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

Vergouwen, M.D.I.

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Chapter 10

General discussion
New hypothesis for pathogenesis of delayed cerebral ischemia

The results of the studies presented in this thesis show that the pathogenesis of DCI after aneurysmal SAH is more complicated than previously thought. In patients with DCI several pathways seem to be activated, ultimately resulting in cerebral microthrombosis and a local form of a disseminated intravascular coagulation. Besides vasospasm related hypoperfusion, increased coagulation activity and inhibition of fibrinolysis all seem to play an important role in the formation of microthrombi. Indeed, in autopsy studies microthrombi have been observed consisting of fibrin and activated platelets. Since not all patients with DCI have vasospasm, and conversely, not all patients with vasospasm have DCI, cerebral microthrombosis might be a conditio sine qua non. In other words, patients who have angiographic vasospasm only develop symptoms of DCI when at the same time the coagulation cascade is activated or the fibrinolytic system impaired. Patients without vasospasm can also have symptoms of DCI as a result of microthrombosis. Since several studies found a strong association between angiographic vasospasm and DCI, vasospasm might be a confounder. This is probably the explanation why treatments aiming to prevent vasospasm, for example endothelin receptor antagonists or prophylactic balloon angioplasty, had no beneficial effects, despite the fact that vasospasm is associated with DCI. The role of increased coagulation activity and of impaired fibrinolytic activity will be discussed below.

Increased coagulation activity

Although bleeding in aneurysmal SAH lasts not more than a few seconds, large amounts of blood are usually present in the subarachnoid space directly after the hemorrhage. Blood in the subarachnoid space results in local inflammatory reactions, and is ultimately broken down spontaneously into blood degradation products. Inflammatory reactions and blood degradation products in the subarachnoid space stimulate the adventitia, the outer layer of the vessel wall, which results in the release of tissue factor. Tissue factor is the main initiator of intravascular coagulation, since it activates thrombin, which in turn converts fibrinogen to fibrin (Figure). High levels of tissue factor are present in the cerebrospinal fluid of patients with aneurysmal SAH within 4 days after the hemorrhage and predict the occurrence of cerebral infarction and outcome after SAH.

At the same time, blood degradation products and inflammatory processes in the subarachnoid space result in endothelial dysfunction, leading to the release of von Willebrand factor (vWF) antigen, which in turn activates platelets and increases coagulant activity. An increased stress response, as a direct consequence of the hemorrhage, might aggravate endothelial dysfunction, and increase the risk to develop DCI. Moreover, decreased ADAMTS13 activity in patients with aneurysmal SAH might result in larger vWF multimers and make patients more prone to develop microthrombi leading to symptoms of DCI.
Chapter 10

Inhibition of fibrinolysis

Acute stressful events lead to increased levels of PAI-1, which results in inhibition of fibrinolysis. Although direct evidence of impaired fibrinolytic activity in patients with aneurysmal SAH is scarce, patients with DCI have significantly higher levels of PAI-1 antigen in the cerebrospinal fluid compared with patients without DCI, suggesting that overactive inhibition of fibrinolysis is associated with DCI. Indirect evidence of the role of the fibrinolytic system in the pathogenesis of DCI comes from a study which showed that in aneurysmal SAH patients a genetic predisposition for impaired fibrinolytic activity is associated with an increased risk of DCI. Furthermore, antifibrinolytic agents have been found to increase the risk of DCI and impede recovery from DCI.

It remains unknown why clinical signs and symptoms of DCI only occur four days or later after the hemorrhage. Several co-existing factors might be involved. First, this delay might result from an inflammatory response in the subarachnoid space, which takes several days to arise after the hemorrhage. Another reason might be that the adventitia of the vessel wall is only stimulated after blood in the subarachnoid space is broken down into blood degradation products. However, since patients with traumatic SAH usually do not develop delayed cerebral infarctions, this factor might not be obligatory in the pathogenesis of DCI after aneurysmal SAH. In this thesis it was shown that an increased stress response is associated with DCI. Prolonged stress during several days might result in endothelial dysfunction severe enough to develop symptoms of DCI. Furthermore, decreased ADAMTS13 activity is associated with DCI. It might take several days for ADAMTS13 activity to decrease.
Implications and future directions

A. Pathogenesis of delayed cerebral ischemia

Little is known about the factors that increase coagulation activity and impair fibrinolysis in the pathogenesis of DCI. The role of Weibel-Palade bodies in the vascular endothelium needs further investigation. Weibel-Palade bodies are storage sites in the endothelium which can rapidly respond to changes in its micro-environment by the release of various substances. Well-known stimulators of Weibel-Palade bodies are (among others) thrombin, complement factors, and epinephrine. In patients with SAH, Weibel-Palade bodies are probably activated by thrombin, present in the subarachnoid space as a direct result of the hemorrhage, inflammatory reactions, or from the stress response. After stimulation, Weibel-Palade bodies release substances such as von Willebrand factor, endothelin, tissue plasminogen activator (tPA), P-selectin, and interleukin-8 (IL8). Recent studies indicate that substance release from Weibel-Palade bodies can be selective. Therefore, in patients with DCI only procoagulatory substances might be released, and not substances such as tissue plasminogen activator which is profibrinolytic. The fact that substance release from Weibel-Palade bodies can be selective might also explain why vasospasm not always results in clinical signs and symptoms of DCI, and vice versa, not all patients with DCI have vasospasm. For instance, in patients with vasospasm without symptoms of DCI, endothelin might be released from Weibel-Palade bodies, resulting in vasospasm, without release of procoagulatory substances. In patients with symptoms of DCI without vasospasm procoagulatory substances are released without release of endothelin, and in patients with both vasospasm and symptoms of DCI both endothelin and procoagulatory substances.

