Vascular damage and dysfunction in hypertensive emergencies
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Introduction and outline of this thesis

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Chapter 1
INTRODUCTION

High blood pressure (BP) is one of the major risk factors for cardiovascular disease (stroke, myocardial infarction, heart failure), renal disease and mortality worldwide. In the majority of patients, hypertension is caused by a combination of genetic, behavioral and environmental factors (primary or essential hypertension), while only a small proportion of hypertensive patients have a single identifiable cause of high BP (secondary hypertension). Most patients with hypertension are asymptomatic and BP lowering treatment in these patients is aimed at reducing the long-term risk of cardiovascular and renal disease. However, in some patients with hypertension, BP may rise to critical values, causing acute, sometimes irreversible, damage to target-organs such as brain, heart, and kidneys. Rapid diagnosis and treatment of this severe form of hypertension or “hypertensive crisis” is required to prevent or limit organ damage in the acute phase.

Hypertensive crisis is frequently encountered at the emergency department and is defined as severe hypertension, usually >220 mmHg systolic and >120 mmHg diastolic BP with manifest (emergency) or imminent (urgency) target-organ damage. There is no cut-off value for BP in the definition of hypertensive crisis, because development of acute organ damage depends more on the magnitude and velocity of BP elevation from baseline rather than on actual BP values at presentation. This means that acute organ damage is more likely to occur at lower absolute BP values in young and previously normotensive patients compared to older patients with chronic hypertension.

Hypertensive crisis is a heterogeneous disorder with a large variation in clinical presentation, depending on the type and extent of organ damage. Examples of acute organ damage include aortic dissection, ischemic and hemorrhagic stroke, acute heart failure with pulmonary edema, ischemic coronary disease, renal failure, retinopathy and thrombotic microangiopathy. Two relatively common forms of hypertensive crises comprise hypertensive crisis with retinopathy and pre-eclampsia. These two hypertensive emergencies are the focus of this thesis and will be introduced in more detail below.

Hypertensive crisis with retinopathy and pre-eclampsia are both considered to be hypertensive emergencies that require rapid treatment to prevent or limit acute organ damage. Hypertensive crisis with retinopathy is a renin-mediated form of hypertension that predominantly affects patients with untreated essential hypertension. Because of long-existing untreated hypertension, BP may reach extremely high values at presentation. Pre-eclampsia affects pregnant women in the second half of pregnancy. Anti-angiogenic factors produced by the placenta are responsible for endothelial dysfunction and hypertension in these women. Because these women are often previously normotensive, symptoms and hypertensive organ damage may already arise at relatively low BP values. Anti-angiogenic medication for the treatment of malignancies may also cause a pre-eclampsia-like state.
Hypertensive crisis with retinopathy (malignant hypertension)

Traditionally, *hypertensive crisis with retinopathy* is referred to as malignant hypertension. In an observational study from 1939, when treatment of hypertension was not yet possible, Keith, Wagener and Barker showed that patients with severe hypertension and grade IV retinopathy had a remarkably poor prognosis, as more than 90% of patients died within 1 year. Patients with severe hypertension and grade III retinopathy had a slightly better prognosis with 65% of patients deceased after 1 year. The term malignant hypertension was introduced for patients with grade IV retinopathy and accelerated hypertension for patients with grade III retinopathy. The difference in survival disappeared with the advent of antihypertensive medication leading to incorporation of both grade III and IV retinopathy in the definition of malignant hypertension since the 1980s.

The annual incidence of malignant hypertension is currently 1-3 per 100,000 individuals and is more common in multi-ethnic populations. Secondary causes of high blood pressure are more frequently observed in malignant hypertension compared to chronic non-malignant hypertension, but the majority of patients have unrecognized or uncontrolled primary hypertension. Limited access to healthcare and non-adherence to medication contribute to the development of malignant hypertension in these patients. These socio-economic
factors, together with the much higher prevalence of hypertension among patients of sub-Saharan African origin, result in a 4 times higher prevalence of malignant hypertension among sub-Saharan African immigrants.  

