Cerebral autoregulation: from minutes to seconds
Immink, R.V.

Citation for published version (APA):
Immink, R. V. (2013). Cerebral autoregulation: from minutes to seconds

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Onderzoek is eindeloos

CEREBRAL AUTOREGULATION
- FROM MINUTES TO SECONDS -
R.V. IMINK 2013

Abbreviations
ABP arterial blood pressure
ARI autoregulatory index
CA cerebral autoregulation
cHHb cerebral deoxygenated Hb content
cO\textsubscript{2}Hb cerebral oxygenated Hb content
CPP cerebral perfusion pressure
CrCP critical closing pressure
CSFP cerebrospinal fluid pressure
CVR cerebral vascular resistance index
f breathing frequency
FinAP finger arterial pressure
gCBI global cerebral blood flow
Hb hemoglobin
HF high frequency
HR heart rate
HUT head-up tilt
IAP intra arterial pressure
LBNP lower body negative pressure
LF low frequency
LS lacunar ischemic stroke
MABP mean arterial blood pressure
MCA\textsubscript{V} middle cerebral artery blood velocity
MCAS middle cerebral artery territory stroke
MRI magnetic resonance imaging
MVCP mean venous cerebral pressure
NIHSS National Institute of Health stroke scale
NIRS near infra-red spectroscopy
P\textsubscript{a}CO\textsubscript{2} arterial carbon dioxide pressure
P\textsubscript{a}O\textsubscript{2} arterial oxygen pressure
P\textsubscript{ET}CO\textsubscript{2} end-tidal carbon dioxide pressure
Q cardiac output
S\textsubscript{a}O\textsubscript{2} arterial oxygen saturation
SNP sodium nitroprusside
RS reference subjects
sCA static cerebral autoregulation
SGB stellate ganglion blockade
SV stroke volume
SVR systemic vascular resistance
TCD transcranial Doppler
V\textsubscript{E} pulmonary ventilation
V\textsubscript{E}/Q pulmonary ventilation perfusion ratio
VLF very low frequency
VCO\textsubscript{2} carbon dioxide production
VO\textsubscript{2} oxygen consumption
VT tidal volume
\Delta P(a-et)CO\textsubscript{2} arterial to end-tidal carbon dioxide difference.

Search the
Cerebral Autoregulation
- From Minutes to Seconds -
Cerebral Autoregulation
- From Minutes to Seconds -

ACADEMISCH PROEFSCHRIFT

Ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. D.C. van den Boom
ten overstaan van een door het college voor promoties ingestelde
commissie, in het openbaar te verdedigen in de Agnietenkapel
op vrijdag 11 januari 2013, te 10:00 uur

door

Rogier Vincent Immink

geboren te Middelburg
Promotiecommissie:

Promotores: prof. dr. A.F.M. Moorman  
prof. dr. J.J. van Lieshout

Co-promotores: dr. G.A. van Montfrans  
dr. J.M. Karemaker

Overige leden: prof. dr. M.A. van Buchem  
prof. dr. J.B.L. Hoekstra  
prof. dr. M.W. Hollmann  
prof. dr. C.J. Kalkman  
prof. dr. J. Stam

Faculteit der Geneeskunde
Chapter 1 Introduction

Chapter 2 Methods

Chapter 3 Posture Change and the Cerebrovascular Response

3.1 The postural reduction in middle cerebral artery blood velocity is not explained by $P_aCO_2$

3.2 Transient influence of end-tidal carbon dioxide tension on the postural restraint in cerebral perfusion

3.3 A stellate ganglion block does not affect the postural reduction in cerebral perfusion

Chapter 4 Microvascular Disease and the Cerebrovascular Response

4.1 Dynamic cerebral autoregulation in acute lacunar and middle cerebral artery territory ischemic stroke

4.2 Dynamic cerebral autoregulatory capacity is affected early in type 2 diabetes mellitus

Chapter 5 Malignant Hypertension and the Cerebrovascular Response

5.1 Impaired cerebral autoregulation in patients with malignant hypertension

5.2 Cerebral hemodynamics during treatment with sodium nitroprusside versus labetalol in malignant hypertension.

Summary
General Discussion
Samenvatting
Dankwoord
References
Een schrijver verget nooit de eerste keer dat hij een paar munten of een loftuiting accepteert in ruil voor een verhaal. Nooit verget hij de eerste keer dat hij het zoete gif van de ijdelheid in zijn bloed voelt en gelooft dat, als hij er nu maar in slaagt zijn gebrek aan talent voor iedereen verborgen te houden, de droom van de literatuur in staat zal zijn hem een dak boven het hoofd te verschaffen, een warme maaltijd aan het einde van de dag en, waar hij het meest naar hunkert: zijn naam gedrukt op een miezerig stuk papier dat ongetwijfeld langer zal leven dan hij. Een schrijver is veroordeeld tot de herinnering aan dat moment, omdat hij al verloren is en zijn ziel een prijs heeft.

