Is Reduced CBV a Reliable Surrogate Marker for Infarct Core and Can It Be Used to Identify Lesion Mismatch?

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Purpose: Current research indicates that stroke patients who will benefit from advanced reperfusion therapy can be identified and their treatment can be adjusted based on their stroke pattern, i.e. on the volume of the infarct core and penumbra. If there is significant amount of tissue that could be salvaged, the patient's outcome might improve if perfusion can re-established and maintained. To identify the stroke pattern, diffusion- (DWI) and perfusion-weighted (PWI) MRI has been used successfully. Here, the acute hyperintense DWI lesion with and ADC below a certain threshold are deemed a reliable marker for infarct core. However, MRI is often not available in an emergency setting or unsafe to perform (due to lack of information about potentially MR-unsafe implants). In such situations, computed tomography perfusion (CTP) is used instead, with cerebral blood flow (CBV_{CT}) maps derived from CTP being the surrogate marker for infarct core. Therefore, it is of practical interest to know whether infarct core assessment based on CBV is equivalent to the core identified on DWI and ADC. In this context, several studies compared MR and CT datasets [1,2]. However, these studies suffered from a limited anatomical coverage for their CTP scans and a substantial time difference between CT and MR scans. To overcome these limitations and to investigate equivalence between DWI- and CBV-based methods, we studied stroke core identification on DWI and DSC-MRI CBV maps (CBV_{MR}). We also investigated agreement of these techniques when used to identify possible lesion volume mismatch. We hypothetized that such comparison could benefit from a better anatomic coverage of DSC and reduced time difference between DWI and PWI.

Methods: N=59 cases including both reperfusing and non-reperfusing patients with sufficient quality baseline DWI and PWI data from the DEFUSE [3] database were analyzed (Figure 1). These patients were imaged between 3 and 6 hours after stroke onset and prior to treatment with a thrombolytic agent. DWI and PWI data were spatially coregistered using SPM5. On DWI, the stroke core was identified using two criteria of which at least one must have been positive: 1) hyperintensity above MEAN+2.7*SD of the healthy tissue on b=1000 DWI images or 2) ADC < $615 \times 10^{-6} mm^2/s$. For CBV, the infarct core lesions were manually outlined by a neurologist on relative CBV_{MR} maps, blinded to the DWI maps ('blindedCBV' analysis). Due to imaging artifacts present and bolus problems on DSC, outlining of CBV lesions was often difficult and equivocal. Therefore, we additionally outlined the CBV_{MR} lesions using DWI maps as a guide for lesion location and shape ('unblindedCBV'). Critically hypoperfused tissue was defined as the PWI lesion with a Tmax > 6s. Mismatch was defined as (Tmax >6s) volume vs. infarct core volume ≥1.2 and an absolute mismatch volume ≥10ml. Mismatch identification agreement with DWI- and CBV-based stroke was quantified by Cohen's kappa statistics. Finally, stroke core identified on DWI and CBV_{MR} was compared to lesion volumes outlined on 30-day follow-up FLAIR images (N=16).

Results: Results are summarized in Table 1. Presented results show:

1) Comparison of stroke core lesion outline on blindedCBV and unblindedCBV vs. DWI, by means of correlation, regression lines and statistical significance (p-values). Results are stratified for the whole patient population (N=59), for patients with large (>10ml, N=27) and small lesions (<10ml, N=32).
2) Comparison of stroke core volumes identified by CBV_{MR} and DWI vs. final 30-day FLAIR volumes in patients where reperfusion was achieved (reperfusion defined as a reduction in the baseline PWI lesion volume >30% at 3-6 hours after tPA treatment).
3) Mismatch identification agreement between DWI, blindedCV and unblindedCBV methods.

In test of of lesion presence detection, the blindedCBV method reported 3 cases in which CBV_{MR} lesion was >2ml, but no DWI lesion was present, and 1 case where CBV_{MR} was not detected, but DWI > 2ml. In unblindedCBV analysis, 5 cases were reported where no CBV_{MR} lesion was outlined when DWI lesion >2ml was present and vice versa, 1 case were reported with CBV lesion >2ml with no DWI lesion present. In all such cases the lesion size was <7ml (CBV_{MR} or DWI).

