Evaluating a 3D deep learning pipeline for cerebral vessel and intracranial aneurysm segmentation from computed tomography angiography–digital subtraction angiography image pairs

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OBJECTIVE Computed tomography angiography (CTA) is the most widely used imaging modality for intracranial aneurysm (IA) management, yet it remains inferior to digital subtraction angiography (DSA) for IA detection, particularly of small IAs in the cavernous carotid region. The authors evaluated a deep learning pipeline for segmentation of vessels and IAs from CTA using coregistered, segmented DSA images as ground truth.

METHODS Using 50 paired CTA-DSA images, the authors trained (n = 27), validated (n = 3), and tested (n = 20) a deep learning model (3D DeepMedic) for cerebrovasculature segmentation from CTA. A landmark-based coregistration algorithm was used for registration and upsampling of CTA images to paired DSA images. Segmented vessels from the DSA were used as the ground truth. Accuracy of the model for vessel segmentation was evaluated using conventional metrics (dice similarity coefficient [DSC]) and vessel segmentation–specific metrics, like connectivity-area-length (CAL). On the test cases (20 IAs), 3 expert raters attempted to detect and segment IAs. For each rater, the authors recorded the rate of IA detection, and for detected IAs, raters segmented and calculated important IA morphology parameters to quantify the differences in IA segmentation by raters to segmentations by DeepMedic. The agreement between raters, DeepMedic, and ground truth was assessed using Krippendorff’s alpha.

RESULTS In testing, the DeepMedic model yielded a CAL of 0.971 ± 0.007 and a DSC of 0.868 ± 0.008. The model prediction delineated all IAs and resulted in average error rates of < 10% for all IA morphometrics. Conversely, average IA detection accuracy by the raters was 0.653 (undetected IAs were present to a significantly greater degree on the ICA, likely due to those in the cavernous region, and were significantly smaller). Error rates for IA morphometrics in rater-segmented cases were significantly higher than in DeepMedic-segmented cases, particularly for neck (p = 0.003) and surface area (p = 0.04). For IA morphology, agreement between the raters was acceptable for most metrics, except for the undulation index (ρ = 0.36) and the nonsphericity index (ρ = 0.69). Agreement between DeepMedic and ground truth was consistently higher compared with that between expert raters and ground truth.

CONCLUSIONS This CTA segmentation network (DeepMedic trained on DSA-segmented vessels) provides a high-fidelity solution for CTA vessel segmentation, particularly for vessels and IAs in the carotid cavernous region.

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KEYWORDS vasculature segmentation; deep learning; digital subtraction angiography; computed tomography angiography; brain aneurysms
Intracranial aneurysms (IAs) are localized outpouching within the circle of Willis that can rupture, causing deadly subarachnoid hemorrhages. While approximately 2%–6% of the US population harbors an unruptured IA, most afflicted do not know they have one, as the lesions are largely asymptomatic. Aneurysm detection and treatment planning relies on medical imaging by digital subtraction angiography (DSA), MR angiography (MRA), or computed tomography angiography (CTA). CTA is the most widely used modality, since it is noninvasive and has better spatial resolution than MRI-based methods. However, CTA has been shown to have poor accuracy in detecting small IAs and those in the cavernous region where delineation of the carotid artery and skull is difficult. Pradilla et al. reported a false-positive rate of 21% and a false-negative rate of 22% in detection of unruptured IAs on CTA compared with that on DSA, noting that most IAs that were not detected were < 5 mm (97% of missed IAs) and on the internal carotid artery (ICA; 76% of missed IAs). Moreover, the lower resolution of CTA can lead to miscalculation of important IA metrics, such as neck size, that can be overestimated because of “kissing vessel artifact.”

