CHAPTER 1

GENERAL INTRODUCTION
1.1 INTRODUCTION

During pregnancy, approximately 6-25% of women are diagnosed with some form of hypertension.\textsuperscript{1-6} Although appropriate prenatal care has reduced the number of poor outcomes, hypertensive disorders of pregnancy are still among the leading causes of maternal mortality and severe morbidity in both developed\textsuperscript{6-8} and developing countries,\textsuperscript{9, 10} accounting for more than 50,000 maternal deaths annually.\textsuperscript{3} While the absolute mortality is much lower in developed countries, hypertension has nevertheless been implicated in approximately 20% of maternal deaths,\textsuperscript{8, 9, 11} with cerebrovascular complications being the primary cause in over 50%.\textsuperscript{7, 11, 12} Both the incidence of hypertension and the morbidity/mortality rate are affected by geographic, social, economic, and racial differences,\textsuperscript{11, 13, 14} with the incidence of the latter two rising.\textsuperscript{15, 16} This trend is thought to be caused by changes in maternal characteristics, such as increasing number of mothers with advanced maternal age, presence of comorbidities and higher pre-pregnancy weight.\textsuperscript{3} Although rare, eclampsia, the onset of seizures or coma in a preeclamptic woman, is still the most feared pregnancy complication, with a mortality rate of approximately 1% in developed countries,\textsuperscript{7, 17-19} but as high as 26% in developing countries.\textsuperscript{20-22}

1.2 HYPERTENSIVE DISORDERS OF PREGNANCY

Hypertensive disorders of pregnancy range in a spectrum from chronic hypertension (CHTN) to gestational hypertension (GHTN), preeclampsia (PE), and superimposed preeclampsia in the setting of chronic hypertension (SiPE).\textsuperscript{23} All are part of a dynamic process, where CHTN can progress to SiPE, and GHTN to PE and patients can deteriorate rapidly.\textsuperscript{23}

Hypertension itself is defined as a systolic blood pressure (BP) of 140 mmHg or greater, a diastolic blood pressure of 90 mmHg or greater, or both, documented on at least two occasions, at least 4–6 hours apart.\textsuperscript{13} In case of a BP $\geq 160$ mmHg systolic and/or $\geq 110$ mmHg diastolic, hypertension is confirmed within a short interval.\textsuperscript{23}

Proteinuria is defined as $\geq 300$ mg per 24-hour urine collection, protein/creatinine ratio $\geq 0.3$, or 1+ dipstick reading if other methods are not available.\textsuperscript{23}
Preeclampsia (PE) is a systemic disorder that is typically characterized by new-onset hypertension and proteinuria in pregnancy after the 20th week of pregnancy in a previously normotensive woman. In the absence of proteinuria, PE is diagnosed as hypertension with new development of thrombocytopenia, impaired liver function, renal insufficiency, pulmonary edema, or cerebral or visual disturbances.\textsuperscript{23}

Despite being the focus of many studies, the exact pathophysiology of preeclampsia remains unclear. The leading hypotheses are based on disturbed placental function in early pregnancy leading to placental under perfusion, and possibly hypoxia and ischemia, followed by release of components from the intervillous space into the maternal circulation, causing an angiogenic imbalance and an enhanced maternal intravascular systemic inflammatory response. This leads to generalized maternal endothelial dysfunction and, hence, symptomatic clinical disease, by which the fetus, central nervous system, lungs, liver, kidneys, systemic vasculature, coagulation, and the heart may be affected.\textsuperscript{1} Involvement of the brain can cause eclampsia: grand mal seizures or coma in a woman with preeclampsia, in the absence of other neurologic conditions that could account for the seizure.\textsuperscript{13}

Risk factors for the development of PE are advanced maternal age, nulliparity, history of preeclampsia, and multifetal gestations.\textsuperscript{1, 24} Preexisting medical conditions such as chronic hypertension, diabetes, obesity, renal disease and chronic autoimmune diseases also increase the risk for PE.\textsuperscript{1, 24} The precise mechanism of these risk factors are not fully understood, but several factors are related to underlying maternal endothelial dysfunction, which may increase susceptibility of the vasculature to the effects of circulating factors.\textsuperscript{25} This theory is supported by the fact that patients with chronic hypertension, diabetes, proteinuria or obesity develop PE at a lower level of angiogenic disturbance.\textsuperscript{26, 27} Nulliparity and multifetal gestations, which are also associated with increased preeclampsia risk, have a slight disturbance even without having PE.\textsuperscript{25}

