the next 45 sec? Did the metabolites or the myocardial spillover into the blood change by 20% in the time interval from 120 sec to 165 sec?

Considering that a majority of the arterial input function is already delivered within 120 sec of the injection, the amount of ^{13}N-ammonia circulating in the blood between 120 sec and 165 sec is less than 20% of the total arterial blood ^{13}N-ammonia accumulated during the 165 sec. Therefore the residual metabolite error would have to be very high in order to change the blood flow by 20% with the Patlak model. That seems unlikely and rules out residual circulating metabolites errors as the culprit for the change in MBF as a function of time with the Patlak method and leaves us with spillover of myocardial data into the blood pool area. This error can make a difference in blood flow due to the perceived increase in the arterial concentration measured by PET in the ventricle. However, this error should affect the compartment model data also and both MBF values should be decreased. If so, there should not be a change in MBF with the Patlak method over the compartment model method unless there is something drastically sensitive to arterial input function errors in the Patlak method. If so, application of the Patlak method for MBF measurement is too unreliable to use in a clinical situation.

Another Explanation

The most plausible explanation to the change in MBF with the Patlak method as a function of time, is that the requirement of k2 = 0 in the Patlak method does not hold for the case of ^{13}N-ammonia in the heart. In other words, ^{13}N-ammonia has to be bound to the myocardium during the analysis time and none of the ^{13}N label can be released from the heart muscle during that time if the Patlak method is to be applicable. It is believed that ^{13}N-ammonia is converted to glutamine by the glutamate-glutamine reaction in the heart (*5*). Glutamine is released from the heart muscle and, at high flows, the rate at which it is released increases (*5*). Therefore, the assumption that the egress of the ^{13}N label from the heart is negligible at all levels of flow is not correct. The rate of ^{13}N egress from the heart may be low at normal flows, but at high flows it may cause significant error in estimating MBF. The faster the rate of egress, the greater the error will be as a function of time. This error will be enhanced more for the Patlak method for measuring MBF than the compartment model due to some inherent differences between the two methods discussed in greater detail below.

The two-compartment model fits a set of modeled data to the acquired data for the time of analysis, and arrives at parameters for the model that represent a best fit to all the data. The error caused by egress of the ^{13}N label from the heart muscle is small in the early time following the injection of ^{13}N-ammonia and gets bigger as a function of time. Therefore, underestimation of myocardial concentration of ^{13}N-ammonia 120 sec postinjection will have a smaller effect on the total data collected during the 120 sec. The Patlak method computes the MBF for every data acquisition interval based on the ^{13}N-ammonia in the myocardium at that time. The MBF value computed at 120 sec in time will be more underestimated due to egress of ^{13}N label than at 60 sec postinjection. And, at 210 sec, the error in MBF will be even greater than at 120 sec. The net effect is to decrease the slope of the Patlak plot as a function of time and decrease the measured MBF. This error due to k2 not being zero causes the Patlak plot to become nonlinear, and a linear fit to that data will distort the estimates of the rate constant K, or the value of MBF in this application.

Is the Patlak Method Applicable to MBF Measurements with ^{13}N Ammonia?

The authors warn us of errors caused by the use of the Patlak method for MBF with ^{13}N-ammonia when the data analysis times get too long. They recommend using an analysis time interval of 70–120 sec for dogs and 70–165 sec for humans. But, there is no special time limit specified for the compartment model, it can be used for all of that time without major errors in MBF as a function of time. The Patlak method applied to MBF measurements with ^{13}N-ammonia only produces good results within a certain time interval which changes from dogs to humans. Why does the Patlak analysis method applied to ^{13}N-ammonia in the heart only produce good results under an extremely constrained environment? Why do these conditions have to be changed when imaging a different species of animal? What would happen to MBF values in the case of a patient in which the delivery of the tracer to the heart is delayed due to longer lung transit times? Do we have to set up special constraints for each of these situations when using the Patlak analysis method to measure MBF with ^{13}N-ammonia? Is this analysis method really applicable for clinical use?

Conclusion

I have an inherent problem with species-specific mathematical models that only provide accurate measures of MBF at a certain time after injection of the tracer. If the Patlak method applied to MBF measurements with ^{13}N-ammonia underestimates flow by 20% when the analysis time is changed from 70–120 sec to 70–165 sec, there is something drastically wrong with the application of the model. The Patlak analysis method works well when the assumptions are satisfied. And, when they are not, as in this case, it doesn't. There is no need to force-fit the Patlak analysis method to an application in which unreasonable constraints have to be placed on its use, when other proven models work better. Nor is it necessary in a clinical application to sacrifice the robust nature of the compartment model method until something equally robust and reliable can be found. The few minutes of computation time saved using the Patlak method with ^{13}N-ammonia does not justify the possibility of error in clinical applications.