Such challenges pose a significant problem for image-based computational pipelines that are being developed to analyze IA morphology and hemodynamics (via computational fluid dynamics), toward treatment planning, risk assessment, and outcome prediction. Intrinsically, the first step in such pipelines involves segmentation of the cerebral vasculature to create a 3D vessel model. Currently, vessel segmentation is performed manually, making it unreasonable for clinical implementation due to the high time/resource cost, subjectivity, and inaccuracy associated with manual input. Recently, deep learning approaches have been implemented across various medical imaging applications, including brain vessel segmentation. Successful segmentation networks for cerebral vasculature segmentation have been trained to output segmentation based on DSA inputs (trained on segmented DSA as ground truth). Alternatively, networks trained on CTA data have only been tested on healthy arteries and not on IAs that can be small and have complex morphologies or vessels in the cavernous carotid region. In this study, we sought to develop a deep learning network that could accurately segment the cerebral vasculature and IAs (even in the cavernous carotid region) from CTA images using segmented DSA as ground truth. To do this, we collected and registered paired CTA and DSA images, trained a DeepMedic-based network using coregistered, expertly segmented DSA, and independently tested it in a separate cohort of cases. We compared the network output to expert-segmented CTA images to show the improvement in segmentation accuracy, further analyzing if experts and the algorithm could detect IAs in the cavernous region and accurately measure important IA morphology metrics (such as size ratio).

Methods

Data Cohort

We used CTA and DSA images from aneurysm patients at the Gates Vascular Institute in Buffalo, New York. Approval for the collection and review of deidentified images of patients with IA was obtained from the University at Buffalo Institutional Review Board. Consent was waived for this retrospective study. Cases were excluded if 1) CTA/DSA images were not available, 2) the registration quality was poor (possibly due to movement artifacts between acquisitions), 3) there was poor contrast filling in DSAs, and 4) images were obtained after IA treatment.

Medical Imaging Parameters

CTA images used for this study were acquired on an Aquilion ONE scanner (Canon Medical Systems). The tube voltage and tube current were set to 135 kVp and 370–600 mA, respectively, for noncontrast CT, and 120 kVp and 150–205 mA, respectively, for CTA. The reconstructed voxel size for CTA was 0.5 × 0.5 × 0.5 mm³, respectively. For CTA, Omnipaque 350 contrast agent (iohexol, GE Healthcare) was given at a rate of 5 mL/sec in CT perfusion during image acquisition. For DSA image reconstruction, the mask and fill runs were performed using a Canon Infinix Angiography Unit (Canon Medical Systems). For the fill rotation, Omnipaque was injected for 6 seconds at a dosage of 4 mL/sec during a 3D spin. The acquired images were subtracted and reconstructed using the manufacturer’s software on a PACS with a matrix size of 512 × 512 × 512 with an isotropic voxel dimension of 0.223 mm.

Image Preprocessing

The overall model development process employed for this study is illustrated in Supplemental Fig. 1. The first step in the pipeline is image preprocessing, and the steps therein are as follows.

Registration and Resampling

All CTA images were registered onto the paired DSA images using semiautomatic workflow (Fig. 1). Landmarks (ICA bifurcation) were manually isolated from the CTA and DSA images using the region of interest (ROI) cropping tool in 3D Slicer. The landmarks were coregistered using the ElastiX toolbox in 3D Slicer, and the transformation matrix was noted. The stored transformation matrix was used to transform the complete 3D CTA image onto the 3D DSA image for the final registration. Registrations were qualitatively examined by an expert rater (board-certified radiologist with > 12 years of experience and advanced training in neuroradiology) to assess the registration quality, and the cases with poor registration were excluded from the study. Coregistered CTA images were upsampled to match the resolution of DSA using the windowed sinc interpolation method in 3D Slicer.

ROI Identification

The methodology for automated ROI extraction from CTA-DSA image pairs is illustrated in Fig. 2. First, we manually isolated an ROI encompassing the major vessels (i.e., ICA, middle cerebral artery to the M1–M2 segment, anterior cerebral artery to the A1–A2 segment, and basilar...
artery) from a publicly available CT brain atlas. We registered our CTA images onto the brain atlas using the affine registration algorithm from the BRAINSFit module in 3D Slicer and saved the affine transformation matrix. The ROI drawn on the CT atlas was then transformed onto all CTA images using the inverse of the affine transformation matrix. The extracted volumes from the CTA-DSA pairs were used for further analysis.

FIG. 1. CTA image registered over the paired DSA image. A and B: The DSA image (A) is registered and visualized in 3D (green) overlaid on the 3D isosurface CTA image in the transverse, coronal, and sagittal views (B). C and D: The CTA slice (C) with the ROI of the DSA image (dark gray background, yellow outline, and green vessels) registered onto the CTA slice in the transverse, coronal, and sagittal views (D).