Pathophysiology
Clinical studies and animal experiments have shown that activation of the renin-angiotensin-aldosteron system (RAAS) plays a central role in the pathophysiology of malignant hypertension. Virtually any cause of BP elevation, for example cessation of antihypertensive medication, can trigger RAAS activation if the BP elevation is high enough to induce endothelial damage. In the kidneys, damage to small arteries and arterioles leads to renal ischemia and consequently to renin secretion by juxtaglomerular cells and RAAS activation. At the same time, pressure natriuresis is initiated to limit BP elevation. Eventually, this leads to hypovolemia, thereby contributing to RAAS activation. The subsequently produced angiotensin II is a powerful vasoconstrictor that further elevates BP and gives rise to a vicious circle of BP elevation, endothelial damage, renal ischemia and RAAS activation (Figure 1).

Figure 2: Simplified representation of the vicious circle underlying hypertensive crisis with retinopathy

In addition to elevation of BP, angiotensin II has direct cytotoxic effects on the vessel wall via activation of pro-inflammatory cytokines such as IL-6 and NF-κB. Moreover, endothelial damage activates the coagulation cascade, leading to formation of thrombi that further obliterate the microcirculation and induce mechanical destruction of erythrocytes.
Histopathological changes
Autopsy studies have identified fibrinoid necrosis and myointimal proliferation of small arteries and arterioles as histopathological hallmark of malignant hypertension.\textsuperscript{10} Fibrinoid necrosis reflects seepage of fibrin through necrotic vessel walls, whereas myointimal proliferation leads to narrowing of the vessel lumen. This vascular damage can be observed in virtually all organs. In addition, ischemic glomerular changes are observed in the kidneys (Figure 2), including collapsed glomerular tufts, widening of Bowman’s capsule with collagen depositions, hyperplasia of juxtaglomerular cells and tubular necrosis.

Figure 3: Histopathological changes in hypertensive crisis with acute renal insufficiency

Myointimal hyperplasia and fibrinoid necrosis in an almost completely occluded arteriole (arrow). Collapsed glomerular tuft with widening of Bowman’s capsule (asterisk). Figure adapted from: B.J.H van den Born and G. van Montfrans, Malignant hypertension. In: Jörres et al. Management of Acute Kidney Problems pp 305-316, Springer-Verlag Berlin Heidelberg 2010

Clinical presentation and complications
Depending on the extent of organ damage, clinical presentation is highly variable. Patients may be asymptomatic, but can also present with seizures or cortical blindness. Most patients complain of headache and visual disturbances, followed by gastro-intestinal complaints such as nausea, vomiting and abdominal pain (Table 1).
Table 1: Presenting symptoms of patients with hypertensive crisis and retinopathy in Amsterdam, The Netherlands

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>62</td>
</tr>
<tr>
<td>Visual disturbances</td>
<td>56</td>
</tr>
<tr>
<td>Gastro-intestinal complaints, including weight loss</td>
<td>36</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>21</td>
</tr>
<tr>
<td>Neurological symptoms</td>
<td>10</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>83</td>
</tr>
<tr>
<td>Severe renal insufficiency (creatinine &gt;300 µmol/l)</td>
<td>31</td>
</tr>
<tr>
<td>Renal insufficiency (creatinine 115-300 µmol/l)</td>
<td>36</td>
</tr>
<tr>
<td>Thrombotic microangiopathy</td>
<td>32</td>
</tr>
</tbody>
</table>