Gestational hypertension (GHTN) is defined as hypertension that develops in pregnancy after 20 weeks gestation and which returns to normal within 12 weeks postpartum. Proteinuria or systemic
symptoms as seen in preeclampsia are absent.\textsuperscript{23} GHTN is the most frequent cause of hypertension during pregnancy, affecting 6-17\% of healthy nulliparous women.\textsuperscript{5, 28} Preeclampsia may be subsequently diagnosed if proteinuria or other sign of preeclampsia develop. This occurs in 26-46\%,\textsuperscript{29, 30} and the likelihood of progression increases with earlier gestational age at presentation.\textsuperscript{29, 30}

Maternal risks and incidence of adverse outcomes associated with gestational hypertension are generally less than those with preeclampsia. However, severity of hypertension is an important predictor of risks, and women with severe gestational hypertension may be at higher risk of adverse maternal and perinatal outcomes than women with mild pre-eclampsia.\textsuperscript{28}

\textit{Chronic hypertension} (CHTN) in pregnancy is defined as hypertension present before pregnancy or before the 20\textsuperscript{th} week of gestation. Hypertension first diagnosed after 20 weeks gestation, and persisting 12 weeks postpartum, is also considered chronic hypertension.\textsuperscript{31} The incidence of chronic hypertension is rising, and currently affects 7.7\% of the women in the reproductive age range in the United States.\textsuperscript{32} Concurrently, the prevalence of pregnancies complicated by CHTN is increasing (from 1.01\% in 1995-1996 to 1.76\% in 2007-2008).\textsuperscript{33}

CHTN is associated with increased rates of adverse maternal and fetal outcomes both acute and long term, including premature birth, fetal growth restriction, fetal demise, placental abruption, superimposed preeclampsia, pulmonary edema and cesarean delivery.\textsuperscript{31, 33-35} These complications are related to the duration of the disease, severity of the hypertension, presence of end organ damage, comorbidities, and noncompliance with prenatal visits.\textsuperscript{31, 33, 34}

\textit{Preeclampsia superimposed upon chronic hypertension} (SiPE) is new onset proteinuria after 20 weeks of gestation in a woman with chronic hypertension. In case of baseline proteinuria, SiPE is defined by a sudden increase in proteinuria, worsening or resistant hypertension in the last half of pregnancy or development of signs and symptoms of severe preeclampsia.\textsuperscript{31}

The risk for developing SiPE is increased in women with a
history of SiPE, raised body mass index, African-American ethnicity, who were diagnosed at least four years earlier and who had a booking diastolic blood pressure >100 mmHg.\textsuperscript{24, 35, 36} The incidence of SiPE has been reported to be between 12 and 29\% of women with CHTN,\textsuperscript{35-38} and up to 52\% in cases of severe chronic hypertension in the first trimester.\textsuperscript{39} Differentiating SiPE from an exacerbation of chronic hypertension can be difficult.

### 1.3 Cerebrovascular complications of hypertension in pregnancy

While multiple maternal organs can be affected, cerebral involvement is one of the most feared complications as it can lead to death or significant short- or long-term morbidity.\textsuperscript{8, 11} The risk of cerebrovascular complications during pregnancy is increased in all hypertensive disorders,\textsuperscript{32, 40-42} but is most pronounced in severe pre-eclampsia.\textsuperscript{41, 42} The neurological complications range from headache, visual disturbances and hyperreflexia to tonic-clonic seizures, coma and cerebrovascular accidents. Gross and microscopic histopathology have demonstrated intracerebral hemorrhage, petechiae, cerebral edema, vasculopathy, ischemic brain damage, microinfarcts, and fibrinoid necrosis.\textsuperscript{43, 44} Magnetic resonance imaging (MRI) has shown abnormal scans with non-specific foci of increased signal in the deep cerebral white matter on T2-weighted images in 50\% of the women with severe pre-eclampsia.\textsuperscript{45} Widespread diffuse cerebral edema or localized hypodense lesions have been found with computed tomography (CT) imaging. In the absence of serious neurological symptoms, imaging is predominantly unremarkable.\textsuperscript{43}

The pathophysiology of these cerebrovascular complications remains poorly understood. Two opposing theories are both based on endothelial dysfunction, and poor cerebral autoregulation: the “vasoconstriction/hypoperfusion,” and the “hypertension/hyperperfusion” theories.\textsuperscript{46} The first theory suggests that endothelial dysfunction, caused by systemic toxicity, leads to vasoconstriction, ischemia, and subsequent brain edema due to increased permeability of endothelium.\textsuperscript{46} This theory is supported by the vasospasm seen on cerebral angiograms in some women with eclampsia\textsuperscript{47, 48} the fact that
vasogenic edema is typically found in the watershed zones and the systemic vasoconstriction seen in preeclampsia.