Column #	Table 1	Comparison of CBV lesion volume to DWI			Comparison of DWI/CBV stroke core with 30day FLAIR			# of mismatch	# of no mismatch	Comparison to DWI/PWI mismatch			
	Used Method	Correlation r^2	Regression Line	p-value	Correlation r^2	p-value	Regression Line			Sensitivity	Specificity	κ	Blinded vs. unblinded
1	DWI	-	-	-	0.64	<0.0001	DWI=0.47*FLAIR+0.87	39	20	-	-	-	-
2	blindedCBV (N=132)	0.64	CBV=0.46*DWI+0.60	<0.0001	0.54	0.0007	CBV=0.15*FLAIR+1.72	43	16	0.97	0.75	0.76	0.83
3	unblindedCBV (N=132)	0.82	CBV=0.88*DWI–1.32	<0.0001	0.56	0.0005	CBV=0.37*FLAIR+0.81	41	18	0.95	0.80	0.77	
4	blindedCBV (>10ml)	0.60	CBV=0.51*DWI-2.19	<0.0001	-	-	-	-	-	-	-	-	-
5	unblindedCBV (>10ml)	0.77	CBV=0.93*DWI-4.31	<0.0001	-	-	-	-	-	-	-	-	-
6	blindedCBV (<=10ml)	0.03	CBV=-0.25*DWI+3.44	0.3738	-	-	-	-	-	-	-	-	-
7	unblindedCBV (<=10ml)	0.12	CBV=-0.55*DWI+0.65	0.0529	-	-	-	-	-	-	-	-	-

Discussion: The results indicate that assuming direct equivalence between CBV_{MR} and DWI might be overly simplistic and unrealistic. Whereas underlying pathologic processes in brain will most probably result in similar regions of reduced CBV and hyperintense DWI (as indicated by unblindedCBV analysis), the imaging artifacts in bolus-tracking perfusion will prohibit the CBV-based stroke core identification to be as accurate as with DWI.

- This is clearly shown in lines 2 and 4 in Table 1, where blindedCBV readings heavily underestimated lesion volume compared to DWI (by ~50%). The results also indicate that small lesions (<10ml) cannot be reliably identified on CBV.
- The blindedCBV method was able to predict mismatch with sensitivity of 0.97 and specificity 0.75 (with respect to DWI)
- 4 cases that were identified as non-mismatch with DWI were considered mismatch-positive with CBV_{MR} in blindedCBV.

Infarct core volumes were typically smaller than 30-day FLAIR volumes in patients with early reperfusion. This may be explained by incomplete reperfusion or fluctuations in perfusion deficits over time; DWI underestimated final infarct volume by ~50%, unblinded CBV by 60% and blinded CBV by 85%. We speculate that CBV-based stroke core metrics can be used for mismatch identification, but mismatch identification may differ from those based on DWI. Though this study was limited by multiple confounding factors (non-linear effect of gadolinium in bulk blood and in tissue, T1 and imaging artifacts, *etc.*) that are not present in CT, we believe that general equivalence between CBV_{CT} and CBV_{MR} should hold true. We conclude that using CBV to estimate core may overestimate the number of patients considered to have a mismatch compared with DWI.

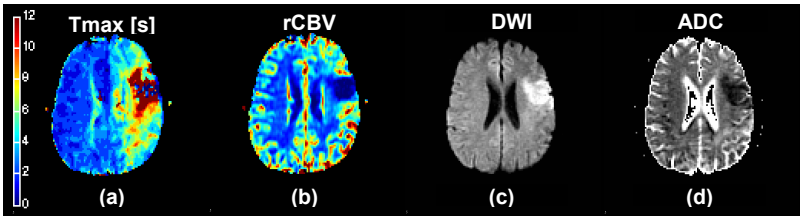

Figure 1: Example of case from DEFUSE database. Maps: (a) Tmax, (b) relative CBV, (c) isotropic DWI for b=1000, and (d) apparent diffusion coefficient (ADC).

References:

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