FIG. 2. Automated ROI extraction from CTA-DSA pairs using a CT brain atlas. A and B: CT brain atlas (A) with a template ROI (in red) drawn using 3D Slicer. The CTA image (B) is then registered onto the atlas (A), with the inverse of the transform then applied onto the template ROI. C: The inverse transform to the template ROI results in a transformed ROI on all respective CTA images.
Ground Truth Generation

Ground truth segmentations were semiautomatically generated for the CTA ROIs from the coregistered segmented DSA images. First, an automated level-set segmentation algorithm with an isosurface initialization was used to extract an initial segmentation of vasculature inside the DSA ROI. High-quality ground truth was generated after 2–3 iterations of segmentation, cleaning, and expert verification. After the coregistration of the CTA-DSA pair, the DSA segmentation was corrected for motion and other such artifacts. Finally, as DSA runs were done for only 1 hemisphere, for completeness of CTA ROI vessel segmentation, vessels that were imaged on the DSA but visible on CTA ROI, (i.e., ipsilateral and posterior vessels), were manually segmented (see Fig. 3 for an example case). The DSA images were also used for setting the ground truth for IA detection by manual raters from CTA images obtained in the same patients. For the testing cohort, an expert identified IA locations from the 3D DSA images as the ground truth for IA detection.

Data Normalization

During preprocessing, we performed thresholding between the intensity range of 100 Hounsfield units (HU) to 700 HU, and further normalized the intensities by the maximum intensity in the CTA image. This intensity range was selected based on reports of nominal HU ranges for iodinated contrast.16 The intensity range was confirmed for our data set by recording the vessel intensity ranges from 5 randomly chosen CTA images in our cohort cases.

DeepMedic: Architecture and Training

The convolutional neural network (CNN) architecture employed in this paper, DeepMedic, was the same as the ones used previously for cerebrovascular segmentation from DSA and MRA images.10,11 The DeepMedic architecture, originally presented by Kamnitsas et al., is shown in Supplemental Fig. 2.28 It is an 11-layer deep network which has a fully connected structure consisting of only convolutional layers. Similar to our previous work, the model training is performed in 3D patches with an output patch size of 24.19 The network has two inputs, a normal resolution patch of size 40×40×40 and a low-resolution patch of size 22×22×22 downsampled from a 64×64×64 patch around the normal resolution patch. Training is regularized using dropout at the 4th and 8th layers and at the 9th and 10th layers at rates of 20% and 40%, respectively. In addition, L2 regularization was added to the network to avoid overfitting.

For training and testing of DeepMedic, we used CTA and DSA image pairs from 50 patients and divided them into a training cohort (60%) with an internal validation group (6%) and an independent testing cohort (40%). During training, a total of 2000 unique locations per local- ized CTA image (i.e., patient) were randomly sampled, ensuring that 50% were vessel centric. A hybrid, binary cross-entropy and dice similarity coefficient (DSC) loss function,17 which is biased toward punishing false-positive predictions, was used during training.

Segmentation Network Testing and Evaluation

During testing, the same preprocessing steps were performed on all CTA images. Input patches extracted with a 50% overlap (in all 3 dimensions) were given to the trained model with a traditional sliding window, and 3D volumes were reconstructed by stitching predicted patches. Quantitative evaluation of the DeepMedic-generated segmentations was performed using a vessel segmentation–specific metric, connectivity-area-length (CAL).18 It has been shown that CAL is better at evaluating segmentation accuracy of vascular structures than generic metrics like DSC, precision, and recall.18 Using an in-house MATLAB code, we evaluated CAL for DeepMedic segmentations and completed this performance evaluation over 3 regions: the overall vasculature in the ROI, large vessels with a diameter > 1 mm, and small vessels with a diameter < 1 mm.