Besides bilateral ischemic retinal lesions, patients with malignant hypertension frequently present with acute renal insufficiency, thrombotic microangiopathy and hypertensive encephalopathy. One third of patients with malignant hypertension have severe renal insufficiency at presentation and more than 60% of patients have proteinuria (>300mg/24 hrs). Although kidney replacement therapy may be required in the acute phase, recovery of renal function has been reported until two years after the hypertensive crisis with BP lowering treatment.\(^{11,12}\) Nonetheless, a relatively large proportion of patients will progress to end-stage renal disease. Acute renal insufficiency and proteinuria is caused by ischemic glomerular damage resulting from fibrinoid necrosis and thrombotic occlusions of small arteries and arterioles. This thrombotic microangiopathy is clinically reflected by consumption of platelets and fragmentation of erythrocytes, which can be observed in approximately 30% of patients with malignant hypertension. As a result of this deleterious effect of thrombotic microangiopathy on the kidneys, presence of hemolysis and low platelet count is an important predictor of renal failure and possible recovery.\(^{12}\)

Neurological symptoms consistent with hypertensive encephalopathy occur in approximately 10-15% of patients with malignant hypertension. Hypertensive encephalopathy is a clinical diagnosis based on 1) severe hypertension in combination with neurological symptoms such as lowered consciousness (delirium, agitation, lethargy, coma) or seizures 2) absence of an alternative explanation for the neurologic symptoms and 3) resolution of the symptoms after adequate BP control has been achieved. Histopathological changes in hypertensive encephalopathy include edema, microscopic haemorrhages and infarctions.\(^{13}\) Cerebral edema can be visualised on T2-weighted MRI showing a characteristic pattern of posterior reversible encephalopathy syndrome (PRES), Figure 3. PRES may also be observed in several other life-threatening diseases including thrombotic thrombocytopenic purpura, eclampsia, sepsis and can also be triggered by immunosuppressive drugs such as tacrolimus and cyclosporine. Diagnosing hypertensive encephalopathy may therefore be difficult. The
presence of severe hypertension and grade III of IV hypertensive retinopathy may help distinguish hypertensive encephalopathy from other causes of PRES.

Figure 4: Cerebral edema in hypertensive encephalopathy, typically located in the parieto-occipital region

Cerebral edema in patients with hypertensive encephalopathy can be visualized using T2 weighted MRI. This characteristic radiological image is also referred to as posterior reversible encephalopathy syndrome (PRES) and may also be observed in other diseases including thrombotic thrombocytopenic purpura and eclampsia.

Treatment
Diagnostic procedures at presentation are aimed at identifying the presence and extent of organ damage and may provide information on the underlying cause of the hypertensive crisis. The primary goal of treatment is to limit or prevent further hypertensive organ damage rather than achieving normal BP values. A rapid but controlled lowering of BP with only 25% of the mean arterial pressure at presentation is required in the first 24 hours. Patients with malignant hypertension have been shown to have an impaired cerebral autoregulation, posing them at risk for cerebral hypoperfusion with too large drops in BP.3
Prognosis
The survival of patients with malignant hypertension has drastically improved with the availability of effective antihypertensive medication to 90% after 5 years. Before the availability of adequate treatment, mortality was mainly caused by heart failure, renal failure and stroke. However, a current mortality rate of 10% after 5 years is still relatively high, considering the relatively young age of patients included in the studies. Whether patients with malignant hypertension still remain at increased risk of dying is unknown, as survival of these patients has not been compared with adequately matched controls without malignant hypertension. Although traditional cardiovascular risk factors such as excess smoking, dyslipidemia and uncontrolled hypertension have been associated with malignant hypertension, it is presently unclear whether these traditional risk factors contribute to excess mortality.