Although it would be interesting to further investigate the role of Weibel-Palade bodies in the pathogenesis of DCI needs further investigation, it is currently not an easy scenario, since it is not possible to study Weibel-Palade bodies in vivo. Presently, Weibel-Palade body function can only be studied indirectly by measuring von Willebrand factor in blood, as done in this thesis. Furthermore, no adequate animal models for DCI after aneurysmal SAH are available. In existing animal models of SAH, a cerebral artery is perforated. Although it is possible to investigate whether the animal develops spastic arteries, it is much more difficult to evaluate whether the animal develops signs and symptoms of DCI. Therefore, it will be difficult to study the relation between Weibel-Palade bodies and the development of DCI in an animal model. It can be concluded that as long as Weibel-Palade bodies cannot be studied in vivo and no adequate animal models are available, it is worthwhile to search for other ways to obtain further insight in the pathogenesis of DCI.

One way to better understand the pathogenesis of DCI after SAH might result from studying diseases with possibly similar pathogenesis of ischemic cerebral complications. For instance, patterns of cerebral infarctions after aneurysmal SAH on CT/MRI imaging resemble patterns of lesions in patients with preeclampsia, thrombotic thrombocytopenic purpura (TTP), and hypertensive encephalopathy, although in the three latter diseases lesions are usually situated
in the posterior cerebral circulation. Therefore, the pathogenesis of DCI after aneurysmal SAH has similarities to that of preeclampsia, hypertensive encephalopathy, and cerebral complications in TTP. Interestingly, in patients with these different diseases with cerebral complications, vasospasm has been observed frequently.\textsuperscript{11-14} Despite this striking similarity concerning vasospasm, treatment of these diseases with possibly similar pathogenesis of ischemic cerebral complications is not aimed at treatment of vasospasm. The hypothesis is that the pathogenesis of these diseases has considerable overlap; what they have in common is endothelial dysfunction. Endothelial dysfunction not only results in spasm, but also in activation of the coagulation pathway.

Similar to the pathogenesis of TTP, reduced ADAMTS13 activity might also play a crucial role in the pathogenesis of cerebral ischemia after SAH. In this thesis it was shown that patients with DCI have decreased ADAMTS13 activity, however not as low as patients with TTP. Because of vascular bed specific hemostasis it could be that local levels of ADAMTS13 activity is lower in the cerebral circulation.\textsuperscript{15} Therefore, in the future it should be tried to obtain blood in patients with DCI who have a jugular line. In case ADAMTS13 activity in blood obtained from the jugular vein is even lower than in blood obtained from the systemic circulation, this will be even more suggestive that ADAMTS13 plays a crucial role in the formation of microthrombi, and as a result DCI.

Another way to gain further insight in the pathogenesis of DCI is to obtain 7-Tesla MRA scans of the brain in patients with and without DCI after SAH. The visualisation of the microcirculation has been shown to be superior with 7-Tesla MRA compared to conventional angiography.\textsuperscript{16} It would be interesting to compare the results of 7-Tesla MRA scans in SAH patients with the results of similar imaging techniques in patients with ischemic complications in TTP, preeclampsia, and hypertensive encephalopathy.

B. Prevention and treatment of delayed cerebral ischemia

Presently, the only drug that decreases the incidence of DCI and poor outcome after SAH is nimodipine. Although the beneficial effect of nimodipine in SAH patients might be attributed to increased fibrinolytic activity, it remains unknown how nimodipine increases fibrinolytic activity.\textsuperscript{17} Since this thesis gives further insight in the pathogenesis of DCI, it also gives direction to further investigations investigating how nimodipine exerts a beneficial effect. In this thesis no studies were done to investigate whether nimodipine also decreases procoagulant activity, but previous studies showed inhibition of platelet aggregation as a result of calcium antagonist use.\textsuperscript{18} Since the thrombin-initiated release of von Willebrand factor by Weibel-Palade bodies is a calcium-mediated effect, the hypothesis is that nimodipine influences substance release by Weibel-Palade bodies. Furthermore, the cleavage of ultralarge von Willebrand factor (ULVWF) multimers is calcium dependent. Recently it was shown that magnesium sulfate, a calcium antagonist used as a successful treatment in eclampsia, enhances the cleavage of newly released ULVWF by ADAMTS13, and reduces platelet aggregation.\textsuperscript{19} Interestingly, the effect of magnesium sulfate on the prevention of DCI is presently investigated in a phase
III randomized controlled trial, after a phase II study showed promising results. It will be interesting to study in the future whether nimodipine also enhances the cleavage of newly released ULVWF by ADAMTS13, and reduces platelet aggregation.

