Conclusions—Time-resolved CTAs derived from C-arm CT perfusion acquisitions provide high quality images that allowed accurate diagnosis of large vessel occlusions. Although image quality of smaller arteries in this study was not optimal (distal to M1, A1, and P1), receiver-operating characteristic curves demonstrated excellent diagnostic value for detecting large vessel occlusions (area under the curve=0.987–1).

Results—Time-resolved C-arm CTA images were successfully generated from 20 data sets (95.2%, 20/21). Two observers independently evaluated image quality and diagnostic content for each case. ICC and receiver-operating characteristic analysis were performed to evaluate interobserver agreement and diagnostic value of this novel imaging modality.

Methods—Studies were done under an Institutional Review Board approved protocol. Postprocessing of data from 21 C-arm CT dynamic perfusion acquisitions from 17 patients with acute ischemic stroke were done to derive time-resolved C-arm CTA images. Two observers independently evaluated image quality and diagnostic content for each case. ICC and receiver-operating characteristic analysis were performed to evaluate interobserver agreement and diagnostic value of this novel imaging modality.

Results—Time-resolved C-arm CTA images were successfully generated from 20 data sets (95.2%, 20/21). Two observers agreed well that the image quality for large cerebral arteries was good but was more limited for small cerebral arteries (distal to M1, A1, and P1). receiver-operating characteristic curves demonstrated excellent diagnostic value for detecting large vessel occlusions (area under the curve=0.987–1).

Conclusions—Time-resolved CTAs derived from C-arm CT perfusion acquisitions provide high quality images that allowed accurate diagnosis of large vessel occlusions. Although image quality of smaller arteries in this study was not optimal ongoing modifications of the postprocessing algorithm will likely remove this limitation. Adding time-resolved C-arm CTAs to the capabilities of the angiography suite further enhances its suitability as a one-stop shop for care for patients with acute ischemic stroke. (Stroke. 2015;46:3383-3389. DOI: 10.1161/STROKEAHA.115.011165.)

Key Words: angiography ■ area under curve ■ cerebral arteries ■ ROC curve ■ stroke

Patients with acute ischemic stroke (AIS), especially those because of a large vessel occlusion (LVO), have poor prognosis. Although intravenous tissue-type plasminogen activator has been shown to offer benefit in some patients with an AIS, its efficacy in those with LVO is poor.1–3 The majority of the AIS patients with LVOs will die or have severe disability despite intravenous tissue-type plasminogen activator treatment.4,5 Therefore, revascularization using endovascular techniques is rapidly becoming the treatment of choice for these patients.6 Although several early trials failed to demonstrate a positive impact on clinical outcome after endovascular revascularization,4,5 several recent trials have confirmed the clinical benefit of revascularization.5,6–12 These also document the critical link between clinical outcome and the interval between onset and treatment. Thus, identifying patients with acute LVOs becomes more important than before for standard medical care of patients with AIS.

Multimodal imaging, that is, a combination of conventional computed tomography/CT perfusion (CTP)/CT angiography (CTA) or magnetic resonance imaging/MR perfusion/MR angiography, is generally accepted as being helpful in evaluation and triage of patients with AIS. However, there is often a reluctance to acquire complete anatomic and physiological imaging studies because of the significant and unavoidable delays, which

