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### Delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage : the role of coagulation and fibrinolysis

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# Chapter 1

Introduction



## **Delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage**

Aneurysmal subarachnoid hemorrhage (SAH) is a life-threatening disease. Patients who survive the initial hemorrhage are at risk to develop complications, especially within the first two weeks. The most feared complication after SAH used to be rebleeding of the aneurysm, which is related to a high risk of morbidity and mortality.<sup>1</sup> However, now that aneurysms are mostly treated soon after the hemorrhage, fewer patients have rebleeding. One of the most feared complications nowadays is delayed cerebral ischemia (DCI) which occurs in about 30% of patients surviving the ictus of the hemorrhage.<sup>1,2</sup> DCI is sometimes reversible, but may also progress to cerebral infarction, which is associated with an increased risk of severe disability and death.<sup>1,3</sup>

The pathogenesis of DCI remains unknown. Clinical signs of DCI are often attributed to the presence of vasospasm, which can be observed on angiography, or indirectly by increased blood flow velocities on transcranial Doppler examination. However, evidence is accumulating that DCI cannot only be explained by vasospasm demonstrated by angiography. In the last decades many clinical trials were performed in search of a drug to prevent and treat DCI. Despite profound research efforts, it is disappointing that only little progress has been made. However, most of these studies focused on the prevention and treatment of angiographically demonstrated vasospasm, which might actually not be the (main) cause of DCI.

### **The basis of the concept vasospasm**

In 1866, the first microscopical observations of the cerebral cortex were published, including the observation that cerebral blood vessels constrict after electrical stimulation.<sup>4</sup> Hereafter, this observation of vasoconstriction has been described several times, not only after electrical stimulation, but also after mechanical stimulation and after application of drugs such as adrenalin.<sup>5-7</sup> In 1942 it was observed that cerebral blood flow was impaired in brain areas with arterial vasoconstriction.<sup>7</sup> The first link with aneurysmal SAH was made in 1949.<sup>8</sup> In an autopsy study, cerebral infarctions were observed in 3 out of 10 SAH patients. For the first time it was speculated that arterial spasm was a cause for cerebral infarction after SAH.<sup>8</sup> Two years later, in 1951, the relation between vasospasm and DCI was taken for granted after the presence of vasospasm had been demonstrated in a small group of SAH patients.<sup>9</sup> Later several studies indeed showed an association between the presence of angiographic vasospasm and DCI.<sup>3,10,11</sup> It was hypothesized that arteries with vasospasm result in blood stasis followed by ischemia and cerebral infarction. The Hagen-Poiseuille equation, which shows that the total volume flowing through a tube varies based on the fourth power of a vessel's radius, was considered to support this hypothesis. Although several studies found an association between angiographically demonstrated vasospasm and DCI, a causal relation has never been proven.

### **Doubts about vasospasm as the only explanation for delayed cerebral ischemia**

In the last 25 years evidence is accumulating that DCI cannot be fully attributed to angiographically demonstrated vasospasm. In 1984 a randomized controlled trial was

published in which the effect of the antifibrinolytic agent tranexamic acid on the incidence of rebleeding and outcome after aneurysmal SAH had been investigated. The results of this study indeed showed a clinically significant reduced incidence of rebleeding after SAH, however no beneficial effect on outcome was observed as a result of an increased incidence of DCI.<sup>12</sup> Later, a similar study was performed but now in patients who were treated with the calcium antagonist nimodipine, which has a beneficial effect on the occurrence of DCI.<sup>13</sup> This study also showed a reduced rebleeding rate, but again no effect on outcome was observed as a result of impeded recovery from DCI. Thus, although both studies showed an important reduction in the incidence of rebleeding after SAH, the results were disappointing since outcome did not improve. From a pathophysiological point of view the results were interesting, since for the first time it was shown that the incidence of and recovery from DCI can be influenced by drugs that impair fibrinolytic activity. This observation implied that the fibrinolytic system plays an important role in the pathogenesis of DCI.

In the 1980's, several studies investigated the effect of the dihydropyridine calcium antagonist nimodipine on the prevention of DCI. The results of these studies showed that nimodipine has a beneficial effect on DCI and poor outcome.<sup>14</sup> The working mechanism of nimodipine was first considered to result from relaxation of the muscular vessel wall, hereby preventing and diminishing vasospasm, and subsequently decreasing the incidence of DCI. However, a systematic review showed that nimodipine reduces the incidence of DCI without a clear effect on vasospasm.<sup>15</sup> Later, it was observed that nimodipine increases fibrinolytic activity in patients with aneurysmal SAH.<sup>16</sup> Nimodipine still is the only effective drug for the prevention of DCI after SAH.