In Part I of this thesis we aimed to quantify the excess mortality risk in patients with a history of malignant hypertension and to investigate whether traditional cardiovascular risk factors contribute to excess mortality in these patients by comparing them with age, sex and ethnicity matched controls from the same area of residence. Our second aim was to assess the long term renal outcome and its predictors in patients with malignant hypertension. Although renal function may recover after the acute phase of malignant hypertension, little data exist on the long term renal prognosis. Thirdly, presence of grade III or IV hypertensive retinopathy has been shown to coincide with disturbed cerebral autoregulation, and is considered to distinguish hypertensive encephalopathy from other causes of encephalopathy. However, several case-reports suggested that grade III or IV hypertensive retinopathy may be absent in patients with hypertensive encephalopathy. We aimed to assess the frequency of grade III and IV hypertensive retinopathy in a relatively large series of patients with hypertensive encephalopathy.

Pre-eclampsia
Hypertension is a frequent complication of pregnancy, with 10% of all pregnant women having either chronic hypertension, gestational hypertension or pre-eclampsia, which may or may not be superimposed on chronic hypertension. Pre-eclampsia is characterized by hypertension and proteinuria in the second half of pregnancy. The definition of pre-eclampsia has recently been revised by the International Society for the Study of Hypertension in Pregnancy (ISSHP). Pre-eclampsia is currently defined as new-onset hypertension after 20 weeks gestation in combination with maternal organ damage, including proteinuria (>300mg/24hrs), renal insufficiency, neurological or haematological complications, uteroplacental dysfunction or fetal growth restriction. Pre-eclampsia is one of the leading causes of maternal and neonatal morbidity and mortality worldwide, especially in developing
countries. Severe pre-eclampsia (BP >160/110mmHg) is a hypertensive emergency that requires immediate treatment to prevent potentially life-threatening complications such as eclampsia, stroke, renal failure and pulmonary edema.

The pathophysiology of pre-eclampsia is likely multifactorial and still incompletely understood. The current hypothesis is that different and yet undetermined mechanisms may cause abnormal placentation, with incomplete remodelling of uterine spiral arteries by invading trophoblast cells. This leads to inadequate placental perfusion and hypoxia. In response to hypoxia, the placenta paradoxically produces anti-angiogenic factors, including the soluble Vascular Endothelial Growth Factor (VEGF) receptor FMS-like tyrosine kinase 1 (sFLT-1). Scavenging of VEGF from the maternal circulation by sFlt-1 leads to endothelial dysfunction and eventually maternal signs of pre-eclampsia.

The mechanism by which scavenging of VEGF leads to BP elevation has been the subject of intensive investigation in recent years. Endothelin-1, a powerful vasoconstrictor, has been identified as a key mediator of hypertension induced by VEGF inhibition. In addition, blockade of VEGF signaling has been shown to induce a shift in sphingolipid metabolism towards increased production of ceramide, a bioactive lipid with anti-angiogenic properties. Ceramide content is elevated in pre-eclampsia, and has been linked to both hypertension and proteinuria in clinical and pre-clinical studies. Whether ceramide is related to VEGF inhibition in women with pre-eclampsia and contributes to BP elevation and proteinuria, has not been studied previously.

VEGF signaling is regulated by the endothelial glycocalyx, which is composed of a complex network of membrane-bound proteoglycans and attached glycosaminoglycans. The glycocalyx lines the wall of both the micro- and macrovasculature and is involved in regulation of permeability, leucocyte adhesion, coagulation and vascular tone. Changes in endothelial glycocalyx composition and function might also contribute to the pathogenesis of pre-eclampsia via disruption of VEGF signaling. Although several changes in glycocalyx composition have indeed been observed in placental tissue and plasma of pre-eclamptic women, the functional consequences of these abnormalities are presently unknown. A reason for the lack of studies addressing functional implications of altered glycocalyx composition in pre-eclampsia, might be the technical difficulty of glycocalyx volume estimation, which is invasive and time-consuming. Recent technological advances have led to the development of a new method, allowing non-invasive real-time estimation of glycocalyx volume in the microcirculation of large study populations. This method has, however, not yet been validated in clinical studies.

