The emerging role of cerebral CTA in carotid diagnosis and individualized treatment planning

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CTA continues to expand as a rapid, noninvasive means of imaging major vascular systems. The increased use of CTA can be attributed to:

- the growing prevalence of vascular diseases secondary to prominent risk factors such as atherosclerosis, hypertension, obesity, and diabetes
- continuous improvements in MD-CT that have led to higher spatiotemporal resolution, increased z-axis coverage, and advanced image processing techniques
- the wide availability of, and easy access to, MD-CT [1, 2].

Carotid CTA

Cerebral CTA (Figure 1) is central to these trends due to the frequency of stroke in the adult population. High-grade carotid stenosis is of particular importance since it can account for about 20% of all ischemic strokes [3, 4].

Advances in MD-CTA workflow, imaging, image postprocessing techniques - such as rapid bone suppression for 3D visualization (See below: Advanced Cerebral CTA Workflow) - are expanding the role of CTA in carotid imaging, and these advances are increasing the accuracy, reproducibility, and efficiency of cerebrovascular diagnosis.

As with other MD-CT applications, MD-CTA also has a role in the trend toward earlier intervention and facilitating better treatment decisions [1, 2]. Recent clinical studies beyond the North American Symptomatic Carotid Endarterectomy Trial (NASCET) demonstrate a trend toward treatment of more asymptomatic patients with less obstructive carotid disease [5-10].

Earlier selection for treatment will be facilitated by assessment of CTA-based risk factors that supplement the conventional use of percent-carotid stenosis classification. Several
hemodynamic factors have gained renewed interest including quantitative CTA analysis of Willisian collateralization. These factors, combined with analysis of the carotid atherosclerotic plaque, are under investigation (See below: Work-In-Progress: Cerebral CTA Analysis of Risk Factors) to provide new biomarkers in the patient’s risk profile and to facilitate more individualized carotid recanalization planning. The three studies with carotid disease shown in Table 1 are used to describe state-of-the-art CTA workflow as well as to analyze collateralization and plaque.

Advanced Cerebral CTA workflow

Specific goals of carotid CTA
The goals of carotid CTA are to:
• accurately measure carotid stenosis according to the NASCET criteria [5] and characterize lesion morphology
• review the Circle of Willis for completeness using 3D projected views of cerebral vasculature in relation to other structures
• detect other vascular lesions, such as dissections and tandem stenosis, in 3D relation to distal cerebral vessels.

Examination procedure
In our examination procedure, once a carotid or cerebrovascular lesion has been suspected or detected (either in asymptomatic or symptomatic patients), a rapid (13 s) high-resolution (0.4 mm isotropic spatial resolution) contrast-enhanced CTA scan is acquired non-invasively using a Philips Brilliance 64-channel configuration CT scanner. The scan covers the region from the aortic arch through the Circle of Willis in the arterial contrast enhancement phase.

Streamlined workflow for CTA: 3D visualization and measurement
Recent advances in CTA analysis are now available on the Philips Extended Brilliance Workspace to facilitate 3D visualization and measurement. After the CTA scan has been completed, bone suppression and vessel extraction are used to enable 3D visualization, stenosis measurements, and novel analysis tools (See below: Work in Progress).

Rapid and reliable suppression of the effects of bony structures for 3D visualization of CTA data has posed challenges in the past. The semi-automated bone suppression software in the Advanced Vessel Analysis (AVA) package (summarized in the flowchart of Figure 2) can rapidly and accurately suppress bone voxels. A brain mask is extracted using a region-growing technique that excludes the bone voxels of the imaged part of the cranium. In the next step, centerlines and luminal surfaces of the carotid and vertebrobasilar arteries are semi-automatically labeled with user-placed seed points. Voxels corresponding to the extracted arteries are then combined with the brain mask to create contrast-enhanced, 3D views of the arteries with suppression of the bone voxels.

To further enhance workflow, a fully automated (“zero-click”) bone suppression technique is being developed. This technique uses a model-based approach (Figure 3) and skull-base landmarks to automatically locate regions of interest for the carotid and vertebrobasilar arteries, alleviating the need for manual seed placement.