The second theory is based on loss of cerebral autoregulation. In the presence of endothelial dysfunction, sudden elevations in systemic blood pressure may exceed the cerebrovascular autoregulatory capacity, leading to forced dilatation of cerebral arteries, causing hyperperfusion, blood-brain barrier disruption and edema. Interestingly, 20-40% of eclamptic patients never develop overt hypertension prior to convulsions or a stroke, suggesting an important role for autoregulatory dysfunction in the underlying pathophysiology.

In 1996, Hinchey et al. described a series of patients with a variety of disorders, including eclampsia, who all had similar neurologic complications (headache, visual disturbances, altered mental status and seizures) and radiologic findings (cerebral edema, mainly posterior), and named this condition reversible posterior leukoencephalopathy syndrome. Severe preeclampsia-eclampsia is considered to be a form of this syndrome, which has been renamed to posterior reversible encephalopathy syndrome (PRES).

It remains unclear why the parieto-occipital lobes are most often involved, but it is hypothesized that the decreased sympathetic innervation of the vertebrobasilar arteries, as compared to that of the internal carotid artery system, plays a role. Although the exact role of the autonomic nervous system on the regulation of cerebral blood flow remains controversial, recent studies do suggest an autonomic, mainly sympathetic, role in cerebral blood flow control, protecting the brain from autoregulation breakthrough and loss of integrity of the blood-brain barrier. The decreased sympathetic innervation in the vertrobrobasilar region may allow autoregulatory breakthrough at a lower pressure than in other more densely innervated areas during acute hypertension.

Long-term consequences of eclampsia and preterm preeclampsia (gestational age <37 weeks) include an increased prevalence of cerebral white matter lesions seen on MRI when compared to control patients who had either a normotensive pregnancy or a pregnancy complicated by term preeclampsia. However, these lesions are found equally in patients with and without seizures, and are mainly located in
the frontal areas of the brain making a direct causal relationship between PRES and these white matter lesions unlikely. The finding does raise the possibility that formerly (pre)eclamptic women are predisposed to develop cerebrovascular disease in later life.

1.4 Cerebral autoregulation

Under normal circumstances, cerebral blood flow is maintained at a relatively constant level, despite changes in blood pressure, through changes in the arterial diameter and hence cerebrovascular resistance (CVR). In 1959, Lassen introduced the term ‘cerebral autoregulation’ (CA) to describe this process.

Measurement of the cerebral blood flow (CBF) was performed using indicator-dilution techniques, such as $^{133}$Xenon or nitrous oxide, which required several minutes to obtain a single CBF value. This measurement was performed twice under steady state conditions: at a baseline blood pressure (BP), and after BP manipulation. The outcomes resulted in the classical CA curve, with a plateau between mean arterial pressures (MAP) of about 50-60 to 150-160 mmHg, where cerebral blood flow is kept constant in the case of normal autoregulation (Figure 1). When the MAP exceeds this range, such
as in acute severe hypertension, autoregulation may be lost, and CBF increases linearly with increase in blood pressure. In this state of forced dilatation, the blood-brain barrier can be disrupted, leading to vasogenic (reversible) edema formation. Because the measurements used for this curve describe mean values of CBF and MAP averaged over several minutes, this concept is now known as static cerebral autoregulation.

This paradigm, however, ignores the dynamic nature of autoregulation. Early animal studies, which used invasive testing for rapid measurement of CBF and BP, showed a characteristic transient CBF response to a sudden change in BP: after initially following BP, the CBF would return to its original baseline in a few seconds. In 1989, this same response was demonstrated in humans, using transcranial Doppler (TCD) and arterial volume clamping to obtain instantaneous values of CBFV and BP, while the BP alteration was induced by the release of thigh cuffs. In addition to the efficiency of CA, which is evaluated by the static CA, this method also addresses the temporal course of CA, and is therefore named ‘dynamic autoregulation’. This thesis will predominantly focus on the dynamic autoregulation during pregnancy.