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are incumbent in acquiring this information. In several well-organized studies, the recorded time delays ranged from 51 to 185 minutes (median time)\(^1\).\(^{10}.\(^{13}.\(^{14}\)) it is impossible to overstate how significant these times are in determining the likelihood of both successful revascularization and good functional recovery. According to 2 similar studies,\(^2\)^\(^{13}.\(^{14}\) a 30-minute or 60-minute delay in recanalization can cause an 11% absolute reduction or 38% relative reduction in good outcome, respectively. To minimize this delay, we proposed to implement a one-stop-shop imaging workflow in an x-ray angiography suite. This proposed workflow enables us to acquire the needed nonenhanced cone beam CT (CBCT), time-resolved CBCT angiography (CBCTA), and CBCT perfusion (CBCTP) with whole head coverage from 1 dynamic acquisition using a flat panel detector-based C-arm CBCT system. Previous studies have demonstrated the ability of nonenhanced C-arm CBCT to identify intracerebral hematoma and predict hemorrhagic transformation for AIS patients treated with thrombectomy.\(^15.\(^{16}\) A previous study in canines as well as preliminary data from human subjects has also confirmed the feasibility of acquiring dynamic C-arm CBCTP data in the angiography suite.\(^17.\(^{18}\) The ability to acquire dynamic perfusion parameters, in our opinion, is a significant advance over methods which allow only measurement of cerebral blood volume using a steady state technique.\(^19.\(^{20})\) Using our recently proposed image processing algorithms,\(^22.\(^{24}\) we have generated from such perfusion data, time-resolved subtracted, full head C-arm CBCTA images, which can be displayed as 4-dimensional volume-rendered reconstructions. To our knowledge, this has not previously been described. This ability brings us 1 step closer to making the angiographic suite an ideal environment in which to implement the one-stop-shop concept for the care of patients with AIS. In this study, we focus on the clinical evaluation of the image quality and diagnostic value of time-resolved C-arm CBCTAs for AIS patients with LV Os.

**Materials and Methods**

**Patient Selection**

All studies were done under an Ethics Committee approved protocol. All subjects were evaluated for diagnosis and treatment decisions by multimodal MR or CT, including MR or CTA as well as perfusion imaging. The choice of imaging technique, as well as the treatment decision, was at the discretion of the treating physician. Seventeen consecutive patients with AIS and a high National Institutes of Health Stroke Scale score were examined with 2D digital subtraction angiography and dynamic C-arm CBCTP as part of their diagnosis and treatment. An anterior circulation LVO was confirmed in 14 patients and a posterior circulation LVO was confirmed in the other 3. Fourteen of these patients eventually underwent endovascular thrombectomy using the second-generation device, Solitaire FR (ev3 Neurovascular/Covidien, Irvine, CA) and 13 (13/14, 92.9%) were successfully revascularized. Dynamic C-arm CBCT data with intravenous contrast injection were acquired according to the treating physicians need either before or after the thrombectomy. A total of 21 data sets were acquired for this study, including 10 preprocedure and 11 postprocedure data sets.

All patients with a possible AIS were referred as soon as possible from the emergency room to the CT unit. After a noncontrast CT to exclude hemorrhage, intravenous lysis was initiated immediately (if the patient was within the 4.5-hour time limit) CT and CTP were then done. An experienced stroke neurologist and a neuroradiologist were always available and met in the CT unit to decide on a treatment strategy. The Door-to needle-time averaged 21 minutes.

**Data Acquisition**

Dynamic C-arm CBCTP data were acquired using a biplane flat detector angiographic system (Axiom Artis zee; Siemens Medical Solutions, Forchheim, Germany). Contrast was injected into a peripheral vein with the use of a dual-syringe angiographic power injector (Medtronic Accuton HP-D, Saarbrücken, Germany). Sixty milliliters contrast material (Imeron 350; Bracco Imaging, Milan, Italy) was injected at a rate of 5 mL/s followed by 60-mL saline flush. Briefly, nine bidirectional rotational scans (5 forward rotations and 4 reverse rotations) were performed; contrast was injected 5 s after the start of the acquisition so that the first 2 are the baseline set of nonenhanced (mask) images and the following 7 are contrast enhanced (fill) images. Rotation angle was 200° by \(\approx 5\)-s rotation time each; 248 projections were acquired during each rotation (angulation step 0.80/frame). Each projection was acquired at 77 kVp and 0.36 \(\mu\)Gy/frame dose level. This acquisition protocol resulted in a sampling rate of \(\approx 5\) s, with a total acquisition duration of 41 s. Clinical dose levels for a state-of-the-art CTP scan with a 16-cm (whole head) coverage are on average 5.0 mSv.\(^25\) A multisweep C-arm CBCT acquisition, the basis for perfusion CBCT, exposes the patient to a radiation dose of 4.6 mSv at the same coverage level.\(^26\)

