Acute Normalization of apparent Diffusion Coefficient Values may not reflect tissue recovery in acute stroke patients

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Introduction

Diffusion-perfusion mismatch (DPM) has been widely used to assess tissue viability in acute ischemic stroke. One premise of DPM is that diffusion-defined lesion as identified by a decreased apparent diffusion coefficient (ADC) represents irreversibly injured "core". Several lines of evidence, however, have demonstrated that ADC lesions may normalize after reperfusion[1]. In addition, it has been suggested that severely decreased ADC may not necessarily progress to infarction[2]. However, most of these studies were performed beyond the first hours of ischemia and/or not in human patients. Therefore, in this study, we aimed to define the temporal behavior of ADC lesions during hyperacute ischemia (<6hrs) in the presence or absence of reperfusion. Furthermore, we examined the relationship between hyperacute ADC changes and final tissue outcome.
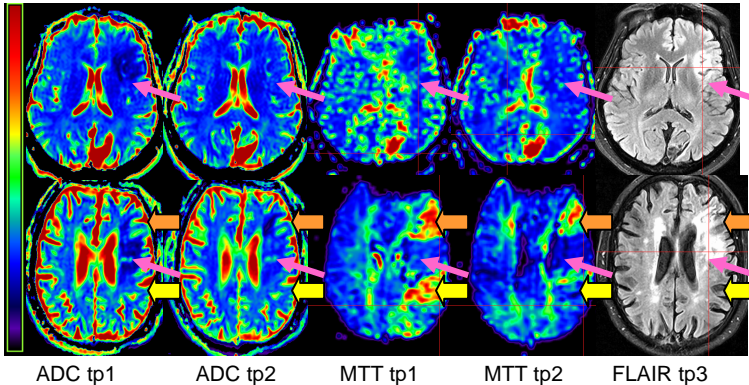

Figure 1. Representative ADC, MTT at tp1 and tp2 and FLAIR at tp3 from two patients. The range of the colorbar is from 20 to 220×10^{-5} mm^2/s for ADC and from 0 to 20 seconds for MTT.

Method

Thirteen acute ischemic stroke patients were prospectively studied. Two sequential MR scans were acquired with onset-to-scan times of 152±39 and 376±30 minutes for the first (tp1) and second (tp2) scans, respectively. Diffusion weighted images (DWI), FLAIR T2 images, and perfusion weighted images (PWI) using dynamic susceptibility contrast (DSC), were acquired at both tps in this sequential order. In addition, FLAIR images were acquired in ten patients one month (tp3) after stroke to delineate the final infarct. Eleven patients received intravenous tPA, while the remaining two patients did not receive tPA due to contraindications. Mean transit time (MTT) and apparent diffusion coefficient (ADC) maps were computed and a rigid image registration was performed to align MTT, ADC and FLAIR images across all tps for each patient. Cerebrospinal fluid (CSF) exhibits high values in both ADC and MTT maps and confounds our results. To minimize its effect, voxels with an ADC value greater than 100×10^{-5} mm^2/s were removed[2]. A voxel with an MTT > 4 seconds of the mean contralateral MTT was defined as "hypoperfused". A "reperfused" voxel was defined as a voxel which was hypoperfused at tp1 but not at tp2. ADC lesions were defined by voxels with ADC values < mean-2*SD of the contralateral hemisphere at tp1. A voxel with normalized ADC was defined as a voxel with abnormal ADC at tp1 but normal ADC at tp2. Based on reperfusion status, two ROIs were defined inside the tp1 ADC lesion: reperfused or non-reperfused regions. Mean ADC values from these two ROIs were obtained to examine the evolution of ADC values in the presence or absence of early reperfusion. In addition, tp3 FLAIR was utilized to examine the final fate of the two ROIs.

Figure 2. (a) ADC (unit 1×10^{-5} mm^2/s) changes in the presence and absence of reperfusion; (b)histogram of tp2 ADC in the reperfused ROI that did (infarct) and did not (noninfarct) go on infarction. The two vertical lines show ADC abnormal threshold (left) and normal mean (right).

