Assessing recovery in comatose cardiac arrest patients with diffusion-weighted MRI

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Introduction: Prediction of recovery of patients after cardiac arrest is traditionally based upon clinical evaluations at ≥3 days [1]. However, the clinical examination is only helpful for reliably predicting poor outcome in patients with very little brain function or absent cortical somatosensory evoked potential responses, and many patients do not fit into these strict criteria, leaving the clinician in a quandary to accurately predict prognosis. Diffusion-weighted imaging (DWI) has been shown to be sensitive to brain injury after transient global ischemia in experimental animal models acutely [2-4], and with secondary injury post reperfusion [4, 5]. Similar results have been found in small case series of cardiac arrest patients [6, 7]. We sought to extend these findings to a larger patient cohort. Because DWI lesions are often diffusely distributed, we examine whether the severity of reduction in the apparent diffusion coefficient (ADC) values can be used to predict good patient recovery as defined by eye opening (either spontaneous or in response to external stimuli) or modified Rankin (mRS) Scale scores at 6 months.

Methods: Comatose cardiac arrest patients who subsequently underwent MRI were retrospectively analyzed (n=72). Median scan time for first study was 2 days, with a range of 0–8 days. Nine patients had additional imaging up to 33 days, for a total of 82 imaging studies. ADC maps were calculated from the slope of the linear regression fit of the log of the DWI (b-value=1000 s/mm^2) and b-zero (b-value=0 s/mm^2) images. The b-zero images were coregistered to the ICBM-452 T1 5th Order Polynomial Warps Atlas using a semiautomated program (MNI Autoreg) [8]. Using the ICBM probabilistic atlases [9], probability masks for the following regions were generated: white matter (WM), cerebellum, frontal, insula, occipital, parietal and temporal lobes, caudate, putamen, and thalamus, using a threshold of 50%. Median ADC values were measured in these regions, as well as in the entire brain. To minimize effects from cerebral spinal fluid, analysis was limited to ADC values ≤ 1200×10^{-6} mm2/s. Spatial differences among the different regions were examined (ANOVA with post-hoc SNK test). Differences in patients with eye opening (EO) were compared (two-tailed Wilcoxon-test) with no EO, a potential sign of poor recovery in patients who had life support withdrawn (and thus would die without the potential for demonstrating recovery at 6 months). We performed similar analysis with 6 months mRS score >3 representing poor outcome. Median ADC values were correlated with EO and 6 month mRS scores (Pearson's product moment). Subset analysis was performed for patients imaged <3 days and ≥3 days.

Results: The putamen exhibited significantly lower (P<0.05) ADC values (700±130 mm^2/s) than the other regions in the brain (cerebellum: 760±100 mm^2/s, frontal lobe: 770±110 mm^2/s, insula 800±mm^2/s, occipital lobe: 740±150 mm^2/s, parietal lobe: 740±140 mm^2/s, temporal lobe: 800±130 mm^2/s, caudate: 770±120 mm^2/s and thalamus: 760±110 mm^2/s) except for WM (720±110 mm^2/s). 28 patients had eye opening (median 1.5 days, range 1–7 days). Median whole brain ADC values in patients with eye opening were significantly higher (see Table 1) than in patients who did not experience eye opening. All regions except for deep gray matter nuclei (caudate, putamen and thalamus) exhibited significantly more severe ADC reductions in patients who did not experience eye opening. Patients with poor outcome (mRS>3) exhibited significantly lower ADC values in all regions except for caudate and thalamus. Subset analysis was performed on studies <3 days (n=45) and ≥3 days (n=37). We found that whole brain ADC exhibited significant differences between patients with and without eye opening for studies < 3 days and ≥ 3 days (see Table 2). For studies <3 days, WM, frontal, insula, occipital, parietal, and temporal lobes showed significant differences in the two groups. However, only WM, occipital and parietal lobes showed a significant difference between patients with and without eye opening for studies done ≥ 3 days. Using 6 month mRS, whole brain ADC values were significantly lower in patients with poor outcome for both early and late imaging studies. For studies <3 days, cerebellum, frontal lobe, insula, occipital lobe, parietal lobe, and putamen exhibited significantly reduced ADC values. For studies performed ≥3 days, WM, cerebellum, frontal, occipital and parietal lobe ADC values were significantly lower in patients with poor mRS.