Het spel van de engel
Carlos Ruiz Zafon
Chapter 1

Introduction
The oxygen supply to the brain depends on the arterial O₂ content and the global cerebral blood flow (gCBF) of 50 to 60 ml·100 g⁻¹·min⁻¹. The cerebral oxygen uptake is ~3 ml·100 g⁻¹·min⁻¹ accounting for 15% to 20% of the basal metabolic rate. In healthy subjects, an acute lowering of gCBF is associated with mild symptoms of cerebral hypoperfusion. Mental confusion becomes prominent with 50% to 60% reduction and cerebral oxygenation becomes affected. A total interruption of the blood supply to the brain for a few seconds will already result in loss of consciousness. Therefore, the supply of blood to brain tissue is autoregulated implicating that the gCBF is maintained constant despite changes in cerebral perfusion pressure. As for the control of brain blood flow, Niels Alexander Lassen made a distinction between metabolic, chemical, autoregulatory and neurogenic participating mechanisms.

**Historical overview**

Whether blood flow to the brain is controlled or not has been subject of debate for ages. Alexander Monro (secundus; *1733 – †1817) proposed in 1783 that, with the brain being embedded within the rigid skull and with intracranial tissue (fluids) virtually incompressible, an increase in arterial inflow was likely to be passively transmitted into an increase in venous outflow.

For, as the substance of the brain, like that of the other solids of our body, is nearly incompressible, the quantity of the blood within the head must be the same, at all times, whether in health or in disease, in life or after death, those cases only excepted, in which water or other matter is effused or secreted from the blood vessels: for these a quantity of blood, equal in bulk effused matter, will be pressed out of the cranium.....

This concept was supported by George Kellie (*1758 – †1829) in his manuscript entitled: “Account of the appearances observed in the dissection of two of the three individuals presumed to have perished in the storm of the 3rd and whose bodies were discovered in the vicinity of Leigh in the morning of the 4th of November 1821 with some reflections on the pathology of the brain.” This hypothesis is known since as the Monro-Kellie doctrine. Over one century later Hill stated:

The whole circulatory system of the brain will have assimilated itself into a system of rigid tubes and in every experimental condition, the cerebral circulation passively follows the change in the general arterial and venous pressure......

In 1846 Burrows disputed whether gCBF was totally dependent on extrinsic mechanisms. His suggestion was that the contents of the skull were to be maintained constant. He recognized the importance of cerebrospinal fluid and its relation to the veins in the cranio-spinal hydraulic system and emphasized that although the brain was incompressible, this was not as important as the fact that changes in brain volume could occur at the expense of volume occupied by other fluids. A few years later, the postulation that also intrinsic regulatory mechanisms are present, was supported by Donders who observed varying pial capillary diameters together
with changes in arterial blood pressure through a glass window which he mounted into a
trephine hole in the skull of animals.
In 1890 Roy and Sherrington230 monitored arterial blood pressure (ABP) simultaneously in the
internal carotid artery and the jugular vein together with intracranial pressure. They were the
first to suggest an existence of (metabolic) cerebral autoregulation:

…… These facts seem to us to indicate the existence of an automatic mechanism by which the
blood-supply of any part of the cerebral tissue is varied in accordance with the activity of the
chemical changes which underlie the functional action of that part…. 

In the 1930s Fog observed in various animals that increasing and decreasing arterial pressure
was accompanied by, respectively, vasoconstriction and vasodilatation of pial arteries.71,73
These responses appeared independent from the method applied to vary arterial pressure, like
hypovolemia or epinephrine administered intravenously or intra-arterially, and was
equally unaffected after sectioning of either the vagus nerve, the cervical sympathetic nerve or
the pressoreceptor nerves (i.e. the carotid sinus nerves).70,72,74 The onset of these responses
took about 3 to 7 seconds and steady state was reached after 1 minute. When ABP was
decreased slowly, pial arteries dilated progressively with a maximal vessel diameter at a mean
aortic pressure of 40 mmHg. Vice versa, a slow progressive increase in ABP resulted in a slow
progressive reduction in vascular diameter whereas an acute rise in blood pressure (>200
mmHg) dilated pial arterioles irreversibly for several hours.151

In 1945, Kety and Schmidt145 developed a technique which allowed for quantification of gCBF
in awake humans based on assessment of internal jugular venous flow (assuming complete
venous drainage of all brain tissue) from the time-dependent uptake of N2O in the brain,146,155 and
then (often) recording of the clearance curve for the tracer.172 To obtain one single
measurement, a subject inhales N2O (15%) in air for 10 to 15 minutes. Following saturation of
cerebral tissue, carotid artery and jugular venous blood are sampled simultaneously and the
arterial-venous concentration difference is determined. gCBF is calculated according to the
Fick principle,67 (the quantity of any substance taken up in a given time by an organ from the
blood which perfused it, is equal to the total amount of the substance carried to the organ by
the arterial inflow less the amount removed by the venous drainage during the same time
period). With this technique gCBF appeared more or less constant when arterial pressure was
raised.144 Although the Kety-Schmidt method for measuring gCBF is generally considered to
measure total CBF (ml 100 g⁻¹ min⁻¹), it is unlikely that this represents flow from all parts of
the brain. Venous drainage from the brain is most often asymmetric with the central sinus
preferentially draining into the larger (right) internal jugular vein, while blood from deep
structures of the brain being directed to the smaller (left) jugular vein. To overcome these
limitations of the Kety-Schmidt method a number of alternative methods of assessing gCBF
have been developed, including labeled microspheres in experimental animals,49,133Xe clearance
A decade later Lassen\textsuperscript{155} reviewed studies that quantified gCBF in man using the Kety-Schmidt technique during controlled hypotension, and proposed the “classical” cerebral autoregulation (CA) curve relating gCBF to mean arterial blood pressure (MABP). The curve represents constant gCBF for a range of pressures with ~60 mmHg as the lower limit of CA. The upper limit of CA was subsequently determined by Ekström-Jodal in hypercapnic dogs in 1971.\textsuperscript{59} Further studies located the upper limit of CA between ~120 and 150 mmHg in normotensive baboons\textsuperscript{252} and between ~155 and 170 mmHg in hypertensive baboons.\textsuperscript{251} When arterial pressure surpassed the upper limit of CA, constriction of cerebral resistance vessels appeared to give way to the high pressure leading to an increase in gCBF.\textsuperscript{168}