**Image Postprocessing**

Three-dimensional isotropic filtered back projection image volume for each rotation was reconstructed and coregistered using the vendor’s proprietary software. A motion correction algorithm is a commercially available component of the DYNA CT application. No other motion correction software was used for image postprocessing. All the image volumes were postprocessed using prior image constrained compressed sensing\(^22.\(^{24}\) to reduce noise and TEmporal RESolution and SAmpling Recovery\(^23\) to enhance temporal resolution and to improve temporal sampling density. After these postprocessing steps, the noise contained in each volume was greatly reduced and a half-second temporal resolution was achieved. The final image volumes were then imported into a research workstation (Siemens Medical Solutions) to perform volume-rendered reconstruction (Figure 1).

The time-of-arrival (TOA) map was estimated based on signal intensity changes over time for each image voxel. For this implementation, the TOA of a voxel was defined as the time point when the signal intensity of this voxel first reaches 30% of its maximum intensity. Linear interpolation was used for more accurate estimation. A 3D TOA map was generated, colored encoded, and then multiplied with the CTA images to form a series of TOA-enhanced CTA images, which not only represent the contrast enhancement of vessels but also contain the contrast arrival times with defined color encoding.

![Image 307x91 to 537x237](http://stroke.ahajournals.org/)

**Figure 1.** A flow chart shows the detailed workflow from data acquisition to completion of image processing when using this new technique. CBCT indicates cone beam computed tomography; CBCTA, CBCT angiography; CBCTP, CBCT perfusion; and PICCS, prior image constrained compressed sensing.
Image Evaluation

The postprocessed time-resolved C-arm CBCTA data were loaded into a research workstation (Siemens Medical Solutions). The volume-rendered C-arm CBCTA images were further optimized using the cutting tool and window adjustment tool embedded in the workstation. Bookmarks were established and stored for each case to facilitate further clinical evaluation. All data were randomized and anonymized. Two experienced reviewers (1 interventional neuroradiologist with >30 years experience and 1 endovascular neurosurgeon with 8 years experience), who were not involved into the treatment of these patients, independently performed a blind evaluation of these data. The reviewers were asked to complete an evaluation form to assess the image quality of large arteries (internal carotid artery, middle cerebral artery, middle cerebral artery-V4, and posterior cerebral artery-P1) and small arteries (distal branches of anterior cerebral artery, middle cerebral artery, and posterior cerebral artery) using a 4-point rating scale (1, Poor: blurring of the vessel contours; 2, Fair: suboptimal arterial enhancement for confident diagnosis; 3, Good: adequate for confident diagnosis; and 4, Excellent: very confident for making diagnosis), and give their diagnosis about large arteries occlusion using a 5-point rating scale (1, Definitely not; 2, Probably not; 3, Unsure; 4, Probably yes; and 5, Definitely yes.). No other clinical data were provided to the reviewers. The digital subtraction angiography results of these cases were also documented as gold standards to enable further statistical analysis. Arterial occlusion was defined as: (1) no visualization of the artery and its first order branches on the early arterial phases of the CBCTAs and (2) if there was retrograde filling of an arterial territory, the filling did not extend to opacify the full extent of the stem of the artery in question.

Statistical Analysis

The statistical analysis was performed using SPSS version 20.0 (SSPS Inc, Chicago, IL). The image quality evaluation data were presented as mean±SD. Because the diagnosis data were ordinal categorical, the receiver-operating characteristic analysis was performed to evaluate the area under the curve, sensitivity, and specificity of time-resolved C-arm CBCTA as a diagnostic modality for LVOs. Intraclass correlation analysis was also performed and Cronbach’s coefficients were calculated to evaluate the interobserver agreement for each variable. The interobserver agreement was described as unacceptable (α≤0.5), poor (0.5<α<0.6), fair (0.6<α<0.7), good (0.75<α<0.9), and excellent (α≥0.9).