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REPLY: The letter to the editor regarding our paper (*1*) asserts that quantification of myocardial blood flow (MBF) using Patlak graphical analysis and ^{13}N-ammonia PET is inappro-

priate. We appreciate the attention paid to this novel approach for quantifying MBF. However, we believe the misinterpretation, as expressed in this letter to the editor, could have been avoided with careful reading and analysis of our data and results.

Mr. Mullani ignores the difference in the modeling approach described in our paper from the one reported by Hutchins et al. (*2*) employing longer dynamic data (for example, from 0 to 10 min instead of 0 to 120 sec as used in our approach). The Results section of our paper clearly states that the kinetic data used for model fitting are always fixed over the time interval of 0–120 sec postinjection. It is incorrect to assume only the graphical method gives results that are dependent on the employed data interval. Possible contamination of the arterial input function by spillover of activity from myocardium and by labeled metabolites similarly affect the estimates by the model and those by the Patlak graphical analysis.

Injected ^{13}N-ammonia is metabolized and its metabolites appear in the blood. The fraction of ^{13}N-ammonia of the total ^{13}N activity in venous blood decreases from 94.0% at 2 min to 82% at 3 min postinjection (*3*). The ^{13}N metabolite correction of the input function in reference 1 was based on data obtained from venous blood in normal subjects at baseline (*3*) appearing to underestimate the true ^{13}N metabolite fraction in arterial blood during physical or pharmacological stress. The spillover of activity from myocardium to blood pool can also cause an underestimation of MBF. Usually, these metabolite and spillover problems must be corrected when MBF is to be quantified. Alternatively, the early data points, which are early enough not to be affected by errors in the input function, can be employed without corrections as demonstrated in our two-compartment modeling approach. In addition, we would like to point out that the error in input function is not linearly translated to final MBF values because of the nonlinear relationship between MBF and input function.

Mr. Mullani's misunderstanding on the time interval used in the Patlak graphical analysis has misled him. We reported (*1*) that "for regional myocardium, the MBF estimates obtained by Patlak graphical analysis using 70–120 sec data points are as accurate as those obtained by the two-compartment model in both dog and human studies." As he misstated in his letter, we did not recommend using "an analysis time interval of 70–120 sec for dogs and 70–165 sec for humans." We proposed different time intervals only for the parametric image generation because of count statistics consideration. Parametric images are noisier in human studies than in canine studies because of the relatively lower injected dose (about 20 mCi in 30-kg dogs versus about 15 mCi in 60-kg humans). With a typical dose of 20 mCi of ^{13}N-ammonia, parametric MBF images of reasonable quality could be generated from 70 to 120-sec data in human studies. The analysis time interval does not need to be changed for different species or for patients with low cardiac output. However, parametric images of MBF generated from the 70 to 165-sec data in human studies have significantly lower noise levels. The tradeoff with the longer data interval is a systematic bias, reflected as an underestimation of the image values of MBF. As demonstrated in our paper, the magnitude of this underestimation is predictable and thus correctable. We therefore recommended the use of a longer data interval for generation of MBF parametric images in human studies. Fundamentally, this is not different from use of smoothing to reduce the image noise when the noise level is too high, with the understanding that the spatial resolution of the smoothed image is also reduced and the partial volume effect increased. As long as the characteristics and limitations are well understood and the method properly used, it should not be condemned. We have not seen a method yet, in modeling or in other areas, that has no limitations. Frequently, the worse case is not due to the method per se, but to misunderstanding and misuse of the method under conditions that reduce either its accuracy or validity.

Unidirectional tracer uptake during the analysis time is assumed in the Patlak graphical analysis. Injected ^{13}N-ammonia is avidly extracted into myocardium and rapidly metabolized into ^{13}N-glutamine which has a very slow turnover rate. This provides a metabolic trapping mechanism with a sufficiently long retention time to allow measurement of flow-dependent extraction of ^{13}N-ammonia by the myocardium. As shown in dog experiments (*4*), myocardial ^{13}N tissue clearance rate is slow and its dependency on MBF is low. Based on the experimentally observed clearance half-times ranging from 65 to 636 min and averaging 272 min for ^{13}N-ammonia over a wide range of MBF (*4*), the amount of label cleared from myocardium within the first 2 min is an average 0.5% and does not exceed 2%. Furthermore, these half-times were stable even under conditions of ischemia and hypoxia (*4*). Therefore, we believe the assumption of $k_2 = 0$ for the first 120 sec or 165 sec after the tracer injection is a good approximation. Examining the earlier observations that we referenced, one certainly could not have argued against this assumption.

