Noninvasive Angiography (Magnetic Resonance and Computed Tomography) in the Diagnosis of Ischemic Cerebrovascular Disease

Techniques and Clinical Applications

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Key Words

Magnetic resonance angiography · Computed tomography angiography · Craniocervical vasculature

Abstract

Noninvasive diagnostic imaging of the craniocervical and intracranial vasculature is a domain of computed tomography angiography (CTA), magnetic resonance angiography (MRA) and Doppler/duplex ultrasound, the latter not being the topic of this presentation. We give a methodological background for both, CTA and MRA, followed by a critical appraisal of both imaging modalities in the diagnosis of ischemic cerebrovascular disease. The contribution of noninvasive vascular imaging to vascular malformations (including aneurysms, fistulas and cerebral-vein thrombosis) is beyond the scope of this paper and therefore not covered.

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Magnetic Resonance Angiography

Magnetic resonance angiography (MRA) is a noninvasive magnetic resonance imaging (MRI) technique for vascular imaging. For patients with neurovascular disease, it can be applied to the intracranial or extracranial

vasculature, or both. Although there are several techniques, most commonly time-of-flight (TOF) sequences are nowadays applied. Rapid MRA sequences, usually 3-dimensional TOF sequences, are a critical component of modern multiparametric MRI protocols for acute-stroke patients [1].

Innovations in MR hard- and software as well as computational speed have enhanced the clinical applications of MRA allowing for the rapid generation of detailed 3-dimensional images of the vascular structures, including rheological (flow velocity) information by using phase contrast MRA (PC-MRA). A detailed overview is given in Turski and Korosec [2]. Flowing blood has different MR properties than stationary tissue. In TOF-MRA, short repetition time saturates stationary tissue, and consequently inflowing spins that move into a saturated slice have a bright signal compared with the surrounding stationary tissue (inflow enhancement). In PC-MRA, the far less frequently used technique in the daily routine, a relationship between blood flow velocity and the phase of a moving spin is utilized to image directional blood flow. This technique of PC-MRA is similar to Doppler ultrasound (DU), the latter however rendering real-time assessments contrary to the former, where the information is averaged over acquisition time [3]. For more detailed information on PC-MRA, we refer to the review by Ko-

Fig. 1. Source images and maximum intensity projection in an anterior-posterior view (top left) and head view (lower right). Normal intracranial vasculature.

rosec and Turski [4]. A third more recent technique is the use of a gadolinium bolus and obtaining very rapid T_1 -weighted imaging during the first passage of the contrast bolus, a technique named contrast-enhanced MRA.

Two-dimensional TOF studies are generated from a stack of 1.5- to 2-mm-thick T_1 -weighted gradient echo slices [2], which are combined to a volume of MR data. Then, the brightest voxels are projected and collapsed into a plane, thresholded and as such presented as maximum intensity projection [5]. The thresholding is the reason for an overestimation of stenosis on TOF-MRA, because low-intensity voxels may be cut off and thus slow flow may fail detection. Therefore, source image analysis and (curved) multiplanar reconstruction without applying thresholds can optimize the identification of slow flow areas [6]. Alternatively, a user-selected pixel signal intensity threshold technique termed shaded surface ren-

dering achieves smoother images [7]. By applying high gradient amplitudes (characterized by the slew rate, at present ≥ 200 T/m/s), signal loss from dephasing effects can also be minimized in 2-dimensional TOF-MRA. Rather than acquiring a single slice, a more practical approach is to perform a 3-dimensional gradient echo acquisition that also demonstrates inflow enhancement – so-called 3-dimensional TOF angiograms. The major strengths of 3-dimensional TOF-MRA are high spatial resolution (voxel size <1 mm³), short scanning times and high signal-to-noise ratio, which are partially offset by a reduced sensitivity to slow flow [2]. Techniques to improve imaging quality in 3-dimensional TOF-MRA are tone pulses (ramped radiofrequency pulses) that substantially reduce the saturation of inflowing (throughflowing) blood. Alternatively, or additionally, magnetization transfer may help to suppress background signal (fig. 1).

Fig. 2. Maximum intensity projection of a contrast-enhanced MRA from the aortic arch to the intracranial vessels. Acquisition time with bolus triggering 1.5 min.