In his landmark paper, Lassen used changes in MABP as a surrogate of cerebral perfusion pressure representing the driving force for visualizing the phenomenon of cerebral autoregulation.\textsuperscript{155} Cerebral Perfusion Pressure (CPP) can be expressed as the pressure forcing blood through the cerebral vessels or the difference between MABP and the sum of mean venous cerebral outflow pressure (MVCP) and cerebrospinal fluid pressure (CSFP);

\[
\text{CPP} = \text{MABP} - \text{MVCP} - \text{CSFP}
\]

\textit{Changing venous outflow pressure}

In daily life, the MABP of the human brain (~90 mmHg) is the main determinant for CA. Theoretically, artificially raising venous outflow pressure would be expected to reduce CPP and thus gCBF in absence of compensatory mechanisms. Under experimental conditions, MVCP usually ranging between approximately 2 and 5 mmHg, has been elevated by, respectively, inflating a cuff around the neck for a few seconds\textsuperscript{184} or by superior vena cava compression.\textsuperscript{129} The outcome of these studies was that notwithstanding rising venous outflow pressure, CPP had declined no further than 60 mmHg, with gCBF more or less maintained. When in dogs CPP was decreased further, gCBF declined and ABP rose.\textsuperscript{43} This rise in ABP referred to as ‘Cushing effect’ may be interpreted as a counter regulatory mechanism to increase cerebral inflow pressure to compensate for the experimentally increased outflow pressure and thus to keep CPP more or less constant.\textsuperscript{94}

\textit{Changing cerebrospinal fluid pressure}

gCBF remains preserved during increasing or decreasing cerebrospinal fluid pressure in animals due to dilatation or constriction respectively of pial arteries\textsuperscript{244} \textsuperscript{245} whereas MABP remains more or less unaltered. When intracranial pressure increases further vasodilatation of the pial arteries is not sufficient to preserve gCBF and ABP starts to increase.\textsuperscript{285} Also in humans with increased intracranial pressure due to intracerebral tumors, gCBF was within the normal range.\textsuperscript{282} The first direct measurements of gCBF with the Kety-Schmidt method were performed in 1948 in patients with intracranial hypertension and with confirmatory findings. The authors found intracranial pressure to increase linearly with MABP whereas gCBF remained unaffected at intracranial pressures up to 33 mmHg. Beyond this level gCBF fell progressively.\textsuperscript{147} Fluctuating CSFP by injecting or removing cerebrospinal fluid in dogs resulted in a virtually unchanged gCBF as long as intracranial pressure was lower than 100 mmHg.\textsuperscript{94} When
intracranial pressure returned to normal levels, a temporary cerebral hyperemia of over one hour was observed.95

**Outline of the thesis**
This thesis focuses on CA in three clinical situations.

**Chapter 2** describes the devices to monitor systemic, cerebral and pulmonary parameters used in this thesis and explains how CA and carbon dioxide sensitivity will be quantified.

**Chapter 3** analyzes why in the upright vs. the supine position gCBF is lower. According to the pressure-flow relationship as formulated by Lassen155 this observation is unexplained since the postural decline in MABP at the level of the brain is within what is considered to be the cerebrovascular autoregulatory range. Two possible explanations for this phenomenon were studied.

At first, earlier reports suggested that when assuming the upright position, the partial arterial carbon dioxide pressure (P\textsubscript{a}CO\textsubscript{2}) decreases\textsuperscript{20} due to an increase in pulmonary minute ventilation.\textsuperscript{36, 191} A low P\textsubscript{a}CO\textsubscript{2} reduces gCBF by cerebral vasoconstriction\textsuperscript{163} independently from CA. This is known as the CO\textsubscript{2} reactivity of the brain circulation. The non-invasively acquired partial end-tidal carbon dioxide pressure (P\textsubscript{ET}CO\textsubscript{2}) is often applied as an estimate of P\textsubscript{a}CO\textsubscript{2}. In chapter 3.1 we tested the hypothesis that the postural decrease in gCBF as estimated by the transcranial Doppler (TCD) derived mean middle cerebral artery velocity (MCA V\textsubscript{mean}) is explained by the concomitant decline in P\textsubscript{a}CO\textsubscript{2}. In chapter 3.2 we addressed whether the control of gCBF during a posture change is independent from the P\textsubscript{a}CO\textsubscript{2}. To test this hypothesis we developed a method to clamp the P\textsubscript{a}CO\textsubscript{2}\textsuperscript{14} when changing tidal volume and breathing frequency (f).