Results

Time-resolved C-arm CBCTA images and color-encoded TOA images were successfully reconstructed for 20 data sets (95.2%, 20/21). CBCTA images could not be generated from 1 data set because of the low concentration of contrast agent in the vasculature. The image quality for large arteries was judged to be excellent (median [interquartile range] is 4 [1] for observer 1 and 4 [0] for observer 2) with good interobserver agreement (α=0.744). The reviewers also agreed (α=0.702) that the image quality for small arteries was not good enough (median [interquartile range] is 2 [1] for observer 1 and 2 [2] for observer 2) to make a confident diagnosis. The detailed results of image quality for each evaluated artery are shown in Table 1.

The 2 observers reached excellent agreement (α=0.922) in making a diagnosis of LVO using time-resolved C-arm CBCTA (Table 2). The receiver-operating characteristic curves demonstrated excellent diagnostic value for detection of LVO (area under the curve=1 for observer 1 and ACU=0.987 for observer 2) of this novel imaging modality. The sensitivity of this novel imaging modality can be ≤100% with a good specificity of 93.6% to 100% at the reviewers’ respective best cut-off value (Figure 2).

Discussion

In this study, we have demonstrated that full head, subtracted, volume-rendered, time-resolved C-arm CBCTAs can be reconstructed from C-arm CBCT dynamic perfusion measurements acquired in the angiography suite at the time of diagnostic or therapeutic interventions. These provided high quality images of large arteries, which can enable our observers to diagnose acute LVOs accurately. The capability to obtain time-resolved CBCTAs derived from C-arm CBCTP acquisitions along with nonenhanced C-arm CBCT and C-arm CBCTP maps, further enhances the concept of the angiography suite being a one-stop shop for the care of patients with AIS.

In current workflow, there are 2 important clinical decisions to make in the selection of patients with AIS for endovascular treatment. The first is to differentiate ischemic strokes from hemorrhagic strokes. The second is to identify those patients who (1) are likely to have an LVO and (2) have appropriate ischemic core

<table>
<thead>
<tr>
<th>Arteries</th>
<th>Observer 1†</th>
<th>Observer 2†</th>
<th>Cronbach α</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large arteries</td>
<td>4 (3–4)</td>
<td>4 (4–4)</td>
<td>0.744</td>
</tr>
<tr>
<td>ICA</td>
<td>4 (4–4)</td>
<td>4 (4–4)</td>
<td>0.877</td>
</tr>
<tr>
<td>MCA-M1</td>
<td>4 (3–4)</td>
<td>4 (3–4)</td>
<td>0.755</td>
</tr>
<tr>
<td>ACA-A1</td>
<td>3 (3–4)</td>
<td>4 (3–4)</td>
<td>0.802</td>
</tr>
<tr>
<td>Basilar trunk</td>
<td>4 (3–4)</td>
<td>4 (4–4)</td>
<td>0.833</td>
</tr>
<tr>
<td>VA-V4</td>
<td>4 (3–4)</td>
<td>4 (4–4)</td>
<td>0.636</td>
</tr>
<tr>
<td>PCA-P1</td>
<td>3 (3–4)</td>
<td>4 (4–4)</td>
<td>0.618</td>
</tr>
<tr>
<td>Small arteries</td>
<td>2 (2–3)</td>
<td>2 (1–3)</td>
<td>0.702</td>
</tr>
<tr>
<td>ACA-distal</td>
<td>3 (2–3)</td>
<td>2 (1–3)</td>
<td>0.645</td>
</tr>
<tr>
<td>MCA-distal</td>
<td>2 (2–3)</td>
<td>2 (1–3)</td>
<td>0.761</td>
</tr>
<tr>
<td>PCA-distal</td>
<td>2 (2–3)</td>
<td>2 (1–3)</td>
<td>0.687</td>
</tr>
</tbody>
</table>

ACA indicates anterior cerebral artery; ICA, internal carotid artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; and VA, vertebral artery.

*The image quality was assessed using a 4-point rating scale (1, Poor: blurring of the vessel contours; 2, Fair: suboptimal arterial enhancement for confident diagnosis; 3, Good: adequate for confident diagnosis; and 4, Excellent: very confident for making diagnosis).

†Data were presented as median (lower quartile–upper quartile).

