The Potential Sensitivity of Cerebral Blood Flow to Cross-Calibration

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Introduction

Dynamic susceptibility contrast (DSC) MR perfusion imaging cerebral blood flow (CBF) estimates have proven to be useful at providing indicators of tissue perfusion for acute ischemic stroke diagnosis.[1] However, absolute CBF quantification remains unresolved primarily as a result of acquisition errors in the measurement the arterial input function (AIF). Recently, some techniques have been derived to address quantification issues arising from AIF partial volume effects (PVE) [2,3], AIF dispersion [4] and deconvolution method limitations.[5] These advanced methods have not yet been widely adopted in clinical practice, in part because they are new, but also because they complicate the perfusion methodology in clinical practice and when used individually, only address one source of error, obviating the need for the extra effort.

Alternatively, CBF values are often cross-calibrated using a normal human-based CBF average from a fixed internal reference region in order to provide meaningful CBF values for clinical purposes. Although the quantitative validity of this method has been criticized,[6] it is likewise difficult to gauge the accuracy of current clinical DSC-MR CBF estimates given the magnitude of the reported error from unresolved quantification issues.[7] An interesting property of population-based cross-calibration is that in addition to correcting for AIF PVE, it removes the impact of other bias (linear) errors arising from methodological sources (*e.g.*, deconvolution filtering CBF underestimation). Additionally, since the relative CBF error associated with the population-based calibration factor is translated into absolute CBF errors, this knowledge may be used to derive the expected sensitivity of CBF estimates along with an associated error margin. The purpose of this work is to evaluate the potential sensitivity of CBF estimates derived from white matter (WM) CBF cross-calibration for detecting ischemia in acute ischemic stroke.

Methods

A population-based mean CBF was derived for normal (often controls) patients from published literature values obtained using positron emission tomography (PET) with $H_2{}^{15}O$ – often considered a CBF gold standard. Only studies measuring WM CBF using segmented global WM masks were excluded from consideration under the rational that PVE with gray matter (GM) may increase the expected normal WM CBF. The weighted mean CBF for WM, μ_{PET}, across all studies was determined as $\mu_{PET} = \sum N_i \cdot \mu_i / \sum N_i$ where N_i and μ_i are the number of patients and the reported WM CBF mean for study i. The pooled standard deviation, σ_{PET}, was determined as $\sigma_{PET} = \{ \sum^n (N_i - 1) \cdot \sigma_i^2 / (\sum (N_i - 1) \}^{1/2}$ where σ_i is the standard deviation reported by study i. The coefficient of variation (or the relative cross-calibration CBF error) was determined as $COV_{PET} = \sigma_{PET} / \mu_{PET}$. Arbitrary upper ischemic CBF thresholds for WM and GM of $I_{WM} = 18$ and $I_{GM} = 35$, respectively, were used to determine the WM and GM ischemic CBF thresholds, $WM_{CBF\text{-}threshold}$ and $GM_{CBF\text{-}threshold}$, respectively, that cross-calibrated CBF (CBF_{CC}) can reliably detect with 95% confidence (one-tailed Z-score) as shown in the Figure.

Results

A total of 149 patients (male and female, ages 19-82) were used from 12 studies.[6,8-18] The population-based mean and pooled standard deviation were $\mu_{PET} = 21.5$ and $\sigma_{PET} = 3.9$, respectively, yielding a relative cross-calibration error of $COV_{PET} = 18.4\%$. The ischemic CBF thresholds with 95% confidence for WM and GM were $WM_{CBF\text{-}threshold} = 13.8$ ml/min/100 g and $GM_{CBF\text{-}threshold} = 26.9$ ml/min/100 g, respectively.

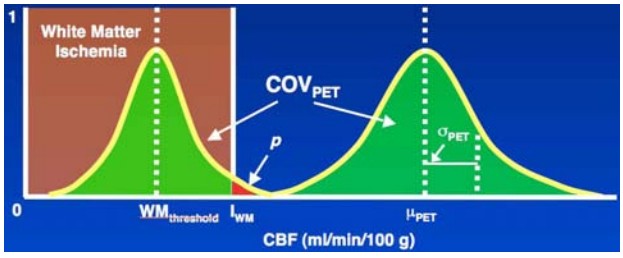

Figure: Cross-calibration ischemic CBF threshold sensitivity. The relative CBF error (COV_{PET}) can be used to determine the sensitivity of CBF estimates derived from population-based calibration factors for detecting ischemia at a given confidence level (1-p). This example illustrates $WM_{threshold}$ evaluation, but the approach is generalizable to other tissues (e.g., GM).

Discussion

The use of population-based CBF cross-calibration for ischemic stroke assumes that (1) there is normal WM in one hemisphere in acute ischemic stroke pathology and (2) DSC-MR CBF estimates can provide accurate relative CBF information. Since PET studies have generally shown a positive correlation between DSC-MR and PET CBF, assumption (1) is the primary source of error in CBF_{CC} estimates. It is uncertain as to whether contralateral normal WM even exists in stroke pathology and this requires further investigation. However, we have shown how knowledge of COV_{PET} can be used to determine the error in the CBF_{CC} estimate for a given voxel. ***Clinical Implications:*** The sensitivity thresholds intuitively mean that we can expect with 95% confidence that CBF_{CC} will be sensitive to ischemia at 13.8 ml/min/100 g for WM and 26.9 ml/min/100 g for GM. CBF_{CC} were determined using a one-tailed confidence so that the CBF_{CC} thresholds favored sensitivity over specificity. This is based on the rational that CBF estimation is best used to assess ischemia that has not resulted in infarction as diffusion-weighted imaging is generally sensitive to infarction.[1] The statistical approach presented here offers a quantitative interpretation of cross-calibrated CBF estimates for the clinical diagnosis of stroke until absolute CBF methodologies are improved (*i.e.*, errors are quantified and validated to be within tolerance for a particular application).

References

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