Contrast-enhanced MRA techniques are excellent to image the aortic arch and carotid bifurcations. As they achieve signal differences between stationary tissue and blood by shortening the T_1 time of blood with gadolinium, they have fewer artifacts than TOF and PC methods (less sensitive to intravoxel dephasing from turbulent flow, no loss of signal due to saturation, less affected by motion artifacts because of the rapid acquisition time). The image acquisition however needs to be timed with the peak arterial concentration of the gadolinium bolus. For the extracranial vessels, a superior diagnostic strength comparable to digital subtraction angiography has been demonstrated [8, 9] (fig. 2).

Computed Tomography Angiography

Computed tomography (CT) imaging is currently the most widely used diagnostic tool for stroke imaging [10] mainly due to its close to 100% high sensitivity for intracerebral hemorrhage, the most important differential diagnosis to ischemic stroke [11]. Therefore, if there is need for additional vascular imaging, the logical next step is to add CT angiography (CTA) to the imaging protocol and

get the vascular information within the same examination. In addition, if indicated, perfusion sequences can be further added to the protocol within the same imaging session [12]. While varying MRA techniques have several practical and theoretical advantages over CTA, the single most serious drawback of stroke MRI is the still overall low availability nearly 10 years after the first reports of its implementation into the clinical routine. Modern CT scanners of the 4th or even 5th generation (volume scanners) are however less expensive and available in most centers even in smaller community hospitals, where they are mostly used for extracranial scanning. Acute stroke is not only treated at specialized academic medical centers; indeed, the majority of patients present first in local general hospitals that have no MRI facilities [13]. An excellent overview of CT, CTA and perfusion CT techniques has recently been presented by To-mandl et al. [14].

CTA is a fast, thin-section, volumetric spiral CT examination performed with a time-optimized bolus of contrast material for the opacification of vessels [14, 15]. Modern multisection CT scanners allow to image the entire region from the common carotid arteries up to the circle of Willis in a single data acquisition. The bolus tracking method to optimally acquire the contrast bolus has been established [16]. Postprocessing techniques are in part similar to those described previously for MRA. However, occlusion or significant calcification of extra- and intracranial vessels can be seen on the source images without any loss of time. Multiplanar reconstructions may aid in curved courses of vessels such as the proximal middle cerebral artery or eventually the internal carotid artery. Three methods of 3-dimensional CTA imaging are in use [17]. The first is maximum intensity projection, which in analogy to MRA is the most commonly used method. However, due to thresholding as in MRA there is a significant loss of information. This technique causes significant loss of information, especially when calcified stenoses are to be interpreted. Shaded surface rendering preserves depth information but loses attenuation information, therefore calcifications may be calculated to be intact lumen. Volume rendering integrates all available information from a volumetric data set [17] and assigns opacity and colors to voxels. While with this technique it is possible to e.g. demonstrate a calcified internal carotid artery stenosis, information may still be lost due to postprocessing so that none of these techniques can substitute for the thorough analysis of source images [7, 14].

Fig. 3. Non-contrast-enhanced CT (upper left) shows mild early CT signs of left-sided ischemic infarction (hypoattenuation of basal ganglia and loss of insular ribbon). CTA-SI (lower left) demonstrate the loss of vascular and collateral contrast enhancement of the complete left middle cerebral artery territory. A CTA maximum intensity projection with shaded surface rendering (right) demonstrates proximal middle cerebral artery mainstem occlusion (arrow).

CTA Source Image Analysis in Acute Ischemic Stroke

As the substrate for thrombolytic therapy is an obliterating thromboembolus, the ability of CTA to detect intracranial vessel occlusion suggests that it is a useful screening tool for identifying patients in whom intravenous or intra-arterial thrombolysis is appropriate [18]. Since the therapeutic time window for thrombolytic therapy is only 3 h and up to 6 h in selected patients, the need for an improved, CT-based diagnostic tool is evident. A normal non-contrast-enhanced CT scan in acute stroke does not imply low specificity of the method; in fact, it represents the favorable situation in which ischemic edema has not developed yet and the chance to avoid irreversible damage is still good. Unenhanced CT does not show the arterial occlusion itself except indirectly as the occasionally seen 'hyperdense artery sign', which displays a fresh intra-arterial thrombus. Furthermore, it does not show the extent of disturbed cerebral perfusion. One might ask if standard postcontrast CT should not suffice to visualize the extent of ischemic tissue. Besides the assessment of a major vessel occlusion, CTA has the potential to deliver information about the presence and quality of collateral circulation. In patients with good leptomeningeal collaterals, contrast enhancement in arterial branches beyond the occlusion occurs. This degree of