IA Detection and Morphology Evaluation

To assess the efficacy of human raters in detecting IAs from CTA images, we asked 3 experts (rater 1, rater 2, and rater 3, who were trained neurointerventionalists in neurosurgery fellowship with > 4 years of experience), blinded to the DSA images, to detect the IAs from the CTA images in testing (n = 20). Rates of accuracy, sensitivity, and specificity were reported for the 3 raters for IA detection from CTA. The raters were also asked to segment the IA sac and a portion of the parent vessel for the detected IAs. To quantify their performance, we subsequently calculated 8 aneurysm morphological parameters from the
manual segmentations and compared them against the IA morphology from DSA ground truth. These parameters included the geometrical parameters, IA size, neck diameter, perpendicular height, and surface area, as well as the shape indices, aspect ratio (AR), undulation index (UI), ellipticity index (EI), and nonsphericity index (NSI) that are used to quantify irregularity of the IA sac. The same was done to assess the performance of DeepMedic in accurately segmenting IA morphology. The IA morphology parameters were computed from the DeepMedic predictions and compared the parameters against the IA parameters from the ground truth DSA segmentation.

### Statistical Analysis

For each group (individual raters and DeepMedic), means and standard errors were reported for comparison of IA morphology performance against ground truth. Statistical significance for comparing 2 groups was assessed by first testing data for normality, then performing the appropriate univariate test (Student t-test for normally distributed data and the Mann-Whitney U-test for nonnormally distributed data, with a significance threshold of \( p < 0.05 \)). To assess statistical significance (\( p < 0.05 \)) across more than 2 groups, 1-way ANOVA was performed. Krippendorff’s alpha (\( \alpha \)) was calculated to analyze the agreement between observations and ground truth on IA parameters. A value of \( \alpha = 1 \) shows perfect agreement between raters and 0 shows no agreement at all. The agreement was deemed to be reliable for \( \alpha > 0.8 \), acceptable for tentative conclusions if \( \alpha \) between 0.67 and 0.79, and not acceptable otherwise.

### Results

We evaluated 55 cases for this study. Of these, 5 CTA-DSA pairs were further removed due to poor contrast on the CTA images. These cases yielded attenuation HU lower than the nominal range of iodinated contrast in the ICA, thereby being outliers to the normal routinely acquired CTA images, and were therefore removed. The remaining 50 CTA-DSA pairs were retained for deep learning. The patient demographics and IA parameters for these cases are reported in Table 1. The average age of the cohort was 63 years, and most patients were female (84%). The IAs included in this study were primarily located on the ICA, middle cerebral artery, posterior communicating artery, ophthalmic artery, and anterior communicating artery and had an average size of 6 mm. The majority of the IAs (58%) were treated, either surgically (clipping) or endovascularly (coiling, Pipeline embolization device [Covidien Vascular Therapies], Woven EndoBridge [MicroVention/Terumo], or a combination). The outcome of most cases was stable at discharge or last clinical follow-up (> 90%), but 3 patients experienced neurological deficits at their latest clinical follow-up. Using these images, a DeepMedic CNN (approximately 1.2 million trainable parameters) was trained, validated, and tested on 27, 3, and 20 CTA-DSA pairs, respectively. Since the model would be trained on smaller 3D patches rather than the whole image, a small validation cohort (n = 3) was enough to generate a sufficient data set (2000 patches per image, so 6000 validation patches) to test whether the model was being overfit to the training cohort. As shown in Supplemental Fig. 3, the loss and DSC during training reached a plateau after approximately 50 epochs, ensuring model convergence.

#### DeepMedic Accurately Predicts DSA Quality Vessels From CTA

The performance of the DeepMedic CNN on the testing cohort (50% overlap in patches) is detailed in Fig. 4. The CAL metric for all 20 test cases was above 0.8, with an average of 0.971 ± 0.007 (Fig. 4A). The DSC, precision, and recall for the test cohort were 0.868 ± 0.008, 0.856 ± 0.004, and 0.887 ± 0.016, respectively. The performance of the CNN model on large (> 1 mm) and small (< 1 mm) vessels was evaluated separately. The performance of...
the model was consistently higher for large vessels compared with smaller vessels (Fig. 4A). Qualitative comparisons between the ground truth and the predictions from DeepMedic are illustrated in Fig. 4B. We observed that no IAs were missed by the DeepMedic segmentation CNN. Specifically, the ICA and the IAs in the cavernous ICA were also segmented using our DeepMedic CNN. Lower segmentation performance in smaller vessels versus larger ones was also observed (Fig. 4B).

