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Application of Calibrated Image Derived Input Function to a Clinical Protocol

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Sirs,

We read with interest the recent article by Christensen and colleagues (1) evaluating eight blood-free image-derived input function (IDIF) methods for dynamic ¹⁸F-FDG PET scans. Echoing the results of previous studies (2–4), the authors found that none of the methods could accurately correct for partial volume effects (PVEs); thus, all gave biased estimates of the reference arterial input function.

To correct this bias, Christensen and colleagues devised a clever method of correcting PVEs based on the parameters of a linear regression between the reference and the IDIF-derived results. This strategy has several advantages. Specifically, it does not require sophisticated image processing techniques, it does not depend on the delicate balancing of reconstruction and image parameters, it can be easily transposed to different anatomical vessels and, more importantly, it provides a practical way to obtain an IDIF even for those tracers for which existing IDIF methods fail (5). Nevertheless, this method might also be vulnerable to errors associated with deviations of the data points from the linear regression.

Here, we sought to expand the results of Christensen and colleagues by testing calibrated IDIF in an actual clinical protocol. We reanalyzed ¹¹C-(R)-rolipram brain scan data from 25 healthy subjects and 26 patients with major depressive disorder (MDD) enrolled in a previous protocol (6). When these data were analyzed using a full metabolite-corrected arterial input function they showed a highly significant reduction of ¹¹C-(R)-rolipram binding in MDD subjects (~20%, p = 0.005) (7).

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In the present analysis, blood vessels and background regions for each subject were first automatically segmented using a clustering algorithm to avoid operator variability (7). The resulting carotid time activity curves (TACs) were then corrected for the individually measured radiometabolites (but not for PVEs) and used as input function to calculate ^{11}C -(R)-rolipram total distribution volume (V_T) with the Logan plot, corrected for the plasma free fraction (V_T/f_p). Finally, these V_T/f_p values were calibrated with linear regression against the reference V_T/f_p values as described by Christensen and colleagues (Fig S1, Supplemental Digital Content 1, <http://links.lww.com/NMC/A24>). Calibration completely removed the average bias (average Logan- V_T/f_p for all 51 subjects was $12.2 \pm 3.9 \text{ mL/cm}^3$ for IDIF and $12.2 \pm 3.4 \text{ mL/cm}^3$ for reference arterial input). Furthermore, calibration could detect a significant Logan- V_T/f_p reduction in MDD patients compared to controls ($\sim 16\%$; $p=0.044$, repeated measures two-way analysis of variance with regions as the within-subjects factor). Indeed, Logan- V_T/f_p from calibrated IDIF was $13.3 \pm 3.4 \text{ mL/cm}^3$ for healthy volunteers and $11.1 \pm 4.1 \text{ mL/cm}^3$ for MDD subjects (the corresponding values obtained from reference input were $13.5 \pm 3.1 \text{ mL/cm}^3$ and $10.9 \pm 3.2 \text{ mL/cm}^3$, respectively).

It should be noted, however, that the analysis using the method proposed by Christensen and colleagues gave an only marginally significant difference of $p = 0.044$; in contrast, the original paper using metabolite-corrected arterial input function detected a highly significant difference of $p = 0.005$ (7). This decreased statistical power can be explained by the imperfect correlation (i.e. residuals during linear regression) between the arterial and IDIF- V_T values. Indeed, although calibration by linear regression effectively corrects bias, it cannot correct for the dispersion of the values (i.e. the residuals of linear regression). The imperfect correlation between V_T/f_p is the direct consequence of the imperfect correlation between the areas under the curve (AUC) of the raw carotid TACs and the arterial input functions from which Logan- V_T values are derived (Fig S2, Supplemental Digital Content 2, <http://links.lww.com/NMC/A25>). The most likely reason why the blood AUCs from the artery and from the images are not perfectly correlated is that the image-AUC is influenced by the subject's vessel size and by spill-in from background tissues.

An ideal blood-free PVE correction method would be able to completely remove all residuals from linear regression, so that the AUC from the carotids and from the artery would line up exactly on the identity line of a linear regression. Even an imperfect PVE correction method—including those evaluated by Christensen—would improve the statistical power of calibrated IDIF to some extent by reducing the sum of residuals of the linear regression. The extent to which a PVE correction method might improve the correlation obviously depends on the effectiveness of the particular method used. It is, however, possible to calculate a theoretical upper value.

The final mechanism common to blood-free IDIF methods is the correction of the carotid signal from artifacts associated with background spill-in and vessel diameter. Using multiple linear regression, we estimated the percentage of variability that could be explained by the background region and the magnetic resonance imaging (MRI)-derived carotid diameter. We found that, combined, background activity and carotid diameter explained 10% of the regression variance. Therefore, if these factors could be perfectly corrected, the p-value in

our ^{11}C -(R)-rolipram study would be 0.032 (Fisher's distribution with 1 and 49 degrees of freedom). Notably, background spill-in explained most of the variance; thus, correcting spill-in alone would result in a p-value of 0.034. However, the statistical significance would nevertheless still be lower than that obtained using full arterial input function ($p = 0.005$) or a blood-based IDIF technique ($p = 0.017$) (7).

Finally, it should be noted that for an IDIF to be truly blood-free, blood samples cannot be used to measure radiometabolite concentrations. When the analyses were repeated using an average metabolite curve (obtained from 12 subjects from a previous protocol (8) and prospectively applied to the 51 subjects of the present study), a further loss of accuracy was observed, and the results with calibrated-IDIF were no longer significant ($p = 0.329$).

In summary, the present analysis used the calibrated IDIF proposed by Christensen and colleagues to successfully validate the findings of a previous clinical protocol, but also entailed a loss of statistical significance. Some caveats are therefore necessary. First, we posit that there is always a trade-off between invasiveness and accuracy. This must be taken into consideration when planning the sample size of a new study. Second, as underscored by Christensen and colleagues, results might vary according to the tracer used. In particular, ^{11}C -(R)-rolipram and ^{18}F -FDG generally display high blood concentrations, and the spill-in contribution is thus likely to have a smaller impact on the blood AUC of the images. For tracers with a faster wash-out from the vascular compartment, the total blood AUC from the images (and from the artery) will be smaller. Therefore, background spill-in is likely to be comparatively more important and, consequently, the sum of linear regression residuals would be greater. Third, these results suggest that calibrated IDIF should be preferentially used for tracers without radiometabolites, in order to avoid the additional source of error associated with estimated radiometabolite correction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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