Data were presented as observer 1 (observer 2). DSA indicates digital subtraction angiography.
to penumbra ratios. Regardless of the techniques used, the time spent in making these 2 decisions are significant and represent bottlenecks in efforts to reduce the interval between stroke onset and revascularization. Mobile stroke unit may offer a good solution for shortening the time of making the first decision.27,28 There is still, however, no really satisfactory solution for significant shortening of the time required to obtain optimal information about the extent of ischemic core and penumbra. Two possible solutions have been proposed before. First, integrated hybrid systems, that is, Angio CT29,30 (a combination of a C-arm angiographic system and multislice CT scanner) and XMR (x-ray and MR system)31,32 (a combination of C-arm angiographic system and MR system), have existed for more than a decade. These hybrid systems are capable of performing conventional CT/CTP/CTA or magnetic resonance imaging/MR perfusion/MR angiography imaging and x-ray–guided endovascular procedures in the same facility.

Figure 2. Receiver-operating characteristic (ROC) curves show excellent diagnostic value of time-resolved C-arm computed tomographic angiography for detecting large vessel occlusions. The area under the curves are 0.987 and 1 for 2 observers, respectively.

<table>
<thead>
<tr>
<th>Area under the curve</th>
<th>p value</th>
<th>Best cutoff value</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Youden’s index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observer 1</td>
<td>1.000</td>
<td>0.000</td>
<td>3.5</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td>Observer 2</td>
<td>0.987</td>
<td>0.000</td>
<td>2.5</td>
<td>0.936</td>
<td>0.936</td>
</tr>
</tbody>
</table>

Figure 3. Time-resolved C-arm computed tomographic angiography (CTA) images (A) demonstrate a right internal carotid artery (ICA) terminus occlusion. The small arterial branches are not seen because of postprocessing in a way that would better shown them on maximal intensity projection (MIP) images (C and D). Arrows in A show the slow filling of the proximal right ICA in the late arterial and venous phases. Arrow in C shows the occlusion point at the right ICA terminus. There is retrograde filling of the A1 segment of the right ACA and the M1 segment of the right middle cerebral artery. The length of the occlusion is well demonstrated on these images (the dural sinuses are washing out). Color-encoded CTA image (B) shows a significantly delayed filling of right ICA. Temporal MIP images (C and D) show the capability of measuring the thrombus length and evaluate the collateral flow using C-arm time-resolved CTA data.
They are, however, expensive (because of the requirement of 2 systems and space for installation). They are significantly limited by the lack of materials that are of equal use in an MR and x-ray angiography environment. Because of these limitations, few experiences have been reported about their use in the care of patients with AIS. Second, simply bypassing the CTA/CTP or MR angiography/MR perfusion evaluation has been proposed as a potential solution. On the basis of some evidence of good correlation between the National Institutes of Health Stroke Scale and the chance of an LVO at the beginning of the Interventional Management of Stroke (IMS) III trial, the National Institutes of Health Stroke Scale score was used to triage patients. However, a recent evidence from a more rigorous study has demonstrated that although high National Institutes of Health Stroke Scale score (≥10) had a good positive predictive value (81%) for LVOs, its sensitivity is low (48%). On the basis of this, as well as the results of IMS III trial, this simple method does not, in our opinion, offer a satisfactory solution. All the most recent trials showing a positive impact of revascularization on clinical outcome have used multimodal imaging to enroll patients. As compared with the alternatives for using multimodality imaging for diagnosis and triage we think that the "one-stop-shop" imaging solution offers significant advantages. Simply by eliminating the time required for patient transfer and movement from 1 modality to another, it could shorten the interval from onset to treatment significantly, especially if diagnostic imaging and interventional therapy are located in different departments/buildings. The ability to obtain quickly with acceptable x-ray and contrast medium doses full anatomic and physiological evaluations seems likely to improve the ability to optimally select patients for intervention. Finally, it is attractive as it is only a modification of acquisition and postprocessing protocols, which does not require any significant hardware modification in current angiography suites.