**Expert Raters Blinded to DSA Missed Aneurysms on the Cavernous ICA**

The 3 blinded, expert raters missed, and in some cases, misidentified, IAs on the CTA images. The confusion ma-
The accuracies, sensitivities, and specificities in detecting IAs were 0.577, 0.577, and 0.731 for rater 1; 0.600, 0.600, and 0.650 for rater 2; and 0.500, 0.500, and 1.00 for rater 3, respectively. Raters 1 and 3 annotated 3 regions each as IAs that had not been marked as IAs on the ground truth DSA. Furthermore, compared with the ground truth, the raters performed significantly worse in detecting IAs on the ICA (p < 0.0001). Overall, the raters missed 23 IAs (out of 60, 20 IAs across 3 raters), of which 22 were on the ICA. Moreover, the sizes of the IAs that the experts missed (2.790 ± 0.433 mm) were significantly smaller than those that were detected (4.892 ± 0.453 mm) (p = 0.006). Representative missed IAs on the ICA are detailed in Fig. 5B.

**Expert Raters Overestimated the Aneurysm Neck**

We compared IA morphology metrics for the IAs detected and segmented by expert raters and the segmentations for the same IAs from DeepMedic. The error rates for IA morphology metrics are reported in Fig. 6A. The average error rate for IA morphology metrics calculated from DeepMedic segmentations was below 10% and was consistently lower than those comparing expert rater segmentations with ground truth. The errors in IA metrics calculated from DeepMedic segmentations were significantly lower than those calculated by expert rater segmentations, specifically for the IA neck (ANOVA, p = 0.007) and AR (ANOVA, p = 0.010). Average metrics from all 3 raters were significantly higher than those calculated from DeepMedic segmentations, in terms of the IA neck (p = 0.003) and IA surface area (p = 0.040). Qualitatively, the raters consistently overestimated the IA neck when manually annotating the IAs on the CTA images. A representative case showing this overestimation and how DeepMedic neck estimation was qualitatively comparable to the ground truth DSA is highlighted in Fig. 6B.

**DeepMedic Prediction Agrees With DSA More Than Expert Raters Blinded to DSA**

The DeepMedic model prediction showed reliable agreement (mean $\alpha = 0.921 \pm 0.019$) with ground truth for simple IA size metrics, such as size ($\alpha = 0.976$), volume ($\alpha = 0.939$), surface area ($\alpha = 0.958$), neck area ($\alpha = 0.971$), perpendicular height ($\alpha = 0.942$), and derived metrics such as AR ($\alpha = 0.928$) (Fig. 7A). Reliable agreement between DeepMedic prediction and ground truth was observed for IA irregularity metrics EI ($\alpha = 0.907$), UI ($\alpha = 0.800$), and NSI ($\alpha = 0.872$). The average agreements of the raters' manual annotations with ground truth in terms of Krippendorff’s alpha were 0.821 ± 0.075, 0.796 ± 0.100, and 0.736 ± 0.105 for each rater (Fig. 7A). Interrater reliability is reported in Fig. 7B. Notably, AR and NSI measurements showed a reliability that was acceptable with tentative conclusions, whereas UI yielded unacceptable reliabil-
ity. Simple metrics such as IA size, perpendicular height, neck, surface area, and volume all yielded reliable measurements. Overall, metrics calculated from DeepMedic segmentations were equivalent or better (specifically for IA irregularity morphometrics, i.e., NSI, EI, and UI) than those calculated by the expert raters.