Estimates of cervical carotid stenosis
Three-dimensional visualization (with bone suppression) can be used to estimate carotid stenosis by rapidly projecting from any viewing direction. Furthermore, the arterial centerlines and segmentation tools from the AVA application can be used to accurately compute the degree of stenosis. This can have important treatment

Table 1: Volume-rendered ICA: comparison of three cases with unilateral ICA stenosis.

<table>
<thead>
<tr>
<th>Case</th>
<th>Stenosis or occlusion</th>
<th>Percent stenosis (Sec. II)</th>
<th>Neuro symptoms</th>
<th>Analysis/biomarkers (Sec. III)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Volume rendered</td>
<td>100</td>
<td>No</td>
<td>Willisian collateralization</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>95</td>
<td>Yes</td>
<td>Willisian collateralization</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>85</td>
<td>Yes</td>
<td>Plaque classification</td>
</tr>
</tbody>
</table>

The internal carotid arteries (ICA) follow tortuous paths through the petrous bone, and traverse the cavernous sinus prior to terminating as cerebral arteries near the thin sphenoid bones.
AVAs tools for estimating stenosis utilize a specialized display that depicts a rotatable, curved multiplanar reformatted (MPR) image longitudinally intersecting the vessel’s 3D centerline [13] (Figure 4, left). Two line segments “Reference” (green: “normal” lumen) and “Characteristic” (red: narrowed or stenosed lumen) are used to specify the location of images reformatted in cross section to the vessel and transverse to the centerline (Figure 4, upper and lower right). The vessel lumen contours are automatically segmented in the “Ref.” and “Char.” images, and the contours are used to compute effective luminal percent stenosis in reference to the NASCET criteria. The percent stenosis for three cases is shown in Table 1.

Work-in-progress: cerebral CTA analysis of risk factors

Investigations are under way to enhance carotid CTA diagnosis and treatment planning with novel image analysis and 3D visualization methods built on the foundation of the AVA application. Further analysis of CTA image data can potentially provide biomarkers for improved risk assessment for cerebral ischemia, and facilitating prediction and reduction of periprocedural complications of carotid endarterectomy (CEA) and angioplasty/stenting (CAS). (A selection of the many abbreviations and acronyms used in CTA is given in Table 2).

Risks for cerebral ischemia

The pathophysiological risk factors for, and etiology of, ischemic stroke are hypothesized to include both embolic and hemodynamic classifications [14,15]. These factors can have complex inter-relationships and different neurological manifestations. One hypothesis is that decreased blood flow due to carotid stenosis could decrease the “washing-out” of emboli that are lodged in distal cerebral vessels, including those that originate from the stenotic lesion. Another hemodynamic factor is the potential collateral flow provided by the Circle of Willis (Figure 5) that may, if sufficiently intact, help maintain CBF in the presence of occlusive cervical artery disease.

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2 Emboli may also originate from other carotid lesions (either stenotic or non-stenotic/vulnerable), from the heart (e.g., due to atrial fibrillation), or from lesions in the ascending aorta.

3 In addition to decreasing “washout”, decreased blood flow is also hypothesized to cause ischemia in the border-zone regions [17] and may also contribute to a decreased vasomotor response (VMR). Recent investigations have shown that reduced VMR is associated with an increased incidence of stroke and TIA [15,16]. However, not all patients with reduced VMR suffer from reduced cerebral perfusion, underlining the multi-factorial origin of cerebral ischemia.
Figure 4. Advanced Vessel Analysis (AVA) display of the EBW for measuring vessel stenosis (Case 2).

Left: Curved MPR longitudinally intersecting the carotid’s 3D centerline (red) used to specify “Ref.” and “Char.”

Upper and Lower Right: Cross sections of ICA (arrows).

