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

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Chapter 1

General introduction

Ischemic Stroke

Stroke is a common neurological disorder and globally the second largest cause of death and disability.[1] Although the mortality rate has decreased over the past 25 years, the burden of stroke remains high and will likely increase with the growing number of people surviving after stroke.[1,2] In 2020 in the Netherlands, around 38.500 people experienced a stroke and around 354.000 patients lived with the consequences.[3]

Stroke is characterized by a sudden onset of focal neurological deficits that are caused by ischemia or hemorrhage in the central nervous system.[4] The majority (84%) of patients with stroke has an ischemic stroke.[1] Ischemic stroke is caused by an occlusion of a cerebral artery that obstructs or reduces blood flow to the relevant draining brain area. When the occlusion and accompanying neurological deficits are temporary and resolve within 24 hours without permanent cerebral damage, the patient is diagnosed with a transient ischemic attack (TIA).[5] In contrast with ischemic stroke or TIA, intracerebral hemorrhage is not caused by an obstruction but by a rupture of a cerebral artery.

Ischemic stroke can have different causes. For research purposes, the TOAST criteria were developed which classify these causes into five subtypes; large-artery atherosclerosis, a cardioembolism, small vessel disease, other etiologies such as carotid dissection, and unknown etiology.[6] Large-artery atherosclerosis is the cause of ischemic stroke in about a quarter of patients and occurs due to an atherosclerotic lesion obstructing blood flow or an embolus that originates from rupture of an atherosclerotic plaque in a more proximal cervical artery.[7] An embolism originating from the heart or the aorta, i.e., a cardioembolism, is another common cause of stroke and is identified in a quarter to one-fifth of patients.[7] Approximately seventy percent of large artery occlusions resulting in acute ischemic stroke affect the anterior circulation and occlusions occur in either the internal carotid arteries, middle cerebral arteries, or anterior cerebral arteries.[8] In the remaining thirty precent the posterior circulation is affected. Other important causes of ischemic stroke are not related to larger arteries but to small vessel disease leading to intracranial atherosclerosis and obstruction of smaller perforating arteries.[7] In addition, some patients have other rare causes of stroke such as a cervical dissection or vasculitis.[7] In studies applying the TOAST criteria to classify stroke etiology, about a quarter of patients have an undetermined cause of stroke that might be explained by limited clinical assessment or by the presence of multiple possible causes. As these subtypes have different etiologies, the risk of recurrent stroke after an initial event is different. Common risk factors for stroke are hypertension, smoking, diabetes, hyperlipidemia,

and other modifiable atherosclerotic risk factors.[9] In addition, there are risk factors that increase the risk of stroke specifically in women. These include pregnancy related complications and migraine as migraine occurs three times more often in women than in men. Although a large proportion of patients with ischemic stroke and migraine are women, increased risk of stroke occurs with migraine in both genders. Meta-analyses indicated that especially migraine with aura, increases the risk of ischemic stroke. Patients with migraine with aura have approximately two times higher risk of stroke whereas this risk is not or only moderately increased in patients with migraine without aura.[10,11] Patients with migraine might also have a relatively poor clinical outcome after stroke as they might be more susceptible for a phenomena called cortical spreading depolarizations (CSDs).[12] CSDs are slow waves of depolarization of neuronal and glial cells followed by hyperpolarization, that spread through the brain parenchyma and are the presumed underlying mechanism of a migraine aura. However, CSDs are also observed in patients without migraine in the case of acute brain damage such as ischemic stroke and are thought to aggravate cerebral ischemia.[13,14] It is unknown whether migraine patients have a faster stroke progression because of their presumed higher susceptibility of CSDs.

Over the last years, major advances have been made in the treatment of patients with acute ischemic stroke. In the nineties, intravenous thrombolysis (IVT) with tissue plasminogen activator was shown to improve clinical outcome in patients who presented within 3 hours after symptom onset.[15] Tissue plasminogen activator is administered to the venous circulation via the arm and aims to dissolve the arterial thrombus and restore reperfusion of the affected brain area. The time window for IVT was extended to 4,5 hours after a study in 2009 showed that there was still an added benefit of improved clinical outcome over the harm by a small increased risk of intracerebral hemorrhage.[16] However, IVT has limited effectivity for large vessel occlusion (LVO) that occurs in approximately one-third of acute ischemic stroke patients.[17] In 2015, the MR CLEAN trial in the Netherlands was the first trial that showed that mechanical removal of an LVO via access to the femoral artery, e.g. endovascular treatment (EVT), was effective in the anterior circulation within 6 hours of symptom onset.[18] This finding was subsequently confirmed by several other trials.[19-22] More recently, the time windows for which IVT and EVT treatment are effective, have been extended even further based on imaging characteristics.[23,24]

Computed Tomography (CT) imaging for diagnosis and treatment decisions

In suspected acute stroke patients, the diagnosis of stroke is established by neurological assessments and imaging of the brain. In the emergency room, CT scanners are available and most practical for acute imaging. Previously, non-contrast CT (NCCT) was the only available imaging modality of the brain. Acute imaging with NCCT is mainly used to rule out intracerebral hemorrhage, since signs of acute ischemic stroke are often only subtle or not observed.[25] However, NCCT is not able to identify patients eligible for EVT, as it does not visualize the obstructing arterial occlusion. This requires CT Angiography (CTA), where iodinated contrast material is intravenously injected and scanning of the brain is performed when the contrast bolus arrives in the arterial circulation.[26,27] In this arterial phase, the cerebral arteries are visualized by a hyperdense signal from the contrast material, while venous filling is not observed.

