Chapter 1

General introduction
GENERAL INTRODUCTION

Stroke
Stroke is a medical condition characterized by the sudden loss of brain functions. With a worldwide yearly incidence of 1.12%, stroke contributes to 4.9% of all deaths.¹ It is furthermore the second largest cause of disability in people older than 50 years.² There are two types of strokes: ischemic and hemorrhagic stroke. Approximately 80% of all strokes are ischemic, and over 2.7 million people die from it each year. Hemorrhagic stroke accounts for 20%, and contributes to 51% of all deaths from stroke.¹

Ischemic stroke refers to stroke that caused by the narrowing or blockage of a blood vessel supplying the brain. It is usually classified in five subtypes according to TOAST: larger-artery atherosclerosis; cardio embolism; small-vessel occlusion (lacunar infarcts); other determined etiology; and cryptogenic stroke.³ Fifteen percent of the ischemic strokes are caused by atherosclerosis in the carotid artery. Carotid artery disease (CAD) causes ischemia through either hypoperfusion or thrombo-emboli.³ Cardio embolism contributes to 27% ischemic stroke and is mainly attributed to atrial fibrillation or rheumatic heart disease.³ Small vessel occlusion, which contributes to almost 23% ischemic stroke, refers to small subcortical stroke lesion with a diameter smaller than 1.5 cm.³ The remaining 2.3% of ischemic stroke for other etiology are from more divers causes, such as arterial dissection, Moyamoya disease, and sickle cell disease. A large portion however is from unknown or obscure origin, and is referred to as cryptogenic stroke. This subgroup contributes to 34.7% of ischemic stroke, and half of it is though to be caused by emboli from an undetermined source.³

Hemorrhagic stroke refers to stroke that is caused by the rupture of a blood vessel with subsequent intracranial bleeding. It is less common than ischemic stroke, and has fewer chance of recurrence compared to ischemic stroke.¹³ However, hemorrhagic stroke leads to severer outcomes, its long term mortality rate is approximately 42-68% vs 23% in cerebral infarction.²⁻⁹ There are two major subtypes of hemorrhagic stroke: intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH). ‘Spontaneous’ is usually added to ICH and SAH to differentiate from traumatic hemorrhage. ICH contributes to 10-20% of all stroke, while only 5% stroke is SAH.³,¹⁰ Unlike other types of stroke, SAH occurs at a relatively young age (mean 55 years¹¹ vs. 74 years in ICH¹²). Its mortality is up to 32-67%. A large portion, 12.4% of SAH patient, dies before reaching the hospital. Among those survivors, more than 20% is disabled.¹³⁻¹⁵ A non-traumatic SAH is usually caused by a rupture of an intracranial aneurysm (IA). These aneurysmal SAH’s are prone to rebleeding, especially within the first week after the ictus. The incidence of aneurysmal SAH is 8/100.000. The prevalence of intracranial aneurysm is much higher: 3/100 persons do have an intracranial aneurysm. However, most incidental intracranial aneurysm does not rupture during lifetime.

Cerebral hemodynamics
The concept of cerebral hemodynamics differs among clinicians and neuroscientist. For an intensivist and cardiologist, hemodynamics means a measurement of the efficiency and efficacy of the cardiovascular system to provide oxygen to the tissues, e.g., pulmonary artery wedge pressure, mixed venous oxygen saturation, central venous pressure. For a neurologist and radiologist, it usually refers to hemodynamic parameters which can be measured, such as cerebral blood flow, cerebral blood volume, mean transit time, time to peak. The word hemodynamics is a combination of hemo- and -dynamics. In the aspect of physics and engineering, hemodynamics is a special type of hydrodynamics, where the liquid is blood. It describes the physical laws that govern the flow of blood in the blood vessels.

