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Automated quantification of cerebral edema following hemispheric infarction: Application of a machine-learning algorithm to evaluate CSF shifts on serial head CTs

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ABSTRACT

Although cerebral edema is a major cause of death and deterioration following hemispheric stroke, there remains no validated biomarker that captures the full spectrum of this critical complication. We recently demonstrated that reduction in intracranial cerebrospinal fluid (CSF) volume (ΔCSF) on serial computed tomography (CT) scans provides an accurate measure of cerebral edema severity, which may aid in early triaging of stroke patients for craniectomy. However, application of such a volumetric approach would be too cumbersome to perform manually on serial scans in a real-world setting. We developed and validated an automated technique for CSF segmentation via integration of random forest (RF) based machine learning with geodesic active contour (GAC) segmentation. The proposed RF + GAC approach was compared to conventional Hounsfield Unit (HU) thresholding and RF segmentation methods using Dice similarity coefficient (DSC) and the correlation of volumetric measurements, with manual delineation serving as the ground truth. CSF spaces were outlined on scans performed at baseline (<6 h after stroke onset) and early follow-up (FU) (closest to 24 h) in 38 acute ischemic stroke patients. RF performed significantly better than optimized HU thresholding ($p < 10^{-4}$ in baseline and $p < 10^{-5}$ in FU) and RF + GAC performed significantly better than RF ($p < 10^{-3}$ in baseline and $p < 10^{-5}$ in FU). Pearson correlation coefficients between the automatically detected ΔCSF and the ground truth were $r = 0.178$ ($p = 0.285$), $r = 0.876$ ($p < 10^{-6}$) and $r = 0.879$ ($p < 10^{-6}$) for thresholding, RF and RF + GAC, respectively, with a slope closer to the line of identity in RF + GAC. When we applied the algorithm trained from images of one stroke center to segment CTs from another center, similar findings held. In conclusion, we have developed and validated an accurate automated approach to segment CSF and calculate its shifts on serial CT scans. This algorithm will allow us to efficiently and accurately measure the evolution of cerebral edema in future studies including large multi-site patient populations.

1. Introduction

Cerebral edema, the pathologic accumulation of excess water inside brain tissue, is a major cause of death and deterioration following ischemic stroke and other brain injuries (Krieger et al., 1999; Rosenberg, 1999, 2000). Under the Monro-Kellie doctrine, compensation for this swelling must occur given the rigid confines of the cranium, with parallel reductions in the volume of other intracranial compartments such as blood and cerebrospinal fluid (CSF). If cerebral edema progresses beyond the point where compensation has been exhausted, then intracranial compartmental pressure will rise, leading to brain herniation (Hacke et al., 1996). By opening the cranial vault (hence bypassing the restrictions of the Monro-Kellie doctrine), decompressive hemicraniectomy (DHC) is effective in preventing herniation and

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death in patients with malignant cerebral edema after large hemispheric infarction (LHI) (Vahedi et al., 2007). This benefit requires early selection of patients with malignant edema for DHC, ideally prior to development of herniation and within 48 h. Current approaches to surgical triage require high stroke severity coupled with large infarct seen either on delayed CT images or acute MRI (Thomalla et al., 2010). However, neither NIHSS nor infarct volume is a direct measure of cerebral edema, leading to misclassification of patients for an invasive neurosurgical procedure or delayed diagnosis until herniation occurs.

We have recently proposed that measuring reduction in CSF volume can provide a more direct and sensitive biomarker of edema. This can be accurately measured after volumetric segmentation of CSF from serial CT scans acquired at baseline and follow-up (FU) in patients with hemispheric infarction (Dhar et al., 2016). This CT-based approach may allow early and accurate identification of those at risk for developing malignant cerebral edema. However, manual segmentation of hemispheric CSF on two or more CT scans is time-consuming and impractical to apply to widespread rapid stroke triage decision-making. It is also impossible for manual delineation to analyze the large datasets from multi-center stroke cohorts required to study the kinetics, predictive factors and genetic underpinnings of cerebral edema formation. Simple threshold-based approaches (as have been used to segment CSF on baseline stroke scans) may not accurately delineate CSF on FU CT scans where hypodense evolving infarct is hard to distinguish from surrounding CSF (Minnerup et al., 2011). The objective of this study was to develop an automated advanced CSF segmentation approach that is able to accurately quantify CSF volumetric changes from serial CT scans in the acute phase of ischemic stroke.