We derived the Patlak graphical analysis equation from the two-compartment model configuration based not on "unreasonable constraints" but on physiological knowledge (*4*). Excellent linear correlation (correlation coefficient = 0.96 – 0.99) with the MBF values estimated by the validated two-compartment model (*5*) in a wide range of hypoperfused, normal and hyperperfused myocardium were obtained in experimental animals, normal human subjects and patient studies (Fig 5B, 8B and 9 in reference *1*). We conclude that the MBF values estimated by the Patlak graphical analysis are as accurate as MBF values estimated by the two-compartment modeling approach. This method is computationally simpler (>3 orders of magnitude shorter in computational time) and allows generation of parametric images that provide absolute quantitative information in a pictorial form for research and clinical use (*6*). There are no other available methods at present that can provide, from ^{13}N-ammonia studies, parametric MBF images of comparable quality and accuracy with a reasonable computational time.

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Rubidium-82 PET—Essential or Not?

TO THE EDITOR: I read the article by MacIntyre et al. (*1*) with interest and surprise. In 202 consecutive patients, they identified 27 with normal (presumably stress) ^{201}Tl SPECT studies who were found to have ^{82}Rb PET perfusion abnormalities. For reasons unspecified ("complicated by the large variations in the time of revascularization following the PET procedure and the uncertainty of whether any revascularization had been planned before the studies"), 17 of these patients subsequently underwent myocardial revascularization. The authors contend that ^{82}Rb PET "must then be considered necessary to provide appropriate medical care for these patients" and that there is "serious deficiency in conventional health care if one were to rely on ^{201}Tl-SPECT imaging." Hold on!

This study provides neither evidence of benefit to patients by virtue of having undergone myocardial revascularization, nor evidence that revascularization was in some way influenced by PET outcomes. While ^{201}Tl-SPECT has well established prognostic value and has been widely applied to stratify coronary risk, one cannot assume that a diagnostically more sensitive test will have greater prognostic accuracy. MacIntyre et al. should consider that their thallium "false-negative" studies might be "prognostically true-negative" so that PET "true-positives" become "prognostically false-positive." If so, their 17 patients have been needlessly exposed to the expense, discomfort, risk and worry of PET imaging, and perhaps, of myocardial revascularization.

These authors' contention that ^{82}Rb PET is "the procedure of choice" is unsupported by their findings.

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1. MacIntyre WJ, Go RT, King JL, et al. Clinical outcome of cardiac patients with negative thallium-201 SPECT and positive rubidium-82 PET myocardial perfusion imaging. *J Nucl Med* 1993;34:400–404.

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REPLY: Dr. Burns is correct in that this study (*1*) did not provide evidence of benefit to patients who had undergone revascularization following diagnosis by PET. Patient benefit involves more complicated analyses that are just now starting to appear in the literature, such as Eitzman et al. (*2*), a topic we will watch with interest. As Burns (*3*) mentions, ^{201}Tl myocardial SPECT has well established prognostic value, and it is expected that somewhat similar values will be found for ^{82}Rb PET.

As we stated in our report, it is difficult to assess what influence the PET procedure had on the decision to intervene. We like to think that our study was the most important factor in the clinician's decision. This decision is not made by nuclear medicine, alas, but by the referring physician who must weigh all information derived from all sources.

It is for that reason that we believe we should provide the referring physician with the most accurate data possible. In this study, PET data were consistent with the management decision and contrary SPECT data were ignored.

We believe that ^{82}Rb PET is still the "procedure of choice." It would be unfair to the referring physician and presumptive on our part to assume the role of prognostician and change our "false-negative" reading and substitute a "prognostically true-negative" (*3*) reading.

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Interobserver Variability in Lung Scintigraphy Interpretation

TO THE EDITOR: We read with interest the article by Scott and Palmer (*1*) on the interpretation of lung scintigraphy in patients with clinically suspected pulmonary embolism. The authors conclude that in spite of attempts to adhere to an established diagnostic algorithm (*2*), observer variability remains considerable and may lead to diminished diagnostic accuracy.

Interobserver variability is inherent in any diagnostic technique and its role in the scintigraphic diagnosis of pulmonary embolism has been evaluated extensively (*3–5*). Recently, we evaluated the potential effect of the use of an anatomical lung segment chart on observer variability in the interpretation of lung scans (*6*). Readers drew their findings into the chart, thus leading to a significant and clinically important reduction in both intraobserver and interobserver variability.

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