Presently, endothelin receptor antagonists are investigated extensively as a potential new drug to prevent DCI. Endothelin is a peptide secreted by the vascular endothelium with strong vasoconstrictive properties. Recently, a large double-blind, placebo-controlled phase II study investigating the effect of the endothelin receptor antagonist clazosentan in patients with aneurysmal SAH for the first time showed a 65% relative risk reduction (95% confidence interval 47%-78%) of angiographically demonstrated vasospasm in the group of patients treated with the highest dose of clazosentan (15 mg/h), however without an effect on the clinically more important predefined combined morbidity and mortality endpoint.<sup>17</sup> These results add to an accumulating body of clinical data that cast doubt on the causal relation between angiographically demonstrated vasospasm and DCI. Therefore, it was suggested that the pathogenesis of DCI should be reconsidered, and that angiographically demonstrated vasospasm might be an epiphenomenon.<sup>18,19</sup>

Although nowadays many clinicians assume that vasospasm is the cause of DCI, it is a fact that not all patients with vasospasm develop clinical signs of DCI and, conversely, that not all patients with DCI have vasospasm. Therefore, alternative explanations of DCI have been sought, such as microvascular spasm, cortical spreading ischemia, and microthrombosis.<sup>20-23</sup> Since evidence from clinical and autopsy studies is accumulating that microthrombosis is

involved in the pathogenesis of DCI, in this thesis the role of microthrombosis is further investigated.

## **Aim and outlines of this thesis**

The aim of the present thesis is to gain better insight into the pathogenesis and treatment options of DCI. A better understanding of the pathogenesis of DCI will increase the chance of success in the search for drugs to prevent and treat this complication.

### ***Part 1. Pathogenesis of delayed cerebral ischemia***

The first part of this thesis focuses on the pathogenesis of DCI. In **Chapter 2** a study is described which shows that DCI cannot only be explained by vasospasm, but that microthrombosis plays an important role. The purpose of **Chapter 3** was to investigate whether a genetic predisposition for impaired fibrinolytic activity, namely the 4G-allele in the plasminogen activator inhibitor (PAI)-1 gene, is associated with an increased incidence of DCI. **Chapter 4** describes a study in which was investigated whether increased cortisol levels early after SAH are associated with the occurrence of DCI. Cortisol is a glucocorticoid hormone which is secreted during stress. Physiological reactions of increased cortisol secretion include an increase of glucose levels, blood pressure, and endothelium dysfunction.<sup>24</sup> Since in patients with aneurysmal SAH hyperglycemia, hypertension, and endothelium dysfunction are associated with DCI, the stress response might play a role in the development of DCI.<sup>11,25,26</sup> In **Chapter 5** a study is presented with serial measurements of von Willebrand factor and ADAMTS13 in patients with and without DCI after aneurysmal SAH. ADAMTS13 is a protease that cleaves ultralarge von Willebrand factor multimers thereby decreasing thrombotic potential. In patients with thrombotic thrombocytopenic purpura (TTP) an ADAMTS13 deficiency results in microthrombotic complications. Since microthrombosis might play an important role in the pathogenesis of DCI, the presence of an ADAMTS13 deficiency was investigated in patients with DCI.

### ***Part 2. Treatment options for delayed cerebral ischemia***

The second part of this thesis focuses on nimodipine (chapter 5 and 6) and statin treatment (chapter 7 and 8). Previously it was observed that nimodipine increases fibrinolytic activity in patients with aneurysmal SAH.<sup>16</sup> In **Chapter 6** the results of a systematic review of the literature is described in which it was studied whether all calcium antagonists increase fibrinolytic activity. The purpose of **Chapter 7** was to investigate the effect of nimodipine in patients with traumatic SAH by a systematic review of the literature and search for previously unpublished data. Despite several randomized controlled trials, there was still much debate whether nimodipine improves outcome in this group of patients, mostly because the results of the largest and most recent study, which was funded by a pharmaceutical company, were only partly presented. In **Chapter 8** the biological effects of treatment with simvastatin in patients with aneurysmal SAH are studied. Previously, two randomized, placebo-controlled phase II studies showed impressive clinical effects of statin treatment on the incidence of radiologically demonstrated vasospasm, DCI, and outcome in patients with aneurysmal

SAH. This was remarkable since these studies were not designed and not powered to find clinical effects. To confirm these results, the effects of simvastatin are presently investigated in a large phase III study. In case this phase III study will show a beneficial effect, it will remain unknown whether this effect will be cholesterol-dependent or result from previously reported pleiotropic effects. Therefore we conducted an exploratory study investigating the acute effects of simvastatin on cholesterol and parameters of coagulation, fibrinolysis, inflammation, and endothelium function in patients with aneurysmal SAH. In **Chapter 9** the focus is broadened by investigating possible pleiotropic effects of statins in patients with a history cerebrovascular disease. In this chapter the results of a systematic review are reported on the incidence of hemorrhagic stroke in patients with a history of cerebrovascular disease treated with statins.

The thesis concludes with a general discussion (**Chapter 10**), an English summary, and a Dutch summary.

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