enhancement can be taken as an estimate of collateral blood flow [19, 20]. In addition to the vessel status, CTA source images (CTA-SI) also improve the contrast of perfused and malperfused brain areas, thus increasing the sensitivity for early ischemic changes not seen on non-contrast scans [21]. The window and level have to be adapted to a hard window (length: 35–40 HU; width: 50–75 HU), a parameter setting also shown to be useful for the detection of early ischemic signs in non-enhanced CT scans [22, 23]. Analysis of CTA-SI must be clearly differentiated from perfusion CT, where in analogy to perfusion-weighted MRI (PWI) a contrast bolus tracking method is applied and hemodynamic parameters may be assessed [24]. CTA-SI analysis is a stronger predictor of clinical outcome than the initial NIHSS score and may predict final infarct volume and clinical outcome. Patients with recanalization do not experience infarct growth, whereas those without complete recanalization do [25] (fig. 3).

Schramm et al. [21] investigated whether CTA-SI allow to detect ischemic brain lesions in patients with acute ischemic stroke, whether their sensitivity is comparable to that of diffusion-weighted imaging (DWI), whether the hypoperfused brain area seen on CTA-SI correlates with the final infarct and whether the qualitatively assessed collateral status does reflect the risk of infarct

Fig. 4. Non-contrast-enhanced CT (upper left) shows only mild hypodensity in the right frontal lobe, whereas CTA-SI (middle and right) show a contrast enhancement of normal brain as opposed to the acute infarction area. Note that optimized window

and level settings are necessary (right) to achieve the best contrast. Concurrent DWI for comparison (lower left). L = Length; W = width.

growth. The clinical and imaging findings of 20 consecutive stroke patients imaged within 6 h after stroke onset with both imaging modalities were analyzed. CT was performed within 2.83 ± 1.33 h followed by MRI within 3.38 ± 1.37 h. The time interval between CT and MRI ranged from 15 min to 1 h (0.55 ± 0.25 h). Of the 20 patients, 16 had a vessel occlusion seen on both CTA and MRA. All but 1 of these 16 patients had an abnormal initial DWI scan. All vessel occlusions detected on CTA were seen on MRA at the same location. Seven patients showed good intravascular enhancement of the perilesional vessels on CTA-SI and were classified as having 'good collaterals', 13 patients showed only poor enhancement around the lesion site and were classified as having 'poor collaterals'. Neither in patients with poor collaterals ($p = 0.807$) nor in patients with good collaterals ($p = 0.6$) did CTA-SI lesion volumes differ significantly from DWI

lesion volumes ($p = 0.601$) at baseline. However, patients with poor collaterals experienced significant infarct growth to day 5 T₂-weighted imaging ($p = 0.0058$), patients with good collaterals did not ($p = 0.176$). Furthermore, patients with good collaterals uniformly had a significantly better clinical outcome on day 90 ($p \leq 0.012$). In a follow-up study, Schramm et al. [26] investigated the diagnostic value of perfusion CT (PCT) and CTA including CTA-SI analysis in comparison with stroke MRI in 22 patients. PCT time to peak and cerebral blood flow maps corresponded well with MR perfusion imaging, while CTA-SI volumes did not differ from DWI volumes. MRA and CTA were congruent in all patients with regard to vessel occlusion or patency and – if occluded – occlusion site (fig. 4). Therefore, in acute stroke patients, CTA-SI and collateral analysis or even better combined with PCT may provide information similar to that of the PWI-

DWI mismatch concept [1]. The volume of the affected brain area that has inadequate blood supply can be estimated by the difference between the CTA-SI lesion volumes and the brain area supplied by the occluded artery, taking the qualitative assessment of the collateral status into account (or PCT cerebral blood flow and PCT time to peak maps). The patients with poor collaterals seem to represent those that may have a PWI-DWI mismatch in analogy to stroke MRI and the patients with good collaterals those patients without tissue at risk (i.e. small stroke, lacunar stroke or tissue at risk already completely infarcted). The combination of CT and CTA may also be more cost effective than stroke MRI. In conclusion, CTA findings are concordant with MRA, and CTA-SI lesion volumes are concordant with DWI lesion volumes, and the volume range of poor collateralized areas according to CTA-SI may reflect the critically hypoperfused part in parallel to PWI. PCT may add useful information only indirectly derived from CT and CTA/CTA-SI analysis.