In more recent years, sophisticated CT techniques became available that enable detection of cerebral ischemia in the acute setting. Especially, CT Perfusion (CTP) images provide important hemodynamic information on cerebral perfusion by repeating CT acquisitions throughout the arterial and venous phase. With CTP source, four perfusion parameters are computed and shown on quantitative maps: cerebral blood volume (CBV), cerebral blood flow (CBF), mean transit time (MTT) and time to peak (TTP). The ischemic area is identified by observing an increased MTT and TTP and a decreased CBF when compared to the healthy hemisphere. The area where CBV is also decreased, is called the infarct core, and indicates brain tissue that is already permanently damaged. The area where CBV is normal represents the penumbra and is tissue that is still salvageable when blood flow is restored.[28]

With the evolving CT techniques, increasingly more CT imaging characteristics are identified that can help to determine stroke etiology, tailor treatment opportunities, and predict outcome. CTP is of value in selecting patients who might still benefit from reperfusion therapies outside the conventional treatment windows of 4.5 (IVT) and 6 hours (EVT).[23,24] CTA can provide information about the collateral circulation, through which blood from adjacent arterial circulations travels via leptomeningeal anastomoses or pial collaterals to the affected brain area, possibly increasing the duration that brain tissue is salvageable.[29] This information is important as it may help in identifying patients with LVO who could still benefit from treatment outside the window of 6 hours.[30] Collateral information can be obtained from scanning in the arterial phase only. However, with multi-phase scanning, the arterial filling in

the brain can be observed in greater detail.[31] Multi-phase scanning provides more information about the extent and timing of collateral filling and is possibly able to better predict the volume of the infarcted brain parenchyma at follow-up.

In the Netherlands, current clinical practice in patients suspected of acute stroke includes NCCT of the brain and CT Angiography (CTA) of the brain and neck. By expanding CTA to the neck region, this can further aid in determining the etiology of TIA and ischemic stroke. By scanning the cervical arteries, the presence of atherosclerotic plaques or a dissection can be identified. Currently, it is possible to scan even further "down" and include the heart, the ascending aorta, and the aortic arch in one scan protocol. In many stroke patients the cause of the stroke remains unclear and part of this might be explained by missing cardiac or embolic sources of atherosclerotic lesions in the aorta.[32] By visualizing the heart and aorta with CTA, additional embolic sources can be identified directly with the initial imaging session.[33] It is, however, unclear how often a cardiac thrombus or aortic atherosclerotic lesion is found and what the clinical consequences are of identifying the latter for secondary preventive management.

Finally, scanning both the intracranial and extracranial circulation provides information about vascular characteristics that may increase the technical difficulty of the EVT procedure. The presence of vascular tortuosity or severe extracranial atherosclerosis might hamper access to the intracranial occlusion with the guiding catheter. Until now the vascular factors that predict a successful approach are lacking.

Outline of this thesis

The aim of this thesis was to identify new CT imaging characteristics to provide more insight into the diagnosis, prognosis, and treatment selection in patients with TIA or acute ischemic stroke.

In **chapter 2** we investigated the added value of performing CTA of the heart and aorta in the diagnostic workup of TIA and ischemic stroke. By identifying cardioembolic and large artery atherosclerotic as a possible cause of the ischemic event we evaluated the yield of CTA of the heart and aorta and the clinical implications for therapeutic management.

The increasing amount of information that is available from sophisticated and more extensive CT scanning protocols might be useful for prognosis in patients with acute ischemic stroke due to a large anterior circulation occlusion. In **chapter 3** we assessed whether dynamic CTA could provide additional information about the

collateral circulation, compared with more commonly performed single-phase CTA, and how this relates to the infarct volume at follow-up. In **chapter 4** and **chapter 5**, we aimed to identify extracranial vascular characteristics that have prognostic value for EVT outcome measures in patients included in the MR CLEAN Registry. Vascular characteristics, such as tortuosity and severe atherosclerosis can increase the technical difficulty of EVT and in some cases even prevent the catheter from reaching the occlusion site via the transfemoral approach. In **chapter 4**, we aimed to identify extracranial vascular characteristics that are associated with procedural duration and revascularization success after EVT. In **chapter 5**, we aimed to develop and validate a prediction model, with extracranial vascular characteristics, for the risk of a failed transfemoral approach.

CTA and CTP characteristics might also improve the prognosis of clinical outcome and mortality in patients with acute ischemic stroke. In **chapter 6**, we aimed to investigate the presence and characteristics of aorta atherosclerosis and associate the presence of atherosclerotic lesions on CTA with recurrent stroke and clinical outcome. In **chapter 7,** we investigated whether patients with migraine, because of their possible increased susceptibility for CSDs, had more severe stroke progression as observed on CTA and CTP, and whether this resulted in less favorable clinical outcome after EVT.

Finally, the findings of this thesis are summarized and discussed, together with the implications for future research, in **chapter 8**.

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