The human brain has a high energy consumption, with barely no capacity to store energy. It requires steady and continuous blood flow to deliver oxygen and nutrients to sustain its metabolism. In a normal state, approximately 750 milliliters blood per minute is pumped into the brain through afferent arteries. When compromised, either through an acute block of blood flow or for instance chronic CAD, reduced blood flow will result in impaired brain function.¹⁶,¹⁷

Cerebral hemodynamics encompasses however not only the delivery of nutrient at brain tissue level, but also the flow of blood through the afferent vessels and the interaction with the vessel wall, which in term can also lead to cerebrovascular diseases. Endothelial cells and smooth muscle cells respond to local hemodynamic changes, such as increased wall shear stress (WSS), through sophisticated mechanobiological mechanisms, consequently results in the change of the cerebral blood vessel wall.¹⁸⁻²⁴ In observational studies, WSS is found not only related to carotid artery plaque formation and rupture,²⁵⁻²⁶ but also correlated with IA formation, growth and rupture.²¹,²⁷,²⁸
Circle of Willis
The Circle of Willis (CoW) is a unique ring-shape arterial structure located at the base of brain. The CoW redistributes cerebral blood flow from basilar artery (BA) and bilateral internal carotid artery (ICA) into six efferent arteries: bilateral anterior cerebral artery (ACA), bilateral middle cerebral artery (MCA) and bilateral posterior cerebral artery (PCA). The left and right part of the CoW are connected via the anterior communicating artery (AComA). The blood flow from ICA and BA is bridged by bilateral posterior communicating artery (PComA). As such, the CoW is the primary collateral pathway to ensure balanced blood perfusion of the whole brain. Figure 1 shows its simplified schematic diagram.

![Figure 1. Simplified schematic diagram of circle of Willis](image)

The CoW is subject to significant morphological variations. The prevalence of CoW variations in the general population is 68% ± 14%. There are many expressions of variation of the CoW. PComA hypoplasia and aplasia is a common variation type (unilateral hypoplasia/ aplasia exists in 19.45% ± 8.63% of the population, while the prevalence of bilateral PComA hypoplasia / aplasia is present in 2.83 ± 14.58%).

The CoW has a pivotal role in the correlation between cerebral hemodynamics and stroke. It is observed that the variation of CoW is associated with increased risk of ischemic stroke. People with PComA variation have a high risk of ipsilateral cerebral infarction, especially in the thalamus. Fetal-type CoW has been identified as an independent risk factor of posterior circulation ischemia. A study with territorial arterial spin-labeling (t-ASL) magnetic resonance (MR) imaging reported that in fetal-type CoW 100% of the thalamus was on the perfusion territory of the ipsilateral ICA, while without fetal-type only 49% of the thalamus was fed by ipsilateral ICA. The various CoW configurations have been found to lead to differences in the distribution of blood throughout the brain-feeding arteries, however at brain tissue level this does not lead to differences in CBF.

The CoW is also correlated with hemorrhagic stroke. Approximately 85% of intracranial aneurysms (IAs) are situated at the CoW, most commonly at the bifurcations and branches of the large arteries. The incidence of CoW variation in IA-patients is significantly higher than in the general population. An asymmetric primary ACA (A1 segment) is correlated with a high risk of AComA aneurysm.

Numerical model
Numerical model is a technique to tackle complex hemodynamics by computational simulation of vasculature scenarios. Numerical modelling of cerebral blood flow is widely applied to investigate complex vasculature scenarios. It has became an alternative method to understand the relationship between hemodynamics and cerebrovascular disease. Like any other dynamic fluid system, the blood flow in the vascular system obeys to the laws of mass conservation, momentum conservation, and energy conservation. Depending on the level of simplification of the arterial network system, a numerical model can be categorized in to zero-, one- and three-dimensional models.

Zero-dimensional (0D) models, also known as lumped parameter models, simplify each arterial segment as one hemodynamic element, assuming a uniform distribution of the fundamental variables (pressure, flow, and volume) within each element (artery segment) at any instant in time. The 0D model is originally derived from electrical circuits, where current represents blood flow rate and voltage represents blood pressure. As such, the resistances, capacitors, and inductors represent the viscous dissipation inside the vessels, the volume compliance of the vessels, and the inertia of blood. Accordingly, the arterial network can be described with a system of ordinary differential equations. The main advantage of 0D models is its simplicity. It can be easily solved with least computational cost, but provides valuable insight in the global behavior of blood flow in the arterial tree, such as the compensation mechanisms in the CoW. The 0D model also serves as a non-reflection boundary in the 1D model.
The one-dimensional (1D) model can be considered as complicated 0D model, de facto built up as a series of 0D compartments. Mathematically, the principal difference between 0D model and 1D model is that 0D model omits the (nonlinear) convective acceleration term in the Navier–Stokes equations, which can be regarded as the first order discretization of 1D systems. In addition, the 1D model can take into account complex flow regimes of the blood (laminar or turbulent flow). Therefore, 1D models are widely employed to study pulse wave transmission dynamics in the arterial network system, such as the effects of the anatomical variations and occlusions.