Results

The mean ADC of contralateral hemisphere was 81.8± 1.9×10^{-5} mm^2/s and the threshold to define ADC abnormal was 66± 2.6×10^{-5} mm^2/s. Representative ADC, MTT (tp1 and tp2) and FLAIR (tp3) maps from two patients are shown in Figure 1. The first patient showed a complete reversal of ADC reduction from tp1 to tp2 (upper row) and MTT was normal in both tps suggesting early reperfusion even before the first scan. Despite the reversal of ADC and early reperfusion, a portion of this region went on to infarct (Figure 1, upper row), indicating that ADC normalization did not reflect a salvage of tissue. In addition, MTT was relatively normal at both tps (upper row, Figure 1), suggesting that there might be a time lag between the onset of reperfusion and ADC normalization. The second patient in Figure 1 also showed similar pattern (pink arrow, lower row, Figure 1). This time lag between ADC normalization and reperfusion was observed in 4 patients. Moreover, two regions in the 2nd patient next to the normalized ADC region exhibited abnormal MTT (orange and yellow arrows, lower row, Figure 1) at tp1. Interestingly, no apparent ADC lesions were observed at tp1 in these two regions. Despite the improved perfusion status, a new ADC lesion was observed (orange arrow) which continued to evolved into infarction. Within the reperfused ROIs, ADC values increased significantly from 56.9±4.0×10^{-5} mm^2/s at tp1 to 67.2±3.3×10^{-5} mm^2/s at tp2 (p<0.01). In contrast, ADC values showed a trend of decrease from 54.3±5.2×10^{-5} mm^2/s at tp1 to 52.3±4.0×10^{-5} mm^2/s (p=0.18) if no reperfusion occurred (Figure. 2a). In addition, a large portion of the infarct and noninfarct regions have an overlap in tp2 ADC, suggesting that the fate of tissue cannot be determined by tp2 ADC after reperfusion (Figure 2b). We found that 51.8±23.5% of the total volume of the tp1 ADC lesion with reperfusion still went on infarction, while 84.6±9.6% of the total volume of the ADC lesion region without reperfusion became infarct.
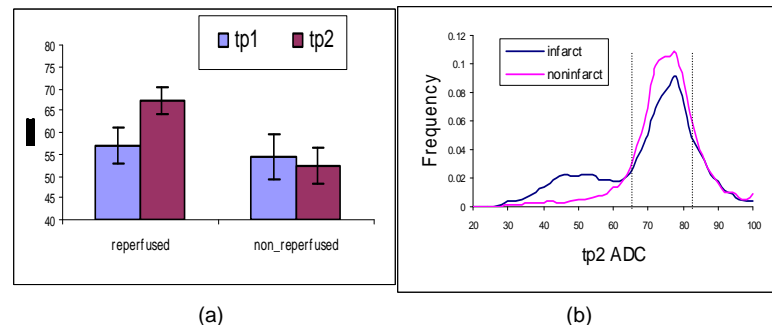
Discussion and Conclusions

In this study, we have found that changes of perfusion have a considerable impact on ADC values in acute ischemic patients. Complete (normalization) or partial reversal of ADC abnormality was observed after reperfusion, while it decreased slightly if reperfusion did not occur. Regions with normal range tp2 ADC could either become infarct or not infarct, suggesting reversal of ADC abnormality within 3 to 6 hours after stroke does not necessarily reflect a recovery of ischemic tissue. Furthermore, a time lag was observed between the changes of perfusion and the changes of diffusion (both normalization (upper row, Fig 1) and worsening (lower row, Fig. 1) in this study. In the clinical setting, patients are usually scanned once and perfusion and diffusion images are usually utilized as surrogate markers to indicate ischemic injury. Since ADC depends on time as well as the status of perfusion, one must be cautious in interpreting a single scan of PWI and DWI since they may not reliably predict tissue outcome.

Reference
1. Li F et al, Ann Neurol, 1999, 333-342; 2. Fiehler et al, Stroke, 2002, 79-86;

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