How should the search for new drugs to prevent and treat DCI continue? Since the pathogenesis of DCI seems to be multifactorial, future studies should focus much less on drugs that diminish vasospasm, but in particular on drugs with pleiotropic effects which influence the coagulation cascade and fibrinolytic system. The most well-known drugs which are supposed to have pleiotropic effects are statins. However, since a study described in this thesis found no pleiotropic effects of simvastatin in patients with SAH, and two recent studies showed that the rate of radiographic vasospasm, symptomatic vasospasm, delayed cerebral infarction, and clinical outcome did not change after implementation of statins in the routine treatment of SAH patients, it remains questionable whether statin treatment is effective to prevent DCI and improve outcome after SAH. An international phase III study investigating the effect of statins in SAH is presently undertaken. However, since single drugs with pleiotropic effects might not be effective enough, future studies should successively, one by one, focus on the separate pathways involved in the pathogenesis of DCI.

Previous attempts to influence procoagulant activity in SAH patients were not successful or inconclusive. A randomized controlled trial investigating the effect of aspirin was stopped prematurely, after an interim analysis showed that the probability of a beneficial effect was negligible. Explanations provided were that a dosage of 100 mg once daily might not be appropriate, or that aspirin might not be the right antiplatelet drug for the prevention of DCI. Another explanation could be that the effect of aspirin is too selective by only inhibiting platelet function and not affecting vasospasm. A Cochrane analysis investigating the effect of antiplatelet therapy showed a strong trend toward a decreased incidence of DCI and poor outcome, but since the results were not statistically significant and antiplatelet therapy was associated with an increased risk of intracranial hemorrhagic complications, the conclusion was that antiplatelet use could not be recommended in SAH patients. Two randomized controlled trials investigating the effect of enoxaparin showed contradictory results, and therefore it remains unknown whether enoxaparin is effective. Positive results were reported in a systematic review on the effect of intrathecal thrombolysis, which resulted in a significant 14% absolute risk reduction of DCI, and a significant 10% absolute risk reduction of poor outcome. However, of the nine included studies, only one study was randomized. In conclusion, previous studies that investigated drugs influencing the coagulation pathway or fibrinolytic system were inconclusive, and therefore large, well-powered, randomized controlled trials are needed to investigate the effects of these drugs on the incidence of DCI.

A study described in this thesis suggests that increased serum cortisol levels early after the hemorrhage are of prognostic value for the occurrence of DCI. Increased serum cortisol levels might lead to endothelium dysfunction and hereby activate the coagulation pathway. Because of the association between increased cortisol levels and DCI occurrence, the increased stress
response needs further exploration as a possible treatment target to prevent DCI. Since cortisol inhibitors such as metyrapone prevent endothelium dysfunction, they deserve further investigation in search of a drug to prevent DCI after SAH.\textsuperscript{28}

Not only for a better understanding of the pathogenesis of DCI, but also for future investigations for the prevention and treatment of DCI, we should study treatments for diseases with similar ischemic cerebral complications. As mentioned earlier, magnesium sulfate, which is effective in patients with (pre)eclampsia, is presently investigated in a phase III randomized trial in patients with aneurysmal SAH. Since microthrombosis might play an important role in the pathogenesis of DCI similar as in TTP, it is also worthwhile to investigate treatment options for TTP in patients with aneurysmal SAH. Before treatments for TTP became available, mortality was 90%. In 1976, blood exchange transfusion was shown to be effective, resulting in an important mortality decline.\textsuperscript{29} Later studies showed that the active principle in blood was shown to be in the plasma fraction.\textsuperscript{30} In a randomized controlled trial, plasma exchange was superior to plasma infusion.\textsuperscript{31} Presently it is known that TTP is caused by ADAMTS13 antibodies, resulting in reduced ADAMTS13 activity. In the near future studies are expected that investigate the effect of recombinant ADAMTS13 in TTP patients. In case recombinant ADAMTS13 is an effective treatment option for TTP, it might also be valuable to investigate whether it treats DCI in aneurysmal SAH patients.

**Conclusion**

The pathogenesis of DCI is more complicated and multifactorial than previously thought. Not only vasospasm is associated with DCI, but also activation of the coagulation cascade and inhibition of fibrinolytic activity, resulting in microthrombosis. Although a causal relation between vasospasm and DCI was never established, the results of this thesis neither prove a causal relation between procoagulant activity/inhibited fibrinolytic activity and DCI. It remains to be investigated whether vasospasm and microthrombosis are complementary or competing hypotheses. However, since previous investigations on the prevention and treatment of DCI focused on vasospasm and were not successful thus far, the coagulation and fibrinolytic system are interesting future research targets in patients with SAH.
References