The three-dimensional (3D) model, commonly refers to as computational fluid dynamics (CFD) model, is governed by 3D Navier–Stokes equations with various turbulence models describing the viscous blood flow. The 3D model reconstructs the detailed morphology of an arterial network to investigate the patient-specific cerebral hemodynamics with medical imaging. The advantage of a 3D model is that it can reveal the comprehensive pressure and flow distribution in a certain segment of a vessel network. The 3D model has been widely used to simulate local hemodynamics at specific arterial sites, particular in IAs and its parent artery. In addition to the common output of 0D/1D models (e.g. blood flow, rate, and pressure), 3D models derive advanced hemodynamic indices in the context of fluid mechanics (e.g. WSS and OSI), which are believed to be associated with relevant cerebrovascular diseases. The disadvantage of the 3D model is that it requires a precise 3D geometry as model input and that it has greater demands on computational resource. Both aspects have largely limited its application.

In order to overcome the limitation of the 3D model, development of hybrid hemodynamic models (combined 0D-1D-3D models) became popular in the last decade. In hybrid models, the 0D model offers a non-reflection boundary at each terminal branch, the 1D model describes the blood pressure and flow pulsations propagating through the arterial tree, and the obtained waveform by the 1D model is used as an inlet boundary of the 3D model. The main benefit of the hybrid models is that it can describe the complex interactions between global scales (arterial network, such as CoW) and local scales (specific arterial sites, such as IAs), while balancing the computational demands.

Although numerical models are based on the rigorous derivation of the fundamental governing equations of fluid dynamics, it is highly sensitive to the model input, particularly inlet/outlet conditions. Therefore, numerical studies have mainly concentrated on hemodynamic mechanisms related to development of cerebrovascular disease. Since numerical models can theoretically provide valuable hemodynamic information in clinical patients, many attempts have been made to develop patient-specific cerebral blood flow models. Nevertheless, there is currently no numerical model that can be used in clinical practice. Patient-specific modelling is a challenging task, because the required input includes not only patient-specific geometry, but also (more importantly) the appropriate physiological parameters per patient. Such parameters may be difficult to be obtained in clinical practice. In addition, an important factor has often been overlooked: the clinician, as key stakeholder of cerebral hemodynamic research and end-user of numerical models, commonly lacks awareness of the role of hemodynamics. Since the present-day clinician prefers to use medical indices to aid clinical decision making, it is of great importance to translate the numerical model and its result interpretation into the clinicians’ common language, i.e. hemodynamic indices.

**Carotid artery disease**

The global prevalence of CAD among the population aged 30-79 years is 1.5%. A healthy lifestyle and pharmacological treatment are commonly prescribed to stabilize the atherosclerotic plaque, prevent embolism, and to stop or delay the progression of stenosis. Carotid endarterectomy (CEA) or carotid artery stenting (CAS) can furthermore repair the compromised cerebral perfusion and remove the source of embolus in case of a vulnerable plaque. Identifying plaque vulnerability can not only help classify the underlying pathophysiology of stroke, but also help avoid perioperative thromboemboli during stenting. Plaque vulnerability usually is evaluated by ultrasound, CT, or MR imaging. Differentiating infarcts caused by emboli or compromised cerebral perfusion can help to identify plaque stability and is also important for treatment strategy. Such differentiation diagnosis is generally made based on infarction location and the known perfusion territory of major cerebral arteries. However, CAD can trigger a wide variability of perfusion territories of brain-feeding arteries. Recently, perfusion image from t-ASL MR showed improved accuracy for identifying watershed zone and the perfusion territory of potentially culprit arteries.

