Multimodal CT imaging for diagnosis, treatment and prognosis in ischemic stroke

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Chapter 8

General discussion

General Discussion

Developments in CT imaging techniques have evolved the assessment of stroke patient over the years. In this thesis we evaluated the value of whole brain dynamic volume CT and extended CT angiography (CTA) in the diagnostic work-up of patients with acute ischemic stroke. These CT techniques enable imaging of the whole brain, obtaining perfusion parameters from CT perfusion (CTP) and information about blood flow through the brain on dynamic CTA. Extended CTA allows imaging to cover the heart until the vertex in one examination. By assessing detailed vascular and tissue imaging characteristics this can aid in diagnosis, treatment decisions, and prognosis in patients with acute ischemic stroke.

Extended CTA for diagnostic work-up and secondary preventive treatment decisions

In chapter 2 and 3 we investigated the value of extended CTA to include the heart and aorta for diagnostic work-up and the value for secondary preventive treatment. In chapter 2 we showed that a cardioembolic source can be identified by CTA screening of the heart and aorta in the immediate diagnostic work-up of patients with TIA or ischemic stroke. Identifying a high-risk cardioembolic source enables early initiation of appropriate secondary preventive medication to prevent stroke recurrence more effectively. Following our study, the "ENCLOSE Study"[1] and a substudy of "Mind the Heart",[2] confirmed our finding that extending the field of view of CTA to include the heart aids in the detection of cardioembolic sources in TIA and stroke patients. These studies found a prevalence of a cardiac thrombus of 12%[1] and 8%[2] and a percentage of 6% when they – similar to our study – excluded patients with previous use of oral anticoagulation (OAC).[1,2] As shown in chapter 3, evaluation of the aortic arch might be less important in the diagnostic work-up, as the presence of severe atherosclerotic lesions was not independently associated with stroke recurrence or patient outcome after 3 months. Also, treatment will not be affected by the identification of an atherosclerotic lesion, since standard secondary preventive treatment is already aimed at treating large artery atherosclerosis.[3]

The "gold standard" for identification of an intracardiac thrombus is transoesophageal echocardiography (TEE).[3] However, cardiac CTA has been shown to be superior to TTE[4] and a good alternative for TEE.[5] Also, in patients with cryptogenic stroke and a suspected cardioembolic source, current American guidelines already suggest the use of either TEE or cardiac CTA for cardiac evaluation for the prevention of secondary stroke or TIA.[3] As TEE is often experienced as a burden by patients because of the invasive nature of this examination, it is plausible that implementing cardiac CTA in the acute phase of stroke assessment will be preferred from a patient perspective.

Whether implementation of the extended imaging strategy is cost-effective in clinical practice remains to be investigated further, for several reasons. First, extending CTA to the heart increases the radiation dose with approximately 2 mSv.[1,4] Although this might have a negligible additional risk for cancer induction in elderly patients,[6,7] this strategy may not be applied on a routine basis, especially younger patients, suspected to have acute ischemic stroke. Second, ECG-gated cardiac CTA as applied in the "Mind the Heart" substudy required an additional 6 minutes of scanning in the acute phase of ischemic stroke,[2] which is a major disadvantage in the diagnostic work up in the setting of acute ischemic stroke. A recent study, however, showed that non-ECG gated cardiac CTA can be implemented in diagnostic imaging with good image quality and without significant delays in time metrics for acute stroke patients.[8] This indicates that small advancements in the imaging protocol will likely result in diminishing time delay, facilitating implementation in routine clinical practice. Finally, the yield of this extended imaging strategy is not negligible but seems relatively low and identification of a high-risk cardioembolic source will only have consequences for patients who are not treated with OACs prior to the ischemic event or based on standard ECG monitoring. To decrease the risk of harm compared to the possible benefit as much as possible, patients should probably be selected for cardiac CTA only if this will have a clinical consequence, e.g., based on their a-priori risk of having a cardioembolic source and not when there is already an indication for a DOAC established.

