the kidneys are filtering plasma carrying high specific activities (bolus) of the tracer.

When we take a mathematical viewpoint of the equation:

$$\int Q(t)\,dt = GFR \int c(t)\,dt,$$

the quantity "$\int Q(t)\,dt$" (evaluated from 0 to 3 min) can be estimated by placing a ROI over the kidneys at time = 3 min. "$\int c(t)\,dt$" (also evaluated from 0 to 3 min) can be expressed as an average value of c(t) over the same time; we do this by dividing the injected dose by the patient's estimated plasma volume. The concentration computed this way should represent the *average* concentration of the tracer during the first 3 min. Even if up to 30% of the radiopharmaceutical disappears from the blood (by time = 3 min, assuming exponential clearance of 0.1189 min^{-1}), the *average* concentration over 3 min is approximately 16% less than the concentration at time = 0. That is, when using our simplified linear relationship $Q = GFR \cdot C \cdot t$, a 30% loss of tracer by time = 3 min introduces approximately a 16% underestimation of GFR. Hence, we would expect a regression slope of 0.84 (not 0.7) when correlating blood clearance and our RUPV method. Since we do not attempt to directly measure each patient's individual change in tracer concentration during the first 3 min, we do not try to correct for this effect.

In reference to Peters' data showing differential rate of "disappearance" of HSA and DTPA from the plasma, it appears that Peters' interpretation is to attribute the DTPA loss (in excess to that expected from GFR) to transfer to an extravascular space. We think that in addition to the loss of approximately 10% of DTPA due to GFR during the first 3 min, the physical characteristics of the tracers (e.g., DTPA = 492 Dalton and HSA = approximately 69,000 Dalton) can result in a larger volume of distribution and faster rate of mixing for DTPA therefore resulting in lower concentrations at time = 3 min. Obviously, the clearance of the tracer is far from ideal and is affected by these and other factors. Initial mixing, protein binding, extravasation to extravascular extrarenal spaces and radiopharmaceutical impurities with separate pharmacokinetics, all complicate the simplifying models we try to apply.

Peters' comment on the effect of the "overestimation of 30% of the dose in Equation 7" in our paper is not clear to us, since we in fact measure the injected dose in a dose calibrator and convert MBq to camera counts. We are sorry if our explanation in the original text was unclear.

With regard to the shortcomings of the RUPV model assumptions, the method provides a simple noninvasive estimation of GFR that is relatively accurate. The introduction of an estimate of patient plasma volume resulted in an improvement in precision (the R value improved from 0.82 to 0.9), supporting the feasibility of using an average tracer concentration to solve the RUPV equation.

The goal of our study was to estimate the absolute GFR in units of ml/min without any further normalization. Normalizing this absolute measure is nontrivial and ultimately could include other factors like age and body build. When needed, we used the currently accepted normalization to a surface area of 1.73 m^2 (which can easily be calculated from each patients' height and weight). We did not investigate the possibility of using a plasma volume or extracellular volume as a normalization parameter.

We appreciate Dr. Peters' insightful comments on our work; it stimulated us to further define and clarify the rationale behind our RUPV estimation of GFR.

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Cardiac Uptake of MIBG in Patients With Aortic Stenosis

TO THE EDITOR: The recent paper by Fagret, et al. (*1*) described MIBG uptake in patients with left ventricular hypertrophy secondary to aortic stenosis. They concluded from their study that: (1) patients with left ventricular hypertrophy and aortic stenosis have lower cardiac MIBG activity and a more rapid washout than normal controls; (2) amiodarone and digoxin partially inhibit myocardial MIBG uptake; and (3) the extraneuronal uptake of MIBG in human hearts accounts for 13% of total cardiac activity. Because of methodologic flaws and incorrect interpretation of the data, all of these conclusions are questionable.

The authors state that their patients "were receiving treatment drugs known to affect myocardial uptake of tritiated norepinephrine or [^{123}I] MIBG." None of the drugs their patients were receiving have ever been reported to decrease myocardial uptake of ^{123}I-MIBG.

Study groups consisted of seven controls (age 30 ± 15 yr, mean ± s.d.), six patients (age 70.5 ± 9 yr) who were receiving amiodarone or digoxin and seven patients (age 62 ± 16 yr) who were not taking these medications. There is a large and highly significant ($p \leq 0.002$) difference between the ages in the patient and the control study groups. It has been shown in many studies that there is a correlation between age and plasma norepinephrine levels. Healthy 70-yr-old subjects have plasma norepinephrine levels that are approximately twice those of healthy 20-yr-olds (*2*). This difference is due to increased appearance rates of plasma norepinephrine with aging (*3*). Direct measurement of sympathetic nerve activity in dogs shows a marked increased in activity with age (*4*). Thus, the decreased uptake and the increased washout of MIBG in patients with aortic stenosis may be due in part to age-related differences. Since there is no data on the affects of aging on cardiac MIBG uptake, it is impossible to know to what extent the changes seen in patients with aortic stenosis are due to age versus cardiac disease.