2. Materials and methods

2.1. Patients

We retrospectively identified patients with hemispheric infarction and cerebral edema of varying degrees from a stroke cohort enrolled in a prospective stroke study at two institutions. Eligibility criteria included: 1) baseline NIHSS ≥8; 2) baseline head CT obtained within 6 h of stroke onset; 3) FU CT obtained at 6–48 h after stroke onset; 4) FU CT confirming hemispheric infarction and some degree of edema (i.e., sulcal and/or ventricular effacement with or without midline shift, MLS); 5) no parenchymal hematoma on FU CT. If more than one FU CT was performed, the scan closest to 24-hours was selected for analysis, as long as it was performed prior to any decompressive surgery. We have included 38 patients with hemispheric infarction, with 26 patients from Washington University/Barnes-Jewish Hospital, St. Louis, MO (center A) and 12 patients from Vall d'Hebron Hospital, Barcelona, Spain (center B). All subjects (or their proxy) provided informed consent and the study was approved by institutional review boards at each center. Demographic and clinical characteristics of the study population are given in Table 1.

Table 1
Demographic and clinical characteristics of the study population.

Variable/center	Washington University, St. Louis	Vall d'Hebron, Barcelona
Number of subjects	26	12
Age, years	61 (52–80)	74 (56–82)
Gender, female	11 (42%)	5 (42%)
Race, white	18 (69%)	12 (100%)
Admission NIHSS	15 (10–19)	17 (11−21)
Treated with tPA	21 (81%)	12 (100%)
ASPECTS on baseline CT	9 (8–10)	9 (8–10)
Time between baseline and FU, hours	18 (13–34)	24 (18–27)
Midline shift, ml[a]	0 (0–2.4)	0.5 (0–1.4)

Notes. Categorical variables are present as n (%); continuous variables are presented as medians (interquartile range).
[a] Infarct volume and midline shift were assessed as visible on early FU CT scans.

2.2. Manual delineation

CSF was outlined using the MIPAV (Medical Image Processing, Analysis, and Visualization) software package, as has been previously described (Dhar et al., 2016). CSF volume was segregated into compartments including hemispheric sulci and lateral ventricles, both ipsilateral (IL) and contralateral (CL) to the side of infarction. The third ventricle and the perimesencephalic and suprasellar cisterns were also outlined and included in total CSF volume. Total hemispheric CSF volume was quantified on each CT scan as the sum of all CSF spaces and change in volume (ΔCSF) was calculated as the reduction in volume between these two scans (i.e., FU vs. baseline volume). Two raters separately segmented CSF on a subset of scans and inter-rater reliability for manual volumetric segmentation of CSF was found to be 0.92. Manual CSF delineation was saved as image masks for comparison with automated segmentation.

2.3. Pseudo-affine image registration

CT images consist of stacks of axial images with a thick slice separation of 5 mm. In order to align CTs from different patients (with different orientation and head size) to a normalized frame to reduce geometrical variability, we adopted a pseudo affine registration to co-register all the CT images to a pre-chosen well-positioned template. In the affine transformation matrix, we restricted shears and rotations involving the foot to head direction, so that a 2D image slice remains a plane after transformation. This warping process only allows 3D translation, in-plane rotation, scaling and shear. Following this registration step, the ground truth (i.e. manual) CSF segmentation masks were also transformed towards the template with the same transformation matrix. Besides making the sulci more consistently oriented, this warping process also allowed us to perform training of one random forest in this template frame for future deployment.

2.4. Random forest CSF classification

Our training-based CSF segmentation is a supervised learning process. Random forests (RF) (Breiman, 2001) has recently been applied to medical image segmentation with promising results (Geremia et al., 2011; Mitra et al., 2014). This hierarchical approach learns how to efficiently classify brain voxels by creating a large forest of multiple independent decision-trees derived from random subsets of the sample of CT scans provided (e.g. sets 1 through N, in Fig. 1A). Initially, all samples in a subset (e.g. set 1 in Fig. 1A) are pushed down from the root node of a tree to either the left or right branches (subsets S1 and S2) depending upon which route will achieve more ordered organization. Data is successively partitioned to optimize discrimination or until: 1) maximal tree depth is reached; 2) the minimal number of samples being divided is reached; or 3) all samples belong to the same class. RF then leverages this cluster of derived models to optimally segment each voxel (i.e. into CSF or other). To optimize classification, the Gini impurity index is reduced through the splitting process. The calculation of this index is given in Eq. (1), with p_k as the fraction of items labeled with value k and the total cluster number K. Gini impurity is a measure of how often an element is incorrectly labeled and it reaches zero when all the cases within a node all belong to a single class.

$$\text{Gini} = \sum_{k=1}^{K} p_k(1-p_k) \quad (1)$$

At each node split, the sum of Gini impurity from the two descendent nodes is less than the parent node. Finally, random forest takes advantage of the concept of ensemble by training multiple trees with the repeated sampling of the training set. As a result, this supervised