Comparison of Modalities

Comparative studies, especially in between CTA and MRA, are rare, whereas the literature of MRA/digital subtraction angiography (DSA) comparisons [27] is more prevalent and for CTA/DSA already sufficing for meta-analyses (aneurysms in this study) [28]. In essence DSA remains the gold standard of vascular imaging and should always be considered in situations, where noninvasive modalities leave some doubt about the true nature of vascular lesions. This is even more so, when a therapeutic consequence is derived from the diagnostic results, such as in patients with severe internal carotid artery stenosis versus occlusion.

Direct comparison of CTA and DU suggests that the results from CTA compare favorably with ultrasound and that CTA can also reliably detect intracranial stenosis, emboli and aneurysms of a moderate or larger size [29]. However, CTA is superior to DU in the assessment of basilar artery patency in patients with the syndrome of an acute basilar artery ischemia, particularly in patients with distal basilar artery occlusion [30]. The method is noninvasive, safe and independent from the grade of experience of the investigator (in contrast to DU). In a large series of stroke patients none had any immediate adverse reactions or renal damage after administration of the intravenous nonionic iodinated contrast material [31] and a recently presented, not yet published study (International Stroke Conference, Orlando, Fla., 2006) confirmed

these findings. Newer generations of CT scanners allow for lower contrast doses. While older studies reported an increase in the infarct size after administration of ionic contrast material, an experimental study clearly showed that bolus injection of nonionic contrast material does not affect infarct volume or worsen the symptoms of cerebral ischemia [32]. While comparative safety is driven by X-ray exposure and favors MRA over CTA, availability favors the latter.

Besides a few smaller series, to our knowledge there is no direct, large and blinded study to prove equivalence of both modalities regarding the degree of intracranial stenosis. With regard to collaterals the superiority of CTA over MRA has been established by several authors [21, 26, 33]. A smaller study in 28 patients blindly compared CTA and 3-dimensional TOF-MRA with DSA as gold standard for stenosis graduation [34]. CTA revealed a higher sensitivity than that of MRA for intracranial stenosis (98 vs. 70%, $p < 0.001$) and occlusion (100 vs. 87%, $p = 0.02$). CTA had a higher positive predictive value than that of MRA for both stenosis (93 vs. 65%, $p < 0.001$) and occlusion (100 vs. 59%, $p < 0.001$) and a high interoperator reliability. Recent expert reviews also suggest that CTA may be used more and more frequently to substitute invasive DSA, especially in the extracranial vessels such as the internal carotid and vertebral arteries [35].

With regard to extracranial vascular disease, especially the carotid arteries, Patel et al. [36] performed a comparative study of DU, CTA, MRA and DSA in 67 patients. After screening symptomatic patients from a neurovascular clinic with DU, patients with a severe carotid stenosis on the symptomatic side were admitted for DSA and CTA as well as MRA performed during the admission. All images were read independently. While DU, CTA and MRA all agreed with DSA in the diagnosis of operable versus nonoperable disease in about 80% of patients, CTA tended to underestimate, MRA to overestimate and DU to agree most closely with the degree of stenosis as shown by DSA. A comparable diagnostic accuracy was only achieved when two noninvasive tests gave congruent results; in disagreement, the third modality had to additionally be taken into account to make an accurate judgment as compared to DSA. Therefore, no technique on its own is accurate enough to replace DSA.

In conclusion, MRA and CTA are noninvasive diagnostic tests suited for the diagnosis of pathology in the intra- and extracranial vessels. Both share a similar sensitivity and many of their postprocessing features, and both have advantages and disadvantages. Comparative studies suggest that overall CTA may be slightly superior

to MRA for the diagnosis of aneurysms and intra- as well as extracranial stenotic disease. The use of CTA-SI for the assessment of acute stroke patients and their collateral status may be a useful adjunct of CTA not possible to perform with MRA; however, if MRA is incorporated into a multiparametric stroke MRI, there is no need for CTA-SI analysis. Both modalities have their use, and if one renders inconclusive results, the other may give complementary hints and add to a comprehensive workup of the pa-

tient with neurovascular disease. However, DSA will probably remain the gold standard for a long time to come.

Disclosure Statement

The authors declared no conflict of interest in context with this chapter.

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