CTA and CTP for treatment decisions in the acute phase

In chapter 4 we show that whole brain dynamic CTA can be used to assess the collateral filling over time and that detailed collateral assessments – including both time and extent – showed a stronger relationship with final infarct volume at follow-up than on single-phase CTA. Since then, three randomized controlled trials proved EVT to be effective and safe after the standard time window of 6 hours based on clinical and CT imaging characteristics.[9-11] One trial used single-phase CTA and showed that patients with the presence of a collateral circulation still benefit from EVT after the standard time window up to 24 hours.[11] The two other studies used CT perfusion parameters to identify ischemic core volume and select patients with a mismatch between the ischemic lesion and clinical severity of the stroke.[9,10] Assessment of the collateral circulation offers a more pragmatic approach for patient selection as compared with perfusion-based patient selection, because 1) quantification of infarct core and penumbra on CTP varies with thresholds and

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depends on the postprocessing packages used and 2) single-phase CTA is already included on a routine basis in the diagnostic work-up of ischemic stroke patients.[12] A disadvantage of single-phase CTA, however, is that collateral flow assessment may not be accurately determined because of differences in the velocity of collateral filling and variation in image acquisition timing after contrast bolus injection. Moreover, assessment of collateral flow in case of small distal vessels, e.g., a distal M2 occlusion, is challenging because the area supplied is relatively small and varies between patients. Dynamic CTA may be of additional value here, because of the added information that can be obtained by observing blood flow over time. This allows for accurate selection of the peak arterial phase, a precise delineation of a distally occluded territory and it allows to distinguish the presence of retrograde flow to an occluded area from normal antegrade flow.

At the moment, clinical applicability of whole brain dynamic CTA is limited, since it can only be performed in few hospitals in the Netherlands and analysis of images is time consuming. More rapid evaluation might become possible in the near future by implementing machine learning and automatic image segmentation methods. Indeed, this has been suggested by two studies introducing a decision support tool for single-phase CTA images and dynamic CTA images.[13,14] Future studies should further investigate if automatic collateral circulation assessment can be implemented in clinical practice for the selection of patients who might benefit from EVT.

The role of both CTP and dynamic CTA in the selection of patients for EVT will probably change considering recent publications. Three randomized controlled trials were published showing benefit of EVT treatment up to 24 hours of symptom onset, even for patients with a large infarct core.[15-17] These data were pooled in a meta-analysis, together with observational studies on efficacy and safety of EVT for LVO patients with a large infarct core. The pooled results showed that also for patients with a large infarct core, there is still a benefit of EVT and that EVT is relatively safe.[18] However, the randomized controlled trials used different patient selection criteria, based either on ASPECTS measured on non-contrast CT, infarct-core volume measured on CT or MRI perfusion images, or a combination of both[15-17] Although these results will probably lead to further extension of the selection criteria for EVT, the most effective way to use large infarct measurements for patient selection for EVT in this setting remains to be determined.

The advantage of non-contrast CT is its wide availability in all hospitals, however determining the ischemic area with ASPECTS requires training and is subject to large interrater variation.[19] Previously, CTA images were found to be more sensitively in observing ischemic changes with ASPECTS compared with non-contrast CT images.[20,21] Moreover, an exploratory study indicated that novel automated measurements of infarct core on single-phase CTA can be a useful alternative for parameters from CTP and non-contrast CT for determining the infarct core.[22] Considering the advantage of dynamic CTA over CTP and single-phase CTA, dynamic CTA might improve this performance even further.

Although dynamic CTA might be a promising modality in patient selection for EVT, CTP will probably remain useful in the diagnostic workup for acute ischemic stroke. In chapter 5, we used CT perfusion parameters to evaluate stroke progression in patients with and without migraine and did not identify a difference in progression in these patients. Because CTP assesses the hemodynamics of the brain parenchyma instead of tissue characteristics, it can distinguish patients in whom the symptoms are caused by an occluded vessel from those that suffer from a stroke mimic. Specific perfusion patterns can lead to the diagnosis of certain stroke mimics. For example, epileptic seizures can present as brain parenchyma with decreases in CBV and CBF, together with an increased Tmax, that do not follow the boundaries of vascular territories that match the symptoms.[23] Also migraine with aura is a relatively common stroke mimic that can present on CTP as areas of focal hypoperfusion, defined by an MTT increase or a CBF decrease compared with the contralateral hemisphere, that involve adjacent vascular territories.[24] When CTP is included in the imaging assessment of suspected stroke patients, stroke mimics could be more easily discerned from true ischemic stroke patients. Finally, CTP facilitates identification of an occlusion of a more distally occluded vessel. The affected area is usually clearly shown on perfusion imaging, while the occluded vessel is often quite difficult to detect on CTA because of the small size.[25]