### Table 2. Selected abbreviations and acronyms.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>BA</td>
<td>Basilar Artery</td>
</tr>
<tr>
<td>ACA</td>
<td>Anterior Cerebral Artery</td>
</tr>
<tr>
<td>A1-ACA</td>
<td>Communicating Segment of ACA</td>
</tr>
<tr>
<td>CA</td>
<td>Carotid Artery</td>
</tr>
<tr>
<td>PCA</td>
<td>Posterior Cerebral Artery</td>
</tr>
<tr>
<td>P1-PCA</td>
<td>Communicating Segment of PCA</td>
</tr>
<tr>
<td>AComA</td>
<td>Anterior Communicating Artery</td>
</tr>
<tr>
<td>MCA</td>
<td>Middle Cerebral Artery</td>
</tr>
<tr>
<td>PComA</td>
<td>Posterior Communicating Artery</td>
</tr>
<tr>
<td>ICA</td>
<td>Internal Carotid Artery</td>
</tr>
<tr>
<td>VA</td>
<td>Vertebral Artery</td>
</tr>
<tr>
<td>ECA</td>
<td>External Carotid Artery</td>
</tr>
<tr>
<td>MIP</td>
<td>Maximum Intensity Projection</td>
</tr>
<tr>
<td>EBW</td>
<td>Extended Brilliance Workspace</td>
</tr>
<tr>
<td>AVA</td>
<td>Advanced Vessel Analysis</td>
</tr>
<tr>
<td>CAS</td>
<td>Carotid Artery Stent</td>
</tr>
<tr>
<td>DEP</td>
<td>Distal Embolization Protection</td>
</tr>
<tr>
<td>CEA</td>
<td>Carotid Endarterectomy</td>
</tr>
<tr>
<td>NASCET</td>
<td>North American Carotid Endarterectomy Trial</td>
</tr>
<tr>
<td>Ref Diameter</td>
<td>Vessel “Normal” Location</td>
</tr>
<tr>
<td>Char Diameter</td>
<td>Location of Vessel Lumen “Stenosis” or “Narrowing”</td>
</tr>
<tr>
<td>$\Gamma$</td>
<td>Flow Conductance [mm³/poise] $\propto$ Radius/Length</td>
</tr>
<tr>
<td></td>
<td>Flow Resistance = Flow Conductance$^{-1}$</td>
</tr>
<tr>
<td>Combined $\Gamma$</td>
<td>$= (\Gamma_{A1} + \Gamma_{AComA} + \Gamma_{A1}) \parallel (\Gamma_{PComA} + \Gamma_{P1})$ where “$+$”= series and “$\parallel$”= parallel</td>
</tr>
<tr>
<td>VMR</td>
<td>Vasomotor Reactivity/Response</td>
</tr>
<tr>
<td>CBF</td>
<td>Cerebral Blood Flow</td>
</tr>
</tbody>
</table>

Flow Conductance and Resistance Formulas:

\[ \text{Flow Conductance} = \text{Radius} \times \text{Length} \]
\[ \text{Flow Resistance} = \text{Flow Conductance}^{-1} \]

Combined Flow Resistance:
\[ \text{Combined Flow Resistance} = \left( \frac{1}{\Gamma_{A1}} + \frac{1}{\Gamma_{AComA}} + \frac{1}{\Gamma_{A1}} \right) \parallel \left( \frac{1}{\Gamma_{PComA}} + \frac{1}{\Gamma_{P1}} \right) \]
Figure 5. Volume rendering (upper) and Maximum Intensity Projection (lower) of the Circle of Willis on the EBW.

Upper and lower left: Case 1. Completely occluded right ICA (yellow arrow) with collateral flow (white arrows on MIP) to MCA.

Upper and lower right: Case 2 with ICA stenosis (red arrow) and missing PComA segments (black arrow on MIP).

Estimated diameters in mm (green numbers) and flow conductances $l^1$ (cm$^3$/poise, white numbers) are represented. External carotid arteries are not shown.

Figure 6 Quantitative CTA analysis.

Figure 6a. Straightened MPR showing portion of right carotid artery from Case 3 in Table 1.

Figure 6b. Results showing lumen (yellow) and vessel (red) surfaces and non-calcified plaque (green).
Assessment of potential hemodynamic risk: Williisan collateral analysis

Despite the potential benefits provided by collateral blood flow, only about 20-34% of the population are estimated to have a complete Circle of Willis [18-20]. Arterial segments may be missing or hypoplastic in the anterior or posterior portion of the Circle (see diagram in Table 2) where:

- Anterior portion (ACirc) consists of A1-ACAs and AComA and
- Posterior portion (PCirc) consists of P1-PCAs and PComAs.