1.5 Cerebral autoregulation measurement

Transcranial Doppler

While ultrasound evaluation of extracranial vessels was first described in 1965, the bony skull has long hindered the ultrasonic evaluation of the intracranial vasculature. However, Aaslid et al. showed in 1982 that low-frequency ultrasound (2-MHz pulsed Doppler) does penetrate the skull through certain natural cranial windows, where the cranial bone is relatively thin. The transtemporal window, located above the zygomatic arch, is most often used for CA studies, because it allows for insonation of the main intracranial arteries. The middle cerebral artery (MCA), the largest and anatomical most ideally located, is used in most CA studies. A limitation of using TCD is that only the cerebral blood flow velocity (CBFV) can be obtained, and the method therefore relies on the assumption that changes in CBFV are directly proportional to changes in CBF, which
is only true if the vessel diameter is constant. Available literature shows that the MCA does not change in diameter despite significant changes in PaCO$_2$ or BP$^{79-81}$ and that it maintains its diameter during pregnancy.$^{82, 83}$ If this constant diameter is assumed, CBFV can be used as indicator for assessing CBF changes. The non-invasive nature and high temporal resolution make it possible to acquire the CBFV waveform and its transient changes in humans.$^{78}$

**Non-invasive blood pressure measurement**

Because studies of CA evaluate the ability of the CBFV to return to baseline after a sudden change in BP, continuous recording of BP is required. While most critical care patients have an arterial line that can be used for this purpose, non-invasive techniques for the continuous measurement of BP are needed for research purposes including human subjects. The arterial volume clamping technique described by Peñaz, and converted by Wesseling into Finapres (Finger Arterial pressure), which measures the arterial pressure waveform at the finger, made this possible.$^{84}$ Comparison of estimates of CA derived from Finapres and from intra-aortic measurement demonstrated a good level of agreement between both methods.$^{85}$

**Quantification of cerebral autoregulation**

In their initial study, Aaslid et al. used the rate of regulation (RoR), defined as $(\Delta \text{CVR}/\Delta T) / \Delta \text{BP}$, to quantify the autoregulation response. This indicates the slope of the CBFV return to its baseline $(\Delta \text{CVR}/\Delta T)$ after a sudden BP drop $(\Delta \text{BP})$, and was shown to decrease with increasing levels of end-tidal CO$_2$ (EtCO$_2$)$^{75}$.

Tiecks et al. developed a more refined model using a second-order differential equation.$^{69}$ This autoregulation index (ARI) ranges from 0 (absence of autoregulation, CBFV passively follows ABP) to 9 (best measurable autoregulation, (Figure 2). Each of its values corresponds to a step change in CBFV that is expected by the theoretical step change in BP, characterized by three parameters: the time constant (T), the damping factor (D), and the autoregulatory dynamic gain (K). The curve that best fits the measured CBFV response defines the corresponding value of ARI.$^{69}$
Figure 2) The 10 theoretical curves with associated ARI and an example of a measurement of which the best corresponding value was ARI = 3. Used with permission from R.B. Panerai; Cerebral Autoregulation: From Models to Clinical Applications (2008) 

Figure 3) Parameters extracted by transfer function analysis from continuous blood pressure (ABP) and cerebral flood flow velocity (CBFV) measurements, converted into the frequency domain, and transformed back to the time domain to give an estimate of the impulse and step response. Indicating relatively normal (continuous line) and severely impaired (dashed line) autoregulation. Used with permission from R.B. Panerai; Cerebral Autoregulation: From Models to Clinical Applications (2008) 

FREQUENCY DOMAIN

TIME DOMAIN

Time (s)

ABP (mmHg)

CBFV (cm.s⁻¹)

CBFV step response (a.u.)

ARI = 0

Coherence

Amplitude (%/%)  

Step resp. (%/%)  

Impulse resp. (%/%)  

Phase (rad)

Time (s)
To study CA, several maneuvers have been developed to induce the BP changes while measuring the CBFV response, including thigh cuff inflation, Valsalva maneuver, low frequency breathing, posture changes, lower-body negative pressure and pharmacological methods. However, in some groups of participants, these interventions and a sudden drop in blood pressure might not be safe, and the procedures might not reflect a physiological situation. The method was therefore adapted to use spontaneous fluctuations of BP, after applying a fast Fourier transform algorithm to obtain the transfer function parameters coherence, gain and phase in the low frequency range of the frequency-domain. The inverse discrete Fourier transform of gain and phase transforms them back to the time-domain and gives an estimate of the CBFV impulse and step responses (Figure 3). This method correlates well with the thigh cuff test and is now a generally accepted method for the study of the dynamic cerebral autoregulation.