Secondly, standing up elicits a gravitational displacement of blood to the abdomen and the legs affecting the preload to the heart and Cardiac output (Q) is reduced. Sympathetic activation with an increase in heart rate (HR) and systemic vascular resistance (SVR) maintain MABP as sympathetic activity raises.\textsuperscript{78} Although cerebral conductance vessels, like the MCA, have α- and β-adrenergic nerve receptors\textsuperscript{42} their influence remains a matter of debate.\textsuperscript{253, 266} In Chapter 3.3 we took the opportunity to evaluate the potential role of sympathetic activation for regulation of gCBF during orthostatic stress provided by chronic pain patients for whom the treatment was supplemented by an unilateral stellate ganglion blockade (SGB). SGB suppresses ipsilateral sympathetic activity to the arm, neck, and head. Thus, the patients were asked to stand up before and after the block while cerebral and central hemodynamic variables were monitored.

**Chapter 4** focused on the efficacy of CA capacity during cerebral ischemia and microvascular disease. In chapter 4.1 we tested the hypothesis that cerebral ischemia impairs CA. We therefore monitored beat-to-beat MABP and bilateral MCA V\textsubscript{mean} in two distinct subtypes of stroke, that is, large trombo-embolic MCA territory stroke (MCAS) and in small vessel lacunar stroke of the basal ganglia (LS). CA was evaluated in the time- and frequency domains as the delay of the MCA V\textsubscript{mean} counter-regulation during spontaneous changes in MABP and the cross-spectral MCA V\textsubscript{mean}-to-MABP phase lead, respectively. In chapter 4.2 we hypothesized that in subjects with type 2 diabetes and manifest microvascular complications but without symptomatic cerebrovascular disease, CA capacity may become impaired in absence of
cardiovascular autonomic neuropathy.
In chapter 5 we investigated patients with malignant hypertension (i.e. an ABP level above the upper limit of CA). When CA is compromised gCBF becomes dependent upon ABP. The traditional teaching is that in order to prevent the occurrence of cerebral hypoperfusion by pharmacological treatment the initial reduction in ABP should not be more than ~25% of the presenting value. In chapter 5.1 we analyzed CA before, during and after immediate ABP treatment with intravenously administered sodium nitroprusside (SNP). In chapter 5.2 we addressed whether the effects on MCA $V_{\text{mean}}$ of SNP, a nitric oxide donor, are comparable to those of labetalol, a mixed $\alpha$- and $\beta$-adrenergic antagonist.
Chapter 2

Methods
2.1 Parameters

2.1.1 Systemic
   Blood pressure
   Hemodynamics

2.1.2 Cerebral
   Middle cerebral artery blood velocity
   Frontal lobe cerebral tissue oxygenation

2.1.3 Pulmonary
   Ventilatory parameters
   Partial end-tidal carbon dioxide pressure
   Partial arterial carbon dioxide pressure

2.2 Quantification of Cerebral Autoregulation

2.2.1 Static cerebral autoregulation

2.2.2 Dynamic cerebral autoregulation

2.3 Quantification of Cerebral Carbon Dioxide Reactivity
2.1 PARAMETERS

2.1.1 Systemic

Blood Pressure
In the studies presented in this thesis continuous ABP was monitored either non-invasively as
finger arterial blood pressure (FinAP) measured by servo controlled photoelectric
plethysmography (Portapres M2, Finapres M5 or Nexfin; Netherlands Organization for
Applied Scientific Research, Biomedical Instrumentation, TNO-BMI, Amsterdam, The
Netherlands or NexFin, BMEye, Amsterdam, The Netherlands). Intra arterial blood pressure
(IAP), as oscillometric blood pressure (ABP; HEM-705CP, Omron, Kyoto, Japan
or
invasively via a catheter (1.1 mm ID, 20 gauge) placed in the brachial or radial artery of the
non-dominant arm (IAP after calibrating and zeroing to the midaxillary level) with the patient
in the supine position. The FinAP cuff was applied to the middle finger of the dominant hand
placed at heart level supported by a sling. To detect changes in FinAP correctly, a built-in
expert system (Physiocal) tracks the unloaded diameter of the finger artery to establish and to
adjust the arterial unloaded volume.24 Changes in FinAP accurately track changes in IAP during
normotension and moderate hypertension 25, 57, 76, 116-121, 132-288 and the studies in chapter 5
extend these observations to extreme hypertension.

