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## Is the Patlak Graphical Analysis Method Applicable to Measurement of Myocardial Blood Flow with Nitrogen-13-Ammonia?

**TO THE EDITOR:** A recent publication by Choi et al. (*1*) tested the applicability of the Patlak graphical analysis method for the computation of myocardial blood flow (MBF) with $^{13}$N-ammonia and PET. The authors conclude that the "regional MBF estimates obtained by the Patlak graphical analysis method are as reliable as those obtained by the two-compartment model fitting." However, their data show that the Patlak method derived MBF has large errors in MBF that are a function of data analysis time, and that the Patlak method is not as reliable as the compartment model method for MBF measurement with $^{13}$N-ammonia (Table 1). The author's conclusions are inappropriate in view of their data and their results. Using the author's data, I will show that the application of the Patlak method for measuring MBF with $^{13}$N-ammonia is inappropriate for clinical application.

The authors' data can be viewed slightly differently to show that there are indeed several problems associated with application of the Patlak graphical analysis method to measurement of MBF with $^{13}$N-ammonia. I will present the author's data for dog and human studies to show that results obtained with the Patlak method change with time of data analysis, and that perhaps the inherent assumptions of the rate constant k2 = 0 may not be appropriate for $^{13}$N-ammonia.

### Dog Data

The dog data obtained for MBF uses microspheres (*2*) as the gold standard of flow measurements in the heart. The data are also analyzed by the accepted and published compartment model (*3*) and a final analysis is made using the Patlak graphical method. Results obtained with the three analyses are summarized below:

$$\text{compartment model flow} = 0.92 \times \text{microsphere flow},$$

$$\text{Patlak method flow} = 0.81 \times \text{compartment model flow}.$$

From the two results stated above, we can surmise the relationship between microsphere flow and the Patlak flow to be as follows:

$$\text{Patlak method flow} = 0.75 \times \text{microsphere flow}.$$

This result suggests that the Patlak method underestimates MBF by approximately 25% compared to microsphere determined flow when using $^{13}$N-ammonia in dogs.

### Human Data

The MBF values obtained from human studies show a decrease in MBF as a function of time with the Patlak method, compared to MBF derived from the compartment model. The authors' data are represented to show drastic changes that occur in MBF over a short period of time with the Patlak method (Table 1). Increasing analysis time from the 70–120 sec period to the 70–165 sec period reduces the MBF measured by the Patlak method by 20%. In other words, a 45-sec increase in data analysis time will produce a 20% change in MBF. An increase in analysis time to 210 sec reduces the computed MBF with the Patlak method by 28%.

**TABLE 1**
Errors in Patlak Method of MBF Measurements

| Data analysis time | Compartment flow | Patlak method flow | % error in MBF |
|---|---|---|---|
| 70 – 120 sec | 100% | 104% | 0% |
| 70 – 165 sec | 100% | 83% | 20% |
| 70 – 210 sec | 100% | 75% | 28% |

Note: The table demonstrates errors in the Patlak method of MBF measurements in the heart with $^{13}$N-ammonia compared to the compartment model method. Data for the compartment model are normalized to 100%. Original data obtained from Choi et al. (*1*).

### Data Interpretation by the Authors

The authors are aware of the underestimation of MBF using the Patlak method with $^{13}$N-amonia. They attribute this change in MBF as a function of time to "errors in arterial input function" caused by $^{13}$N-metabolites and spillover from the myocardium to the blood pool. They state that "these errors in arterial input functions were more obvious in dog studies than in human studies because of faster metabolism of $^{13}$N-ammonia in blood and because of faster accumulation of $^{13}$N activity in the relatively smaller canine heart." So, it seems that the problems of decreasing MBF as a function of time of analysis for the Patlak method is more severe with the dog data than with humans. However, these errors do not seem to affect the measurement of MBF with the compartment model as much as the Patlak method.

### A Different Data Interpretation

The authors have applied a correction for the $^{13}$N metabolites in the blood to the human data, based on published values reported by Rosenspire et al. (*4*). They also claim that 1-ml blood samples were drawn at 40, 80, 120, and 180 sec to determine the time-dependent distribution of $^{13}$N-ammonia and $^{13}$N metabolites in the blood. We can assume therefore that some form of metabolite correction was made in both dog and human data analyzed by the authors and that the underestimation most likely is not due to metabolite correction.

Moreover, the compartment model analysis seems to be less affected by the metabolites and errors in the arterial input function than the Patlak method. The author's explanation of this is that "Patlak graphical analysis is more affected by inaccuracies related to input functions because contamination of the input function either from $^{13}$N metabolites or from spillover from myocardial tissue to blood pool become more prominent at later scan times." The obvious question that comes to mind is, following a metabolite correction, why is the residual error in metabolite correction causing a 20% drop in MBF in humans when the analysis time is increased by 45 sec? And, if there are only 6% metabolites circulating in the human blood at 120 sec postinjection of $^{13}$N-ammonia, what is causing the error in the Patlak method to be 20% over

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-