The transfer function parameters coherence, gain and phase by themselves are also used as a measure of autoregulation. Coherence, which is similar to a correlation coefficient, provides an indication of the correlation between the components at each frequency. A high coherence (approaching 1.0) would suggest that CBFV follows BP, and thus that the CA is impaired. However, this can also result from low noise levels, and therefore gives information about the reliability of gain and phase estimates at each frequency. Gain represents the degree to which the variables are amplified and is increased with worsening CA, but is also affected by CBFV and critical closing pressure. Phase indicates the time delay of the autoregulatory response, where a positive phase shift (indicating that CBFV changes before BP) indicates intact autoregulation. An inherent problem with phase is wrap-around, when absolute values of phase greater than $\pi$ radians are interpreted as being in the interval $\pm \pi$, confounding the analyses. These three parameters combined indicate the extent to which the input signal, BP, is reflected in the output signal, CBF. While all three variables are needed to give a reliable estimate of cerebral autoregulation, several studies have based their conclusions on changes in only one of these.
Factors affecting dynamic cerebral autoregulation functionality

The exact mechanisms of cerebral autoregulation remain unclear, but include metabolic, myogenic, and neurogenic regulation.\textsuperscript{92} Metabolic regulation adjusts blood flow to metabolic demand, arterial tension of carbon dioxide (PaCO$_2$) and oxygen supply. The main physiological determinant of CA is PaCO$_2$. Hypercapnia causes vasodilation, increased CBF and CBFV and a decreased autoregulatory response, whereas hypocapnia has the reverse effect.\textsuperscript{75,90,93} Activation of the brain increases the demand for oxygen and possibly weakens the CA function,\textsuperscript{93-96} but mental activation is not controlled for in most studies.

Myogenic regulation indicates the effect of transmural blood pressure changes on vascular smooth muscle tension to keep blood flow constant. Under normal circumstances, brain vessels possess intrinsic vascular tone, and the cerebral arteries constrict in response to increased pressure, and dilate in response to decreased pressure. This is also known as the “Bayliss effect.”\textsuperscript{97}

While the cerebrovascular bed is well innervated by sympathetic nerve fibers,\textsuperscript{57,97} the exact role of the autonomic nervous system on the regulation of dynamic CA remains controversial.\textsuperscript{58,97} Sympathetic neurotransmitters have a significant vasoconstrictor effect,\textsuperscript{57} but studies on their clinical function in static autoregulation are not consistent, except in the prevention of autoregulatory breakthrough and hyperperfusion during acute hypertension.\textsuperscript{92} Recent work on dynamic CA suggests a role for the autonomic, and possibly primarily sympathetic, nervous system in the short term regulation of CA.\textsuperscript{59,60,98}

Other factors affecting CA are body temperature, intracranial pressure, intra-thoracic pressure, and hematocrit.\textsuperscript{94} Interestingly age does not seem to affect CA.\textsuperscript{99} The effects of gender and hormonal changes, although less well studied, suggest that CA may be enhanced in women.\textsuperscript{100}

Traumatic brain injury,\textsuperscript{101} stroke,\textsuperscript{102} carotid artery stenosis,\textsuperscript{103} malignant hypertension\textsuperscript{104} and neonatal prematurity\textsuperscript{105} may all impair cerebral pressure autoregulation. These patients are at risk for secon-
dary brain injury from ischemia or vasogenic edema. Mild-to-moderate hypertension does not seem to affect the functionality,\textsuperscript{106-108} while the effect of diabetes is conflicting, showing either impaired autoregulation\textsuperscript{109,110} or no difference.\textsuperscript{111,112}

Other estimates of cerebrovascular hemodynamics

The relationship between BP and CBFV can also be expressed by a single parameter the cerebrovascular resistance index:

\[
\text{CVRi} = \frac{\text{BP}}{\text{CBFV}}
\]

This formula assumes that the flow/velocity reaches zero when the perfusion pressure (BP) is also zero.\textsuperscript{113} However, in many vascular beds, including the cerebral bed, flow/velocity can be zero at perfusion pressures greater than zero. This is known as the critical closing pressure (CrCP).\textsuperscript{114} Direct measurement of CrCP in humans is not possible, but linear interpolation of the instantaneous relationship between CBFV and BP during each heart beat shows an interception of the pressure axis at values significantly greater than zero. The inverse of the regression slope represents the resistance-area product (RAP),\textsuperscript{115} which has the same units as CVRi. (Figure 4)