Hemodynamics
Mean IAP and mean FinAP was measured as the integral over one heart beat. HR was the
inverse of the inter beat interval. Stroke volume (SV) was determined by a three-element model
of arterial input impedance (Modelflow).278 SV was calculated from the blood pressure
waveform using the model flow method incorporating age, sex, height, and weight (BeatScope
1.0 software; BMEye, Amsterdam, The Netherlands).133 This technique tracks fast changes in
SV,98, 131, 133, 278 SV was expressed as percentage change of the initial value,
Q was HR times SV
and systemic vascular resistance (SVR) was the ratio of MABP and Q. When calibrated against
a gold standard method such as thermodilution or Fick, this methodology provides accurate
estimates of changes in SV in patients with septic shock,133 cardiovascular disease,131, 278, during
orthostatic stress98, 267, exercise254, and under conditions of moderate hypocapnia (P_{\text{ETCO}}_2 =
\sim30 \text{ mmHg}) as induced by orthostatic stress.98

2.1.2 Cerebral

Steady state values for gCBF have been earlier reported as the clearance of gases including
N_2O and ^{133}\text{Xe}, or a tracer such as indocyanine green, or as the arterial-jugular venous O_2
difference. A disadvantage of these methods is that one gCBF measurement takes about 15
minutes185 making these methods impractical for monitoring the autoregulatory abilities of
gCBF in response to rapid changes in cerebral perfusion pressure.

Cerebral tissue oxygenation
The “accidental” discovery of near-infrared energy is ascribed to William Herschel in 1800. The
principle of tissue spectroscopy for oxygen is well known and ‘pulse oximetry’ of the
oxygen saturation of arterial blood is based on the ear oximeters of Millikan published in
1942. Thirty-five years later Jöbsis described brain spectroscopy in cats applying the same method as reported by Millikan. In this thesis the oxygen content of frontal lobe cerebral tissue oxygenation was monitored by near infra-red spectroscopy (NIRS) based on the tissue transparency to light in the near-infrared region and on the \( O_2 \) dependent absorption changes in absorption in cerebral tissue caused by chromophores, i.e. mainly oxy- and deoxy-hemoglobin (cO\(_2\)Hb and cHHb). Using an adapted computation based on Lambert-Beer’s law, changes in light absorption at different wavelengths are measured and tissue oxygenation is monitored. To estimate the concentration changes in cO\(_2\)Hb and cHHb a differential path length factor of 6.0 was applied to account for the scattering of light in the tissue. A continuous wave Oxymon NIRS instrument (Artinis Medical Systems b.v., Zetten, the Netherlands) with three wavelengths (at 901, 848 and 770 nm) and 10 Hz sampling time, or an INVOS 3100 NIRS (Somanetics, Troy, MI, USA) was used. The NIRS optodes were attached on the right side of the forehead to avoid the frontal sinuses and sufficiently lateral to avoid the sagital sinus with the transmitting and receiving optodes placed 5.5 cm apart. Since there is no standard for cerebral oximetry, calibration is not possible. Major consideration is that the relative position of the pigments sampled by NIRS remains unclear. Based on anatomical studies it is suggested that in the cerebral tissue volume sampled by NIRS the amount of hemoglobin in the arterioles is ~20%, in the capillaries is ~5% and in the venules about 75%. This suggests that the NIRS value for cerebral oxygenation is dominated by the local venous \( O_2 \) saturation rather than the tissue \( O_2 \) content. The NIRS determined oxygenation changes in parallel with gCBF as determined by \(^{133}\)Xe clearance and estimated cerebral \( O_2 \) saturation in humans during carotid clamping and declamping compares satisfactorily with jugular bulb venous \( O_2 \) saturation. Olsen et al. determined the lower limit of CA by reducing arterial pressure through a combined pharmacological and physical approach by providing pharmacological \( \alpha \)- and \( \beta \)-adrenoceptor blockade by labetalol and applying subatmospheric pressure to the lower part of the body (lower body negative pressure, LBNP). The level of blood pressure at which the cerebral arterio-venous \( O_2 \) saturation dropped was set equal to the lower limit of CA. The cO\(_2\)Hb correlated weakly with the internal jugular bulb saturation and the absolute values of the cO\(_2\)Hb were higher but, with both methods the lower limit of CA could be determined at an almost identical arterial pressure level. To our knowledge, the upper limit of CA has, for obvious reasons, never been determined in humans.

Also NIRS tracked positron emission tomography derived parameters like cerebral blood volume and flow with cerebral vasodilatation by acetazolamide. Frontal lobe NIRS follows brain capillary oxygen saturation as calculated from the \( O_2 \) content of brachial arterial and right internal jugular venous blood when supine and seated, with inhaled \( O_2 \) air-mixtures (10% to 100%) with and without added 5% carbon dioxide and during hyperventilation, supporting that NIRS is an adequate cerebral capillary-oxygenation-level-dependent measure during manipulation of CBF or inspired \( O_2 \) tension. We report changes in cO\(_2\)Hb and cHHb concentration (\( \mu \)mol\( \cdot \)l\(^{-1} \)) with supine control values as reference set at 0 \( \mu \)mol\( \cdot \)l\(^{-1} \).
**Middle cerebral artery blood velocity**

In 1982 Aaslid et al.\(^4\) proposed to study cerebral hemodynamics with Doppler ultrasound. A critical issue is to what extent blood velocity reflects an actual volume flow. In the unlikely case that blood flow is not laminar, the blood velocity changes out of proportion with volume flow. Changes in velocity are parallel with volume flow only when both the angle of insonation and the diameter of the vessel remain constant. The large cerebral arteries are conductance rather than resistance vessels and changes in systemic arterial blood pressure within the physiological range appear to have a negligible effect on the diameter of the insonated artery.\(^8^7\)\(^-^\)\(^2^4^1\) Validation studies found that changes in MCA \(V_{\text{mean}}\) follow cerebral \(\text{\textsuperscript{133}}\text{Xe}\) clearance.\(^1^9^\)\(^-^\)\(^4^0\)