**Discussion**

In the published literature there have been scarce reports of deep learning–based tools for segmentation of the cerebral vasculature from CTA images. Notably, Ni et al. demonstrated the capability of their deep learning architecture in segmenting the complete cerebral arterial structure from head and neck CTA. Their model reported a DSC of 0.965. However, this was demonstrated in a small testing cohort (only two 3D CTA volumes), and all cases used for training, validation, and testing were from healthy patients. Similarly, Fu et al. reported an end-to-end deep learning pipeline (CerebralDoc) for the reconstruction of the complete vasculature from the head and neck region. The study also reported good performance, with an independent testing DSC of 0.931. Despite their high fidelity for vessel segmentation, such models may not be able to be applied to all cerebral vascular diseases and malformations, particularly ones with small, complex structures, such as IA. Indeed, Pradilla et al. showed that the resolution of CTA is not sufficient to detect and isolate aneurysms (particularly small ones in the cavernous ICA region) with high sensitivity and specificity.
Given these limitations, we hypothesized that training a deep learning segmentation tool using segmented DSA images, which have considerably higher resolution than CTA, could boost the fidelity of segmentation of vessels (and aneurysms), particularly in the cavernous carotid region. Our results demonstrated that the trained DeepMedic model had good performance in segmenting vessels, with a CAL of 0.971 ± 0.007, and DSC, precision, and recall of 0.868 ± 0.008, 0.856 ± 0.014, and 0.887 ± 0.016, respectively, in our independent testing cohort. Furthermore, the model performed well on both large and small cerebral vessels, albeit with lower CAL, DSC, precision, and recall in smaller ones. This is to be expected, however, because of the loss of contextual information around small downstream vessels. While not ideal, lower segmentation fidelity in smaller vessels is not problematic for aneurysm detection and assessment, since IAs are predominantly found on the major arteries of the circle of Willis.

While there have been no other CTA-based deep learning models that have followed our approach (using DSA-derived segmentations as ground truth), there have been reports of other segmentation networks that have been trained for detection and segmentation of IAs from CTA (with segmented CTA as ground truth). For example, Shahzad et al. also used DeepMedic and reported a sensitivity of 0.760 in IA detection and a DSC of 0.800 for IA segmentation. Interestingly, they found a significantly inferior detection rate of IAs on the ICA compared with all other locations. This is to be expected, however, because of the loss of contextual information around small downstream vessels. While not ideal, lower segmentation fidelity in smaller vessels is not problematic for aneurysm detection and assessment, since IAs are predominantly found on the major arteries of the circle of Willis.

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In addition to aneurysm detection, 3D image analysis of IAs is used to assess rupture risk and assist in treatment planning. Morphological metrics, such as IA size, AR, EI, and NSI, are significantly different between ruptured and unruptured IAs, whereas IA neck diameter is an important indicator of recurrence after endovascular treatment. In this work, we further assessed the accuracy of the segmentation network in terms of IA morphology metrics, something that previous IA segmentation studies have not done. Our data show that rater-segmented CTA images had significantly different AR, neck, and surface area and that UI, EI, NSI, neck, and surface area were consistently overestimated versus when they were computed from DeepMedic output. Moreover, compared with ground truth, there was low agreement for AR, UI, EI, NSI, and neck calculated by raters but not when calculated from DeepMedic segmentations. Overall, this assessment provides evidence that such a tool could add clinical value to IA assessment workflows by providing reliable, automated measurements of critical IA metrics that impact risk assessment and treatment decision-making.

This study has several limitations. First, the cohort used to test our deep learning pipeline was relatively small and from a single center. The generalizability of the model can therefore be expanded by further validation in larger, multicenter cohorts. Second, improvements can be made to the widely accepted CNN architecture, DeepMedic. Nonetheless, DeepMedic has shown superior performance.
in cerebrovascular segmentation in prior studies using other imaging modalities, like DSA and MRA. In the future, improvements (e.g., residual connections and vessel loss functions) can be implemented. Third, we manually defined the IA neck for morphology calculation. This may have introduced bias in the computation of IA morphology parameters. Nonetheless, previous studies have shown that the interuser bias in IA morphology due to differences in neck identification are typically low.

Conclusions

We evaluated the performance of DeepMedic architecture for cerebral vessel and IA segmentation from CTA-DSA image pairs. Our model had excellent performance in vessel and IA segmentation, even in the cavernous regions, which matched well with the DSA ground truth segmentations. The pipeline also outperformed the manual rater segmentation of IAs in terms of neck estimation and its definitions. The pipeline also outperformed the manual rater which matched well with the DSA ground truth segmentation, even in the cavernous regions, thus further validating the pipeline for cerebral vessel and IA segmentation from CTA images compared with DSA.

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Author Contributions

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