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{Representative instantaneous velocity–pressure relationship for one cardiac cycle and indicating the critical closing pressure (CrCP) and resistance area product (RAP) before (+) and during (Δ) 5% CO\textsubscript{2} breathing for one subject. R.B. Panerai; Effect of CO\textsubscript{2} on dynamic cerebral autoregulation measurement (1999). Institute of Physics and Engineering in Medicine. Reproduced by permission of IOP Publishing. All rights reserved}
\end{figure}
These two parameters can be calculated as

\[
\text{CrCP} = \frac{-a}{b} \quad \text{and} \quad \text{RAP} = \frac{1}{b}
\]

Therefore, CBFV can be expressed as

\[
\text{CBFV} = \frac{\text{BP} \cdot \text{CrCP}}{\text{RAP}}
\]

Two other indices that often have been used to describe the cerebral hemodynamics in pregnancy are Pourcelot’s resistance index (RI) and Gosling’s pulsatility index (PI).\(^{116}\)

\[
\text{RI} = \frac{\text{CBFV}_{\text{systolic}} - \text{CBFV}_{\text{diastolic}}}{\text{CBFV}_{\text{systolic}}}
\]

\[
\text{PI} = \frac{\text{CBFV}_{\text{systolic}} - \text{CBFV}_{\text{diastolic}}}{\text{CBFV}_{\text{mean}}}
\]

The relationship between PI and cerebrovascular resistance has been debated. While some see the PI as a good substitute for CVR,\(^{117}\) the PI-CVR relationship may be disturbed by changes in upstream vascular resistance due to changes in the mechanoelastic properties of the large vessels.\(^{118}\)

Lastly, a formula for the cerebral perfusion pressure (CPP) was adapted and validated in pregnancy by Belfort et al. to estimate the cerebral perfusion pressure (CPP).\(^{119}\)

\[
\text{CPP} = \frac{\text{CBFV}_{\text{mean}}}{\text{CBFV}_{\text{mean}} - \text{CBFV}_{\text{diastolic}}} \times (\text{BP}_{\text{mean}} - \text{BP}_{\text{diastolic}})
\]

**Subcomponent analysis**

Using a multivariate model of the CBFV, the independent contributions of BP, RAP, CrCP and CVR to changes in CBFV can be analyzed. Separating the different systemic and cerebral influences that account for the CBF response allows the identification of the different hemodynamic contributions to the CBFV response using standardized units of measurement of CBFV at any instant of time.
Therefore, the CBFV response can be broken down into sub-components describing the relative contribution of each. The total percentage change in CBFV during breath holding can be represented in two ways: 1) as the sum of the simultaneous changes in BP, CrCP and RAP; and 2) as the sum of the changes in BP and CVRi. Using this method, it is suggested that CrCP is mainly influenced by the metabolic pathway, while RAP reflects myogenic activity in response to BP transients.

These analyses might give more insight into the physiological interpretation of the cerebral hemodynamic anomalies seen in preeclampsia. This method is used in Chapter 5 to compare the effect of breath holding between women with preeclampsia and a normotensive control group.

1.6 CEREBRAL HEMODYNAMICS IN PREGNANCY AND PREECLAMPSIA

Cerebral hemodynamics in pregnancy

The changes in central hemodynamics during pregnancy have been quite extensively studied and characterized, with both noninvasive and invasive techniques. The systemic cardiovascular changes are characterized by a large increase in cardiac output and plasma volume that is associated with a drop in systemic vascular resistance. The cerebral circulation is dependent on a constant blood supply, and relative intolerant to increases or decreases in blood volume. Our understanding of the adaptation of the cerebral circulation to these systemic hemodynamic changes is limited, because studies on cerebral hemodynamics and cerebrovascular structure are difficult to perform. Various imaging techniques have been applied to study the changes in maternal cerebral blood flow and animal models have been used to study the structural changes in the cerebral vasculature.

Several cross-sectional and longitudinal studies have examined maternal cerebral blood flow during pregnancy, using various techniques (Doppler ultrasound and MRI) and studying various blood vessels (middle cerebral, posterior cerebral and carotid artery). The flow velocity or flow volume and RI/PI in the middle cerebral artery (MCA) seems to be decreased in late-pregnancy when compared to non-pregnant women, while the CPP is
increased.\textsuperscript{[16]} Nevo \emph{et al.} showed an increase in the global CBF.\textsuperscript{[122]}

Very few investigators have studied the other major intracranial arteries (anterior and posterior cerebral arteries).\textsuperscript{[82]} This is most likely due to the greater difficulty in obtaining reliable Doppler signals from these vessels. In Chapter 2, the changes in cerebral blood flow velocity in the maternal anterior and posterior cerebral arteries during normal pregnancy and in the postpartum period are evaluated and compared to known values in the middle cerebral artery.