The TCD derived MCA \(V\) was measured in the proximal segments of the left and/or right MCA (DWL Multidop X4, Sipplingen, Germany) with a 2.5 MHz probe located just above the zygomatic arch. When a sonogram is found three steps have to be taken to make certain that it is actually the MCA that is insonated. First, the velocity pattern should be positive indicating that the flow is towards the probe. Second, the flow signal should remain present when the insonation depth is decreased to \(\sim 35\) mm. Third, the insonation depth is increased and above a insonation depth of \(55\) mm the velocity signal will change because the bifurcation with the anterior cerebral artery will be reached.\(^2^2^4\) Once the optimal signal-to-noise ratio is obtained at a insonation depth between \(45\) and \(55\) mm, the probe is secured with a headband (Mark 600, Spencer Technologies, Seattle, USA). TCD determinations of MCA \(V_{\text{mean}}\) are reproducible with a difference between two measurements of less than 3% with \(R=0.95.\)\(^4^5\) The cerebrovascular resistance index (CVRI) is expressed as the ratio of MABP and MCA \(V_{\text{mean}}.\)\(^2^8^0\) The Gosling pulsatility index of the MCA is taken as an index of cerebral microangiopathy expressed as the amplitude of MCA \(V\) divided by time-averaged MCA \(V.\)\(^1^5^9\)

In the patients suffering acute ischemic stroke described in chapter 4.1 the MCA \(V\) was measured bilaterally. In these patients we checked the patency of the carotid arteries by Doppler imaging with a 4.5- to 5.5-MHz transducer (Hewlett Packard SONOS 2000).

2.1.3 Pulmonary

Ventilatory parameters

Respiratory parameters were obtained from a Zirconia \(\text{O}_2\) analyzer and a nondispersive infrared sensor for \(\text{CO}_2\) (MedGraphics CPX/D, St. Paul, Minnesota) that reported tidal volume (\(V_T\)), breathing frequency, \(\text{O}_2\) consumption (\(V_{\text{CO}_2}\)) and \(\text{CO}_2\) production (\(V_{\text{CO}_2}\)). \(V_T\) multiplied by \(f\) is pulmonary ventilation (\(V_{\text{E}}\)).

Partial end-tidal carbon dioxide pressure

\(P_{\text{ETCO}_2}\) was monitored by a sampling infrared capnograph (Datex Normocap 200, Helsinki, Finland or Tonocap, Datex-Ohmeda, Madison, USA).

Partial arterial carbon dioxide pressure

\(P_{\text{aCO}_2}\), partial arterial oxygen pressure (\(P_{\text{aO}_2}\)), arterial oxygen saturation (\(S_{\text{aO}_2}\)) and \(p\text{H}\) were determined by sampling blood from the radial artery that was anaerobically stored in heparinized syringes and analyzed immediately on an OSM-500 and ABL-3 apparatus.
2.2 QUANTIFICATION OF CEREBRAL AUTOREGULATION

gCBF remains relatively constant despite variation in cerebral perfusion pressure between ~50 and 150 mmHg. Both fast and slow acting regulatory mechanisms are required to span the prevailing demands on gCBF in everyday life.2

2.2.1 Static Cerebral Autoregulation

Static cerebral autoregulation (sCA) reflects the overall efficiency of the cerebrovascular autoregulatory system and is assessed by monitoring the gCBF during different steady state blood pressure levels. Since changes in gCBF are tracked by changes in MCA $V_{mean}$, sCA is considered to be intact when constancy of MCA $V_{mean}$ is maintained during a decrease in MABP at the level of the MCA and is impaired when the MCA $V_{mean}$ changes together with MABP at brain level. To assess sCA for individual subjects, in this study the continuous signals of MCA $V_{mean}$ and IAP were first averaged to 30 seconds episodes and then linearly related to each other.

The steady state response of MCA $V_{mean}$ to a postural change in relation to MABP at brain level was assessed from data sampled from 1 min prior to standing up, and again at 5 min in the upright position. Gravitational displacement of blood to the abdomen and the legs affects preload to the heart and reduces $Q$ by ~15%. An increase in HR (by ~20 min$^{-1}$) SVR (by ~30%) maintain ABP as sympathetic activity raises.99 On top of these large shifts in systemic hemodynamic parameters, the head becomes positioned approximately 30 cm above heart level, resulting in a reduction in CPP of ~20 mmHg.268 This results in a decrease in $\text{etCO}_2$268 and gCBF reflected by the TCD determined MCA $V_{mean}$. In healthy subjects, sCA limits the physiological reduction in MCA $V_{mean}$ to ~15% following a postural change.96,215,265,268