Discussion: Our results demonstrate that ADC maps may be useful in predicting recovery of comatose cardiac arrest patients, consistent with earlier studies investigating the use of DWI for evaluating comatose patients [7, 10]. We also show that the degree of reduction depends on the region of tissue and the time of imaging. In our cohort, no patients with severe whole brain median ADC reductions (< 660 mm^2/s) had either eye opening or good mRS at 6 months. This suggests that marked whole brain median ADC reductions may be a reflection of severe, irreversible brain damage. By relying on whole brain metrics, calculating median ADC values is fairly straightforward and can potentially be used when deciding the likelihood of recovery. A limitation of this study is the reliance on a retrospectively collected data set that may lead to a selection bias. Prospective studies are therefore necessary to confirm these promising preliminary results.

References: 1. Levy DE, et al. *JAMA.* 1985; 253, 1420-6. 2. Dijkhuizen RM, et al. *J. Cereb. Blood Flow Metab.* 1999; 19, 341-9. 3. Pierpaoli C, et al. *J. Cereb. Blood Flow Metab.* 1996; 16, 892-905. 4. Hossmann KA, et al. *J. Cereb. Blood Flow Metab.* 1994; 14, 723-31. 5. Dijkhuizen RM, et al. *Stroke.* 1998; 29, 695-704. 6. Back T, et al. *J. Neurol.* 2004; 251, 388-97. 7. Wijdicks EF, et al. *AJNR. Am. J. Neuroradiol.* 2001; 22, 1561-5. 8. Collins DL, et al. *J. Comput. Assist. Tomogr.* 1994; 18, 192-205. 9. Mazziotta J, et al. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* 2001; 356, 1293-322.10. Arbelaez A, et al. *AJNR. Am. J. Neuroradiol.* 1999; 20, 999-1007.

Table 1: Median ADC and Range in brain regions (1×10^{-6} mm^2/s) along with significance of correlations vs eye opening (EO) and mRS scores. Also are shown are whether differences between patients with good vs poor outcome are statistically significant (*P<0.001, **P<0.01, †P<0.05).

	Whole Brain	WM	Cerebellum	Frontal	Insula	Occipital	Parietal	Temporal	Caudate	Putamen	Thalamus
EO (n=28)	810*	780**	790†	840*	860†	820*	830*	870**	800	740	780
Range	670–910	540–880	690–1070	640–940	720–990	560–1200	630–950	730–990	560–920	480–920	660–990
No EO (n=54)	740	720	760	770	810	720	720	800	760	710	760
Range	380–910	320–870	430–960	380–900	370–990	340–1200	340–930	160–960	380–1200	380–1200	320–1200
P-value	<0.001	0.002	0.01	0.001	0.01	<0.001	<0.001	0.003	0.43	0.08	0.29
mRS ≤3 (n=12)	840*	810**	820**	850**	900†	870*	860**	890†	820	770**	820
Range	740–910	700–880	730–1070	750–940	730–990	730–1200	700–950	750–990	730–920	700–920	670–990
mRS>3 (n=70)	760	660	760	790	810	740	750	820	760	710	760
Range	380–900	320–880	430–960	380–910	370–970	340–1200	340–930	160–990	380–1200	380–1200	320–1200
P-value	0.002	0.005	0.002	0.005	0.02	0.001	0.002	0.02	0.13	0.006	0.08

Table 2: Statistical significance of differences between median ADC values for good vs poor outcome (eye opening or mRS≤3) dichotomized by whether MRI was performed Early (<3 days) or Late (≥3 days) along with number of studies (N) with eventual good outcome.

	Whole Brain	WM	Cerebellum	Frontal	Insula	Occipital	Parietal	Temporal	Caudate	Putamen	Thalamus
Eye Opening											
Early (N=13)	P=0.004	P=0.017	P=0.15	P=0.0025	P=0.049	P=0.013	P=0.003	P=0.009	P=0.27	P=0.21	P=0.49
Late (N=15)	P=0.028	P=0.035	P=0.086	P=0.081	P=0.18	P<0.001	P=0.015	P=0.14	P=0.99	P=0.32	P=0.53
mRS											
Early (N=5)	P=0.032	P=0.068	P=0.049	P=0.035	P=0.026	P=0.012	P=0.026	P=0.068	P=0.13	P=0.035	P=0.16
Late (N=7)	P=0.003	P=0.008	P=0.026	P=0.019	P=0.15	P=0.001	P=0.009	P=0.071	P=0.36	P=0.099	P=0.16