In chapter 6 we showed that extracranial vascular characteristics are associated with the duration of the EVT procedure; in chapter 7 we showed that extracranial vascular characteristics can be used to some extent to predict failure of the transfemoral approach. The identified characteristics of the supra-aortic and carotid arteries that complicate the EVT procedure can provide important information to aid decision making in patients in which the benefit of EVT is uncertain or unknown, e.g., in frail patients. Although not investigated in this thesis, a challenging vascular anatomy might be of similar value to predict the risk of procedural complications. A higher complication risk has been shown for varying baseline patient characteristics, such as patients' sex, prior antiplatelet use, systolic blood pressure and a more distal occlusion location, and for procedural duration.[26,27] However, tortuosity or elongation of the vasculature might also be related to the risk of complications on top of these baseline characteristics. For example, maneuvering of the catheters can become problematic within tortuous vessels, with subsequent increased risk for vessel perforation.

Some have suggested that an alternative approach, e.g. transradial access, might be the preferred route in case of severe arterial elongation or severe atherosclerotic changes.[28] However, this hypothesis is not supported by recent results, since a study showed that performance of an alternative route is related to a worse functional outcome in the MR CLEAN Registry population.[29] Whether an alternative route benefits patients in whom the transfemoral approach failed after one or more attempts should be further investigated.

Future perspectives

The advances in CT imaging techniques result in the identification of vascular and hemodynamic parameters that prove to be useful for patient diagnosis and treatment selection, and thereby improve patient outcome after ischemic stroke. The increasing amount of information support the neurologist and interventionalist to decide on optimal patient management. However, acquisition, analysis and interpretation of these data is time-consuming, and time is of major importance to preserve salvageable brain parenchyma and optimize patient recovery. Further research should therefore focus on strategies to reduce image-acquisition and image-analysis time, especially in the acute phase of ischemic stroke.

Automated image analysis holds promise to improve patient selection by having the potential to quickly identify ischemic core and penumbra, collateral circulation on dynamic CTA and vascular characteristics that can increase the technical difficulty of the EVT procedure. In the field of radiology, automated methods for image processing and analysis with deep learning techniques are increasingly used in research settings to improve efficiency and support decision-making of the (interventional) radiologist. Often, implementation of artificial intelligence in clinical practice is lacking, indicating that efforts should be undertaken to incorporate these techniques into the every-day workflow in comprehensive stroke centers.[30] In addition, advancements in patient logistics prior to hospitalization can lead to further improvement of patient treatment. This can be achieved by using prehospital triage where paramedics score a number of neurological deficits originating from the NIHSS directly in the ambulance, and use this to transport patients with likely LVO stroke directly to a comprehensive stroke center.[31,32]

Recommendations from the American Heart Association/American Stroke Association indicate the need for regional plans for acute stroke care, including identification of patients with suspected LVO stroke based on validated stroke severity scores.[33] In the Netherlands, regional implementation of prehospital triage tool should also be considered.[34] Finally, with the developments of mobile stroke units, i.e., specialized ambulances that are equipped with CT scanners, it is possible to diagnose ischemic stroke and directly administer thrombolysis or improve triage for EVT. Similar results could be achieved with the developments for portable low-field MRI scanners.[35] The use of mobile stroke units have been associated with an increased chance of excellent patient outcome after 90 days.[36] Whether this is beneficial for ischemic stroke patients in regional settings in the Netherlands is currently being investigated.

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