2.2.2 Dynamic Cerebral Autoregulation

Time domain

Dynamic cerebral autoregulation (dCA) refers to the ability to restore gCBF in the face of a sudden change in perfusion pressure and reflects the latency of the system.3 It is quantified by the counter-regulatory capacity to maintain MCA $V$ constant during induced or spontaneous abrupt changes in blood pressure. Tiecks et al.260 introduced a dynamic autoregulatory index (ARI) based on a second-order differential equation. The autoregulatory index ranges from 0 (absence of CA) to 9 (best measurable CA). Each from these ten integer value correspond to a MCA $V$ template response curve. The modeled second-order curve that best fits the measured MCA $V$ curve will then determine the corresponding value of the ARI. This model was validated on blood pressure decreases created with bilateral thigh cuff release but later also on arterial pressure changes during a Valsalva maneuver.260 An ARI of 5 or higher is considered to indicate integrity of CA.260

We manually selected upward and downward BP transients lasting at least 10 seconds at a stable $P_{ETCO_2}$. All 10 second episodes per 15 min tracing were identified and averaged curves.
of all 10 seconds up- and downward ABP transients plotted. In the time domain, dCA is considered adequate with MCA $V_{\text{mean}}$ remaining stable during a change in MABP, apart from $\sim 4 s$ delay, and is considered to be impaired when MCA $V_{\text{mean}}$ follows MABP passively.$^{127}$

**Frequency domain (Figure 1)**

In awake subjects we determined dCA in the frequency domain from the spontaneous oscillations observed in continuous IAP or FinAP recordings. High frequency (HF) rhythmic oscillations (0.15-0.3 Hz) are related to respiration and some consider this to be a marker for vagal modulation. Low frequency (LF) BP oscillations (0.07-0.15 Hz), also referred to as Mayer waves, are considered to be a marker for sympathetic modulation.$^{173}$ although the suggested relationship between spectral components of cardiovascular variabilities and direct measures of muscle sympathetic nerve activity$^{200, 265}$ has been disputed$^{231}$ These oscillations are transferred to the brain vasculature where changes in gCBF are recorded by TCD and output as MCA $V$ signal. The cerebral autoregulatory mechanism acts as a high pass filter. This has several implications. LF oscillations in MABP will also be present but damped in the MCA $V_{\text{mean}}$ signal whereas HF MABP oscillations will pass more or less unmodified. Furthermore, oscillations in MCA $V_{\text{mean}}$ in the low frequency range precede those in MABP with $\sim 50$ to 70 degrees$^{52}$ whereas in the HF range this phase difference declines.$^{22}$ dCA is considered to be impaired when the LF phase lead decreases to $\sim 30^\circ$ as observed in patients with carotid artery obstruction$^{52}$ or malignant hypertension.$^{127}$ dCA in the frequency domain was examined from a 2 to 3 min tracing of beat-to-beat ABP and MCA $V$ data (panel A). MABP and MCA $V_{\text{mean}}$ (panel B) were spline interpolated and resampled at 4 Hz. With Discrete Fourier Transform, the MABP and MCA $V_{\text{mean}}$ variability was expressed as a continuous curve or as the integrated areas in the very low frequency (VLF: 0.02-0.07 Hz), LF and the HF ranges (panel C).

To examine the strength between MABP and MCA $V_{\text{mean}}$, the coherence was used to signify that the two cardiovascular signals co-vary significantly at a given frequency (panel D). The coherence function reflects the fraction of output power (MCA $V_{\text{mean}}$) that can be linearly related to the input power (MABP) at each frequency. Similarly to a squared correlation coefficient, it varies between 0 and 1. From the MABP to MCA $V_{\text{mean}}$ cross-spectrum, the transfer function gain (cm·s$^{-1}$·mmHg$^{-1}$) and the MCA $V_{\text{mean}}$ to MABP phase lead (degrees) were obtained (panel E).$^{292}$ The transfer function gain was normalized for MABP and MCA $V_{\text{mean}}$ to account for the inter subject variability and expressed as % change in cm·s$^{-1}$ per % change in mmHg.$^{205}$ Phase was defined positive where MCA $V_{\text{mean}}$ leads MABP. Theoretically, dCA is assumed to be impaired when the LF phase lead decreases together with an increase in gain. However, the majority of clinical studies did not report simultaneous changes in gain and phase when CA had deteriorated leaving this matter as yet unsettled. Some studies reported an increasing gain together with an unmodified phase$^{22, 292}$ while others found a declining phase with a constant gain.$^{102, 128}$ It remains as yet unsettled whether phase or gain is to be considered as the best parameter of dCA capacity. This thesis follows the concept developed by Panerai who concluded, based on model studies, that when quantifying dCA, phase is the more robust parameter required and that a high value of gain should not be accepted as an indication of impaired CA in the presence of higher values of phase$^{206}$.
Figure 2.2.1 Calculation of the mean middle cerebral artery blood velocity (MCA \( V_m \)) to mean arterial pressure (MABP) phase difference and gain. First, a two or three minute tracing of blood pressure (ABP) and MCA \( V \) was isolated (panel A) and the MABP and MCA \( V_m \) were calculated (panel B). With Discrete Fourier Transform the variability was expressed as a continuous curve (panel C). The squared coherence function is calculated to signify that the two cardiovascular signals co-vary with each other or not (panel D). If the coherence is above 0.5, the MCA \( V_m \) to MABP phase lead and gain can be determined (panel E).
2.3 QUANTIFICATION OF CEREBRAL CARBON DIOXIDE REACTIVITY