The authors claim that there is a significant difference in MIBG uptake between patients treated with amiodarone and untreated

patients. Using the data in their paper, there is no significant difference between these groups using either the Mann-Whitney test ($p > 0.06$) or the Student t-test ($p = 0.078$). Comparing digoxin treated patients to untreated patients by the Mann-Whitney test, yields a p value that barely reaches statistical significance rather than being <0.01. Correcting the significance level for multiple comparisons (two comparisons) would probably make the difference insignificant. Finally, because of the small number of patients in each treatment group (three each), the probability of a Type I statistical error is high.

The authors state that digoxin decreases cardiac uptake of MIBG. They present no data, however, to substantiate this claim. They mistakenly assume that an association between decreased cardiac MIBG uptake and digoxin use implies causation. Presumably, the reason the patients were taking digoxin was that they had more severe heart failure than untreated patients. A possible explanation for the decreased MIBG uptake between untreated and digoxin treated patients is that the patients treated with digoxin had more severe congestive heart failure, and therefore, would be expected to have lower cardiac MIBG uptake. The fact that hemodynamic parameters between the two groups were similar is not surprising since successful treatment of congestive heart failure with digoxin would be expected to improve cardiovascular function. Whereas it has been shown in vitro that ouabain (a digitalis glycoside similar to digoxin in structure and mechanism of action) can inhibit MIBG uptake in adrenal chromaffin cells, 1 μM ouabain (584 ng/ml) had no effect on MIBG uptake (*5*). Significant inhibition of MIBG uptake was only seen at 10 μM (5840 ng/ml). This concentration would be lethal in humans, and thus it is unlikely therapeutic concentrations of digoxin (1–2 ng/ml) would have any effect on cardiac uptake of MIBG.

Even if significant differences in MIBG uptake occur between treated and untreated patients, the study design is flawed making it impossible to interpret such differences. In patients with heart disease who are receiving medications the primary purpose of which is to directly alter cardiovascular function, it is reasonable to assume that any drug-induced alteration in cardiac function would cause secondary changes in sympathetic nerve function that would then produce changes in MIBG kinetics. Since the study design does not allow the authors to know if or to what extent secondary changes in sympathetic nerve function occur with treatment, it is impossible to interpret any changes in MIBG uptake. A much more convincing argument that these drugs block MIBG uptake could be made if uptake were measured in normal controls before and after drug treatment. This method would also reduce interpatient variability, which was large in this study (ejection fractions ranged from 26% to 85%, and 5 of 13 patients had aortic regurgitation) and added to the problem of interpretation of the results.

The authors claim that their study indicates that there is a 13% uptake of MIBG by non-neuronal cardiac tissue based on uptake measured in cardiac transplant patients. These patients were studied an average of 15 mo after cardiac transplantation. The authors failed to reference a large body of literature which indicates that there is sympathetic reinnervation of the heart after sympathectomy. Wilson, et al. (*6*) showed that 1 yr after cardiac transplantation, most patients had significant release of norepinephrine from their hearts after intravenous injection of tyramine, indicating sympathetic reinnervation of the heart. In dogs, cardiac uptake of norepinephrine returns to 57% of its baseline value by 6 mo after complete surgical sympathectomy of the heart (*7*). MIBG uptake in denervated dog hearts had returned to control values 14 wk after myocardial infarction or chemical sympathectomy with phenol (*8*). Studies with ^{11}C-hydroxyephedrine, an agent that is taken up and stored in the sympathetic neurons, shows progressive uptake in transplanted human hearts over time (*9*). Similarly, Dae et al. have shown that transplanted human hearts show increasing uptake of MIBG with time after transplantation (*10*). Patients studied soon after cardiac transplantation have little cardiac uptake of MIBG. We found that patients studied 1–4 mo after cardiac transplantation had a maximum cardiac uptake of 8.7% 2 hr after injection which was not significantly different from zero (*11*). The 13% uptake seen in the transplanted heart by Fagret et al. is likely due to cardiac reinnervation, rather than uptake in non-neuronal tissue.

Finally, the authors state in one portion of their paper that Group 4 patients are cardiac transplant patients, while in another part of the paper they state that Group 4 patients have aortic stenosis and are treated with digoxin.

In summary, it is unclear to what extent aortic stenosis produced abnormalities in MIBG uptake and washout because the authors have used an inappropriate control group. The small differences in MIBG uptake between untreated patients and patients treated with amiodarone are not significantly different. The authors give no data that proves digoxin causes decreased cardiac uptake of MIBG. Flaws in the study design make a difference in cardiac MIBG uptake between patient groups difficult to interpret. Lastly, MIBG uptake in the cardiac transplants patients is more likely due to reinnervation of the myocardium than evidence for non-neuronal uptake of MIBG.

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