In addition to the accurate and reliable detection of LVOs, time-resolved C-arm CBCTAs have several other potential merits. The ability to generate CBCT/SCBTA/CBCTP data from 1 acquisition should, when compared with the use of conventional multi-detector CT, result in significant reductions in radiation dose, contrast dose, and scanning time. C-arm CBCTA is time-resolved, which thus offers what would seem to be a better way for evaluating collateral flow and intracranial thrombus burden than does conventional non-time-resolved single-phase CTA. (Figure 3). Time-resolved C-arm CBCTA images can also be color encoded using TOA information or other temporal parameters, which may facilitate diagnosis and assessment of the extent of changes after an intervention (Figure 4). For this study, emphasis was placed on optimizing the postprocessing algorithm to display LVOs. Thus, the visualization of smaller arteries was suboptimal. We are, however, able to modify the postprocessing technique so that visualization of the smaller arteries will be possible (Figure I and Movies in the online-only Data Supplement). This, however, may come at the expense of some reduction in overall image quality. The image quality for small arteries is influenced by several clinical factors such as subject motion and cardiac function and the volume and injection protocol of contrast agent, and postprocessing parameters such as the threshold of sparse encoding etc, which need further optimization in future studies.

Our study has limitations. First, the sample size was small and the results only reflect the experiences of a single institution during a short time period. To try and remedy this, we are in the process of planning a more inclusive multicenter study. Second, the inability to postprocess the data at the time of their acquisition made it impossible for us to study, in a real world situation, just how the added information provided

**Figure 4.** C-arm computed tomographic angiography (CTA) images from early arterial phase to early venous phase show occlusion of basilar trunk (A). The ellipse in the first image shows the absence of vertebral or basilar filling on the early arterial phase. In the adjacent 2 images, these highlight the slow filling of the distal vertebral arteries and the proximal basilar artery are seen. There is no filling of the mid and distal segments of the basilar artery. B, Color-encoded CTA image shows late filling of distal vertebral arteries and the proximal basilar trunk. C, After endovascular thrombectomy, the occluded basilar trunk was recanalized. There is now filling of the entire basilar trunk and both vertebral arteries. D, Post-treatment color-encoded CTA image demonstrates filling of basilar trunk at a rate similar to that of the bilateral internal carotid arteries. There is still slow flow in the distal segment of the right vertebral artery.
by the time-resolved CTAs could be used and how it might modify the work flow in a way that would shorten the delay between initial diagnosis and thrombectomy. Third, our study did not involve an evaluation of the C-arm CBCTAs usefulness in evaluation of collaterals or thrombus burdens when compared with conventional CTAs or 2D digital subtraction angiographies. We are in the process of collecting data that will enable such a comparison. Finally, the results reported are ones obtained in a research environment using software tools, which may not be fully optimized. It is thus impossible to predict their ultimate impact in the clinical environment.

Conclusions

Our preliminary results indicate that time-resolved C-arm CBCTAs derived from C-arm CBCT acquisitions provided high quality images for accurate detection of LVOs with the potential to be used for patient selection for endovascular stroke therapy within the angiography suite. Because the image quality for small arteries is not good enough for making diagnosis, further study is required to optimize the image acquisition protocol and postprocessing algorithms.

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Disclosures

Drs Schafer and Royalty are paid full-time employees of Siemens Medical Solutions USA to support this project. The other authors report no conflicts.

References


Time-Resolved C-Arm Computed Tomographic Angiography Derived From Computed Tomographic Perfusion Acquisition: New Capability for One-Stop-Shop Acute Ischemic Stroke Treatment in the Angiosuite

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Supplemental Figure I:

An illustrative case demonstrates the capability of displaying small vessels for volume-rendered time-resolved C-arm CTA images. This is a case after successful endovascular thrombectomy which shows normal cerebral vasculature from early arterial phase to late venous phase on anterior-posterior (A) and lateral views (B). Online supplementary videos are available for better displaying.
Legends for supplemental videos:

These two supplemental videos are dynamic displays of a full head, subtracted, volume rendered, time-resolved C-arm cone beam CTA on anterior-posterior (Video 1) and lateral projections (Video 2). These two videos come from the same case as shown in supplemental Figure, which demonstrated good temporal resolution and good image quality for small vessels.