The exact mechanism of the changes in hemodynamics is not known, but might be caused by a combination of changes in carbon dioxide, hormones, cytokines, other circulating factors, and in perivascular innervation.\textsuperscript{[63, 128]} The increased levels of female sex hormones in pregnancy cause respiratory alkalosis and hypocapnia.\textsuperscript{[129]} This effect is almost fully established by 7-8 weeks of gestation.\textsuperscript{[129]} $\text{PaCO}_2$ is one of the main physiological determinants of the cerebral blood flow: a decrease in $\text{PaCO}_2$ increases the cerebrovascular resistance, decreases cerebral blood flow velocity due to constriction of the small arteries, and improves the cerebral autoregulation.\textsuperscript{[93, 130, 131]} Indeed, Brackley \emph{et al.} showed an increase in RI by 4-7 weeks of gestation, compared with pre-pregnancy values, suggesting increased downstream resistance.\textsuperscript{[127]} Estrogens have a direct vasodilator effect on the microvasculature through endothelial nitric oxide synthase.\textsuperscript{[133]}

The changes in cerebral autoregulation during pregnancy have not been studied in humans. In rats, the upper limit of autoregulation of the anterior and posterior circulations is slightly shifted to a higher pressure in late pregnancy, while the lower limit is shifted to the left only in the posterior artery when compared to non-pregnant rats.\textsuperscript{[63]} However, only late-pregnant rats had significant cerebral edema in response to acute hypertension, suggesting that the blood-brain barrier is more vulnerable to disruption during pregnancy.\textsuperscript{[63]} The effect of gestational age on autoregulation functionality in normal pregnancies is studied and compared to non-pregnant controls in Chapter 3.

While it is known that maternal demographic parameters such as age, race, pre-gestational hypertension, diabetes and obesity increase the risk for preeclampsia,\textsuperscript{[1, 24]} their effect on the cerebral blood flow in pregnancy has only sparsely been studied. Pregnant
women with mild chronic hypertension have normal cerebral hemodynamics,\textsuperscript{134} but those with gestational diabetes shown abnormal endothelium-dependent vasodilation after visual stimulation.\textsuperscript{135} In \textbf{Chapters 6 and 7}, the consequence of hypertension, diabetes and obesity on the cerebral autoregulation in pregnancy is investigated.

\textit{Cerebral hemodynamics in preeclampsia}

Several neuroradiological imaging techniques have been used to improve the understanding of cerebrovascular hemodynamic changes and the association with neurological symptoms seen in preeclampsia. Both TCD and MRI have shown increased cerebral blood flow velocity/volume in the MCA and PCA of women with preeclampsia when compared to normotensive controls,\textsuperscript{49,136-138} which persisted at least 48 hours postpartum,\textsuperscript{139} but had returned to normal at 6 to 8 weeks after delivery.\textsuperscript{136} Using TCD, the CPP variation in different hypertensive states of pregnancy has been studied. Belfort \textit{et al.} showed that while preeclampsia can lead to either normal, under- or over-perfusion (as indicated by CPP and compared to 95\% confidence intervals for normal pregnancy), 52\% of women with mild preeclampsia have underperfusion and 59\% of women with severe preeclampsia have overperfusion.\textsuperscript{140} Furthermore, preeclamptic women with headache were much more likely to have abnormal CPP than those without headache,\textsuperscript{141} and the CPP decreased after administration of labetalol\textsuperscript{142} or magnesium sulfate.\textsuperscript{143} Besides increased CPP and CBFV, multiple studies also reported decreased resistance\textsuperscript{83,137,144,145} and the severity of preeclampsia seems to correlate with the degree of any TCD abnormality.\textsuperscript{83,141,144,146}

The functionality of the cerebral vasculature has been studied by breath holding or breathing 5\% CO\textsubscript{2}. The hypercapnia that occurs as a result of these maneuvers leads to cerebral vasodilation and increased CBF, and reflects the ability of the vascular endothelium to adapt to changes in metabolic activity. This vasoreactivity is impaired in patients with conditions that have a predisposition for cerebrovascular disease, such as hypertension\textsuperscript{147,148} diabetes\textsuperscript{147,149} and carotid artery stenosis,\textsuperscript{147,150} and is thought to be the consequence of endothelial dysfunction.\textsuperscript{147,149} Previous studies in preeclampsia have shown conflicting results, with either impaired\textsuperscript{145,151} or unaffected\textsuperscript{152}
Cerebral hemodynamics in normal and complicated pregnancy

vasoreactivity. However, none of these studies measured the CBF velocity (CBFV) or the blood pressure (BP) continuously, and therefore lack information on the temporal pattern of the physiologic changes associated with hypercapnia.