**Prognostic factors in aneurysmal SAH**

Ruptured IAs are responsible for 85% of spontaneous SAH. Hypertension, alcohol abuse, smoking, female gender, age, previous SAH, and Japanese or Finnish ethnic background are well-known risk factors for poor clinical...
outcomes, while regular exercise shows a weak protective effect.\textsuperscript{76,77} As such, muscle mass has recently been proved to correlate with SAH outcome, while high protein intake after SAH reduced the rate of muscle atrophy in Japanese cohort.\textsuperscript{78–80} This indicates that a healthy lifestyle, muscle protein reserve capacity, and high protein intake after onset might help to improve SAH outcome. Whether muscle mass is directly associated with SAH outcome in other population was not further investigated yet and thus of interest for this thesis.

**Sarcopenia** is a condition characterized by loss of skeletal muscle, both of structural mass and function. The European Working Group on Sarcopenia in Older People (EWGSOP2) defined it as a progressive and generalized skeletal muscle disorder that is associated with increased likelihood of adverse outcomes including falls, fractures, physical disability, and mortality. The operational definition is the presence of low muscle strength. If there is also low muscle quality or quantity, in combination with low physical performance, sarcopenia is considered severe.\textsuperscript{81} Sarcopenia was originally considered to impair physical performance and survival in geriatric populations.\textsuperscript{82–84} In overlap with frailty, it was later used as predictor for poor prognosis of chronic or consumptive diseases in the hospital.\textsuperscript{85–88} Sarcopenia reflects the reserve capacity of muscle proteins, it can also predict outcome after major surgery.\textsuperscript{89,90} Inconsistent definition of the terminology ‘sarcopenia’ should be noticed, especially in hospitalized patients, where sarcopenia was usually referred to CT-diagnosed skeletal muscle decrease. Skeletal muscle atrophy is adapted in this thesis to describe such conditions to avoid confusion with the EWGSOP2 defined sarcopenia.

**Myosteatosis** is defined as the accumulation of intramuscular and intermuscular fat.\textsuperscript{91,92} It is another index of muscle alterations, reflecting muscle quality. Myosteatosis is an identical association with increased morbidity and mortality in both community and hospital population.\textsuperscript{93} Fat-free muscle mass reflects the reserve capacity of muscle proteins, is associated with occurrence of complications.\textsuperscript{94–96} Preoperative fat-free muscle mass was found to be negatively associated with in-hospital complications.\textsuperscript{97}

**Outline of this thesis**

The general aims of this thesis were to study novel methods for investigating the hemodynamics within the CoW and explore prognostic factors in aSAH. CAD and IA are two major causes of stroke and their pathologies are both highly correlated with the configuration of CoW. New methods are needed to distinguish the CoW hemodynamics under different configurations, subsequently assistant to explore the underlying effect of CoW hemodynamics in cerebral blood perfusion in CAD from compensatory to decompensated, and in the pathology of IA development (i.e., formation, growth and rupture). If those impacts can be quantified, these new approaches can be expected for personalized management in CAD and IA. Many risk factors for the outcome of aneurysmal SAH have been identified, emphasizing modifiable risk factors contributes to the reduced mortality in the recent decades. However, the remaining mortality and morbidity is still a heavy burden. Exploring other modifiable risk factors is of great clinically significance.

In **Chapter 2**, the distribution of blood flow based on the configuration of the CoW is studied, as well as the stenosis grade of the carotid artery. In **Chapter 3**, a numerical model is introduced to reproduce the distribution of cerebral blood flow, and also to quantify hemodynamic parameters, e.g., flow rate and flow velocity. **Chapter 4** validates this model in patients with SAH. In **Chapter 5**, a systemativ review is performed, in which hemodynamic parameters are identified from other numerical models on the correlation of CoW configuration and the development of IAs. A search of other modifiable prognostic markers that may influence the outcome of SAH, whether CT quantitative measurements of muscle modifications are associated with the neurological outcome and long-term mortality of SAH patient is investigated in **Chapter 6**. The thesis is concluded with a general discussion in **Chapter 7**.
REFERENCES


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