Segments in the anterior or posterior portion may limit collateral flow from the contralateral ICA or vertebrobasilar arteries to the MCA ipsilateral to carotid stenosis (or to other cerebral arteries). Case 2 (Table 1), for example, has missing bilateral PComAs (See Figure 5 right, striped arrow on MIP). Conversely, Case 1 has anterior (a double AComA) and posterior (intact PComA) sources of collateral flow ipsilateral to a 100% occluded ICA (Figure 5 left, white arrows on MIP view) and the patient denies ever having neurological symptoms. Therefore, the diagnosis of a primary carotid lesion alone can potentially lack predictive value for cerebral ischemia and subsequent infarction.

Instead of merely identifying missing segments in the Circle, investigations are under way to quantify Williisan collateralization. Flow conductances, $\Gamma$ (Figure 5, white numbers) were estimated from the length and diameter (Figure 5, green numbers) of each Williisan segment (provided by the AVA software) and overlaid on 3D views. Total (combined) $\Gamma$’s were also estimated for ACirc, PCirc, and a collateral combination of these (outer contours) to the MCA by applying network analysis to segmental $\Gamma$’s. These calculations have recently been extended to the aortic arch.

Assessment of embolic risk: plaque detection and characterization

In addition to the CTA visualization and analysis tools described above, MD-CT could be useful for carotid atherosclerotic plaque detection and characterization [24]. Quantifying the type (e.g., potentially “vulnerable” non-calcified plaques typically associated with increased risk of embolization) and extent of atherosclerotic plaques may have predictive value as a marker for cerebral ischemia and risk of stroke, and may indicate the need for more aggressive treatment. Additionally, the amount of non-calcified plaque may guide specific treatment decisions, such as whether to use CEA or CAS, or whether to use a Distal Emboli Filter (DEP) for neuro-protection with CAS [26].

Investigation is under way to automatically segment the arterial lumen and wall, and then quantify any calcified or non-calcified plaque present using advanced image analysis and pattern classification techniques. Similar techniques have already been performed for coronary CTA [25]. Figure 6b shows the detected calcified and non-calcified plaques for Case 3 (Table 1) overlaid as a color map on a straightened MPR image. As an additional output, the plaque characterization tools can output quantitative measures of total and type-specific plaque burden both locally and over the entire vessel. These measures may facilitate local treatment decisions, as mentioned earlier, or may have a role in prescribing and monitoring drug therapy.

Additional work-in-progress features and investigations

Increasing the capabilities of MD-CT and automated image analysis will enable even further expansion of cerebral CTA in the future:

- Investigations are under way to further characterize non-calcified plaque into tissue types such as fibrous plaque, lipid, and thrombus with dual/multi spectral CT scanning methods and to correlate these results with neurological symptoms. Novel contrast agents have recently been developed which bind to epitopes such as anti-fibrin to target the fibrin content of plaque [27].
- Larger MD-CT detector coverage and cone beam reconstruction will enable multi-regional protocols that combine coronary, carotid, aortic and cerebral scans at lower X-ray doses to access multiple sources of potential emboli and to measure CBF velocity vectors.
- CTA data sets are also being used for virtual angioplasty and stenting simulation. This could include the use of tactile feedback of plaque hardness or softness based on analysis of the CT data [28].
- Studies are under way to determine the presence of cerebral perfusion deficits that could pre-
dispose complications such as hyperperfusion syndrome and provide additional information on the hemodynamic status of the patient. Perfusion data, such as Mean Transit Time (MTT) or regional Cerebral Blood Flow (CBF) and Volume (CBV), can be fused with 3D views of cerebral vasculature in AVA. The results, along with the collateral analysis, are being used for comparisons before and after revascularization therapy.

**Conclusion**
The expression “time is brain” is often used - in a reactive paradigm - when evaluating a patient suspected of suffering an acute stroke. Decisions are made quickly regarding thrombolytic therapy following the assessment of cerebral perfusion deficit with MD-CT. In a more proactive paradigm, treatment planning based on new CTA biomarkers and advancements in less invasive treatment will further reduce procedure time and risk - thereby increasing the number of patients that could benefit from earlier intervention.

Advances in MD-CT imaging and quantitative image analysis tools, such as plaque characterization, collateralization assessment and perfusion analysis, are being combined to provide a more individualized, comprehensive risk assessment in a one-stop approach. This will further expand the role of cerebral CTA in asymptomatic as well as symptomatic patients, and will ultimately decrease morbidity, rehabilitation costs, and mortality associated with brain attack.

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**References**


