are

TABLE 1. ANALYSIS: NORMAL VS. ABNORMAL

Comparison	Normal* No. of patients	Abnormal† No. of patients	Abnormal % of patients	Chi-square test
X-ray	21	9	30%	$P < .001$
First-transit	6	24	80%	
X-ray	21	9	30%	$.100 < P < .250$
Blood-pool	15	15	50%	
X-ray	21	9	30%	$.050 < P < .100$
LAO	13	17	57%	

* Ejection fraction $\geq .50$
† Ejection fraction $\leq .49$

markedly different (i.e., less accurate) than the blood-pool time-activity ejection fraction (Table 1). Indeed, rather dramatic differences in interpretation result. The x-ray contrast method would classify 30% of the patients as abnormal, whereas the first-transit method would classify 80% as abnormal! The blood-pool figure would be 50%. Further detailed analysis is really not necessary to establish that—contrary to the author's conclusion—the two radionuclide studies cannot be equally accurate.

In medicine in general and in nuclear medicine in particular, we must be ever mindful of the significance of our numerical data. Statistical analysis must be used to clarify, validate, and exclude bias and the effect of chance. All too often more elegant and complex statistical approaches, if misused, only obfuscate.

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Reply

We have received the comments regarding the use of linear regression analysis and agree that this technique is frequently abused. We believe, however, that its use in the context of our article is correct. We were comparing the relationship between first transit and equilibrium blood pool methods to radiographic contrast angiography. By visual inspection of the plots which compare these two techniques to contrast studies, the correlation coefficient, and the standard error of the estimate, the relationship is similar for both techniques. The plots, two statements in the text, and the table clearly point out that the nuclear techniques underestimate ejection fraction (particularly the first transit technique) compared to contrast angiography. Thus, if the raw measurements are used, as the writers did, accuracy will appear to be worse with the first transit technique. The point, however, is this: since both techniques have a similar relationship to contrast angiography in terms of coefficient of correlation and standard error of the estimate, either technique may be used to predict the contrast ejection fraction with equal accuracy.

The exact reasons why nuclear and contrast techniques obtain different absolute values for the ejection fraction are complex and beyond the scope of this discussion. It should be noted, however, that the basis for accepting the contrast angiographic measurement of ejection fraction were studies done in this laboratory using linear regression analysis of contrast volume (*1–3*).

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Stomach Artifact in Bone Scintigraphy

Evaluation of 500 consecutive bone scintigrams revealed, in 11 patients (2.2%), localized uptake in the posterior region of the left lower ribs (Fig. 1). These shadows turned

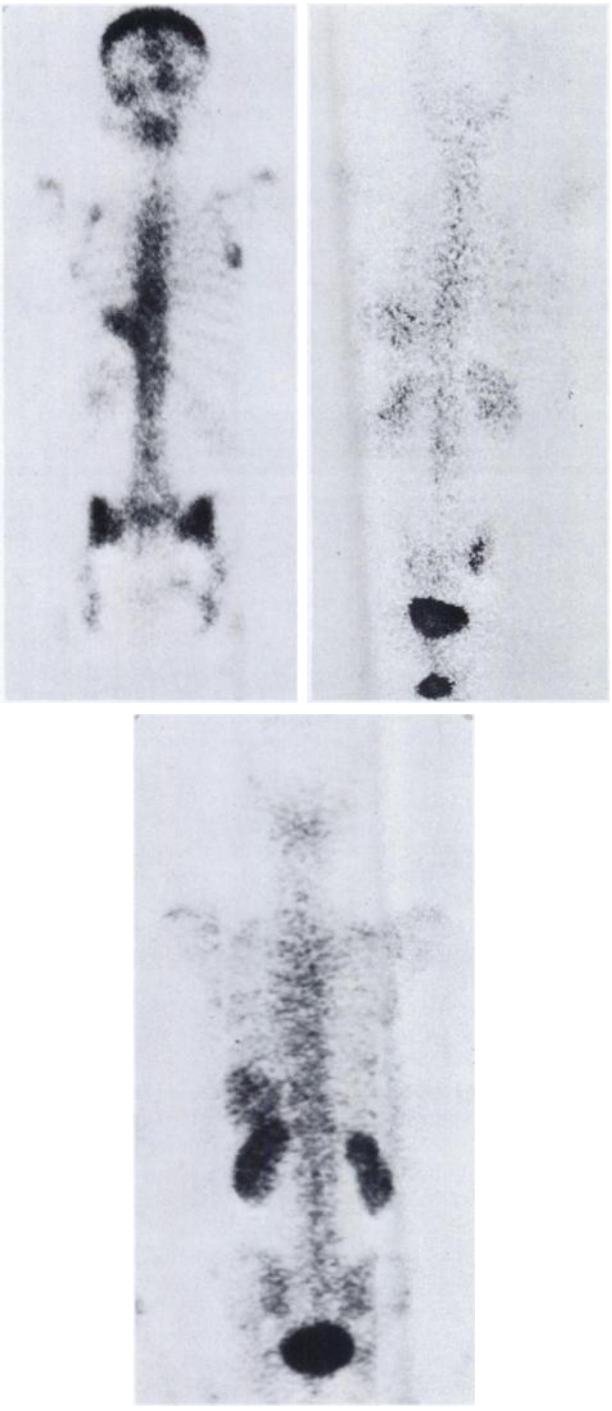

FIG. 1. Stomach artifacts; various degrees of uptake by stomach in different patients.