The principal aim of Part II of this thesis was to investigate the mechanisms by which VEGF inhibition leads to BP elevation. To this end we aimed to assess whether alterations in glycocalyx composition contribute to sFLT-1-induced BP elevation and whether sFLT-1...
induces changes in sphingolipid metabolism that subsequently contribute to hypertension and proteinuria in women with pre-eclampsia. A secondary aim was to investigate whether a recently developed technique for non-invasive real-time glycocalyx volume estimation could be used for assessment of the microcirculation in pregnant women with and without pre-eclampsia.

**Outline of this thesis**

**Part I** describes cardiovascular and renal complications of malignant hypertension. In **Chapter 2**, we compared cardiovascular risk factors, actual cardiovascular disease and mortality of patients with a history of malignant hypertension with age, sex and ethnicity matched normotensive individuals and non-malignant hypertension patients. **Chapter 3** addresses the long-term effect of malignant hypertension on renal function and assesses determinants of renal outcome. Patients presenting with malignant hypertension frequently have neurologic symptoms consistent with hypertensive encephalopathy. However, hypertensive encephalopathy may also exist without grade III or IV hypertensive retinopathy that define malignant hypertension. In **Chapter 4**, we evaluate what proportion of patients with hypertensive encephalopathy present without grade III or IV hypertensive retinopathy.

**Part II** of this thesis describes translational research into the roles of VEGF inhibition, glycocalyx composition and sphingolipid metabolism in the pathophysiology of pre-eclampsia. The production of anti-angiogenic factors by the placenta, including sFLT-1, contributes to endothelial dysfunction and BP elevation in pre-eclampsia. In **Chapter 5**, we explore the mechanisms of sFlt-1 induced BP elevation in mice. Interestingly, patients receiving anti-VEGF treatment for malignancies may develop a pre-eclampsia-like syndrome with hypertension and proteinuria. The results of animal experiments described in chapter 5 point towards an important role of vasocontractile prostanoids in anti-VEGF-induced hypertension. In **Chapter 6**, we translate this observation, by a post-hoc analysis of the effect of aspirin on BP in patients receiving anti-VEGF treatment with bevacizumab in a randomized clinical trial. In **Chapter 7** we compare the composition of the endothelial glycocalyx among pre-eclamptic and normotensive pregnant women by measuring circulating amounts of syndecan-1 and glycosaminoglycans including heparan sulphate, dermatan sulphate and keratan sulphate. We assess whether changes in glycocalyx composition have clinical implications in pre-eclampsia and investigate whether syndecan-1 deficiency contributes to sFlt-1-induced BP elevation in mice. Abnormal placentation, leading to inadequate perfusion and placentental hypoxia likely precedes maternal endothelial dysfunction in pre-eclampsia. **Chapter 8** focuses on differences in placental glycocalyx composition in placental tissue obtained from normotensive pregnant women and pre-eclamptic women. Potential clinical implications of differences in placental glycocalyx composition are described in this chapter. The glycocalyx volume, as estimated by non-invasive visualisation of the sublingual
microcirculation, has been shown to be related to endothelial function in selected groups of patients. However, the method for this analysis was cumbersome and difficult to use in large populations. In Chapter 9 we evaluate whether a newly developed device with software for automated estimation of glycocalyx volume can be used for clinical studies in pre-eclampsia. For this purpose we aimed to validate this technique in a large population, including healthy individuals as well as patients with overt cardiovascular disease. The novel system was designed for real-time estimation of glycocalyx volume by including over 3000 visible measurement sites in the sublingual microcirculation. VEGF inhibition has been shown to stimulate the production of ceramide, which is an anti-angiogenic sphingolipid. Ceramide has been shown to be elevated in plasma of women with pre-eclampsia and has previously been linked to hypertension and proteinuria. In Chapter 10 we compare sphingolipid metabolism among pre-eclamptic and normotensive pregnancies and investigate whether excess ceramide relates to hypertension and proteinuria in women with pre-eclampsia.
REFERENCES


Chapter 1

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