Little is known about the cerebral autoregulation in preeclampsia. Oehm et al. showed a reduced phase shift and elevated gain in three patients with preeclampsia or eclampsia who were being treated with magnesium sulfate, suggesting impaired autoregulation when compared with healthy pregnant controls.\(^{153}\) Other studies interpreted increased CBFV, coupled with increased BP without increased resistance, as dysfunctional autoregulation.\(^{144, 146, 154, 155}\)

In Chapter 4, the ARI is used to test the hypothesis that preeclampsia is associated with impaired dynamic cerebral autoregulation.

Transcranial Doppler for prediction of preeclampsia

While the development of the disorder or its progression cannot be prevented, identification of women at risk will aid in early diagnosis and appropriate management and may improve maternal and perinatal outcome.\(^1\) Because the pathophysiological changes associated with preeclampsia begin early in pregnancy, many clinical, biochemical, and hematologic tests have been proposed as potential predictors for the future development of preeclampsia. For example, the maternal medical history, uterine artery Doppler,\(^{156}\) systemic hemodynamics\(^{157}\) and angiogenic balance\(^25\) are different before the onset of preeclampsia compared with women whose gestations proceed normally. However, none are highly predictive.

The use of TCD for the prediction of preeclampsia is an attractive proposition given its non-invasive modality, relatively low cost and the ease of use. Results have however been conflicting. Riskin-Mashiah et al. showed that women destined to develop preeclampsia had lower resistance index (RI) and pulsatility index (PI) some weeks before the development of preeclampsia.\(^{158}\) The same was true for women with chronic hypertension who subsequently developed SiPE when compared to those with CHTN who did not develop this.\(^{159}\) However, Janzarik et al. did not find this association, with either the dynamic cerebral autoregulation parameters phase or gain.\(^{160}\)
Chapter 8 deals with the hypothesis that second trimester MCA Doppler RI values can be used to predict the subsequent development of preeclampsia. In Chapter 6, the ARI was used to compare those who did and did not develop PE later in their pregnancy.

1.7 AIMS OF THE THESIS

The aim of the research described in this thesis was to contribute towards a better understanding of maternal cerebral hemodynamics during normal pregnancy and in pregnancies complicated by hypertensive disorders, obesity and diabetes.

The following aims were addressed:

- To define the normal range of blood flow velocity and velocity ratios in the maternal anterior and posterior cerebral arteries during normal pregnancy and the postpartum period. (Chapter 2)

- To investigate the effect of gestational age on autoregulation functionality in normal pregnancy and to compare this to non-pregnant controls. (Chapter 3)

- To test the hypothesis that preeclampsia is associated with impaired dynamic cerebral autoregulation. (Chapter 4)

- To compare the cerebrovascular response to breath holding in women with preeclampsia and their normotensive counterparts by using subcomponent analysis (Chapter 5)

- To investigate the cerebral autoregulation in the hypertensive disorders of pregnancy (superimposed preeclampsia, preeclampsia, chronic hypertension and gestational hypertension), and to compare this with a control group consisting of normotensive pregnant women. (Chapter 6)

- To investigate the effect of pre-gestational diabetes type II, gestational diabetes and obesity on the cerebral autoregulation in pregnancy (Chapter 7)

- To investigate the use of transcranial Doppler derived resistance index and autoregulation index for the prediction of the development of subsequent preeclampsia (Chapters 6 and 8).
ABBREVIATIONS

ARI: Autoregulation index
BP: Blood pressure
CA: Cerebral autoregulation
CBF: Cerebral blood flow
CBFV: Cerebral blood flow velocity
CHTN: Chronic hypertension
CPP: Cerebral perfusion pressure
CrCP: Critical closing pressure
CVR: Cerebrovascular resistance
CVRi: Cerebrovascular resistance index
EtCO₂: End-tidal carbon dioxide
GHTN: Gestational hypertension
MAP: Mean arterial pressure
MCA: Middle cerebral artery
PaCO₂: Arterial tension of carbon dioxide
PE: Preeclampsia
PI: Pulsatility index
PRES: Posterior reversible encephalopathy syndrome
RAP: Resistance area product
RI: Resistance index
SiPE: Superimposed preeclampsia
TCD: Transcranial Doppler
Chapter 1 - General introduction

References

Cerebral hemodynamics in normal and complicated pregnancy


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