Changes in $P_a\text{CO}_2$ have a pronounced influence on gCBF independently from CA$^{124}$. Hypocapnia induces a decrease in gCBF of ~1 ml·100 g·min$^{-1}$ per mmHg$^{277}$ by cerebral vasoconstriction whereas gCBF increases by hypercapnia. Reducing $P_a\text{CO}_2$ from 40 to 25 mmHg halves gCBF whereas further reductions in $P_a\text{CO}_2$ are not effective.$^{219}$ Increasing the $P_a\text{CO}_2$ to 80 mmHg increases gCBF by six-fold but ~50% of it is related to endogeneous catecholamine release and activation of neuronal metabolism.$^{16}$

The sensitivity of the gCBF to CO$_2$ is expressed as its percentage change per mmHg in $P_a\text{CO}_2$ (the CO$_2$ reactivity of the brain)$^{162}$ and is quantified non-invasively by relating changes in MCA $V_{\text{mean}}$ to those in the $P_{ET\text{CO}_2}$. The MCA $V_{\text{mean}}$ to $P_{ET\text{CO}_2}$ relationship is non-linear with a lower sensitivity of the MCA $V_{\text{mean}}$ to changes in $P_{ET\text{CO}_2}$ with hypocapnia compared to hypercapnia.$^{114}$ In the normocapnic range, MCA $V_{\text{mean}}$ changes ~3.5% per mmHg $P_{ET\text{CO}_2}$.$^{141}$ However, CA is functioning slightly less efficient during hypercapnia and more under hypercapnic conditions.$^{206}$

The exact mechanism of action has not been fully clarified. It is not the initial change in $P_a\text{CO}_2$ but the concomitant change in pH that modifies gCBF. Applying acid or alkalic solutions dilates respectively constricts cerebral arteries$^{273}$ whereas gCBF has a tendency to normalize during either chronic hypocapnia$^{243}$ or chronic hypercapnia.$^{277}$ More definite evidence about this issue was indicated by Kontos et al. when applying artificial cerebrospinal fluid to the brain of anesthetized cats. They found that the cerebral arteriolar diameter responded to changes in pH when fluid $P_{\text{CO}_2}$ was clamped while in the reversed experiment, clamping the pH with variation of the fluid $P_{\text{CO}_2}$, did not change cerebral vessel diameter.$^{150, 152}$ The site of action remains unclear. In animal studies endothelial damage,$^{275}$ tetrodotoxin (a sodium channel blocking agent),$^{112}$ or selective destruction of cortical neurons$^{111}$ did not alter CO$_2$ reactivity.
Chapter 3

Posture Change and the Cerebrovascular Response
3.1

The postural reduction in middle cerebral artery blood velocity is not explained by $P_a \text{CO}_2$


European Journal of Applied Physiology 2006(96)609-614
INTRODUCTION  In the normocapnic range, MCA $V_{\text{mean}}$ changes ~3.5 % per mmHg carbon dioxide tension in $P_{\text{aCO}_2}$ and a decrease in $P_{\text{aCO}_2}$ will reduce CBF by vasoconstriction (the CO$_2$ reactivity of the brain). When standing up MCA $V_{\text{mean}}$ and the $P_{\text{ETCO}_2}$ decrease, suggesting that $P_{\text{aCO}_2}$ contributes to the reduction in MCA $V_{\text{mean}}$. In a fixed body position $P_{\text{ETCO}_2}$ tracks changes in the $P_{\text{aCO}_2}$ but when assuming the upright position, $Q$ decreases and its distribution over the lung changes, while $V_{\text{E}}$ increases suggesting that $P_{\text{ETCO}_2}$ decreases more than $P_{\text{aCO}_2}$. This study evaluated whether the postural reduction in $P_{\text{aCO}_2}$ accounts for the postural decline in MCA $V_{\text{mean}}$.

METHODS  From the supine to the upright position, $V_{\text{E}}, Q, P_{\text{ETCO}_2}, P_{\text{aCO}_2}$, MCA $V_{\text{mean}}$ and the NIRS determined cO$_2$Hb were followed in seven subjects.

RESULTS  When standing up, MCA $V_{\text{mean}}$ (from 65.3±3.8 to 54.6±3.3 cm$^2$s$^{-1}$; mean±S.E.M.; $P < 0.05$) and cO$_2$Hb (~7.2±2.2 μmol$l^{-1}$; $P < 0.05$) decreased. At the same time the pulmonary ventilation perfusion ($V_{\text{E}}/Q$) ratio increased 49±14% ($P < 0.05$) with the postural reduction in $P_{\text{ETCO}_2}$ overestimating the decline in $P_{\text{aCO}_2}$ (~4.8±0.9 mmHg vs. ~3.0±1.1 mmHg; $P < 0.05$).

CONCLUSION  When assuming the upright position, the postural decrease in MCA $V_{\text{mean}}$ seems to be explained by the reduction in $P_{\text{ETCO}_2}$ but the small decrease in $P_{\text{aCO}_2}$ makes it unlikely that the postural decrease in MCA $V_{\text{mean}}$ can be accounted for by the cerebral CO$_2$ reactivity alone.
Introduction

Cerebral autoregulation indicates that blood flow to the brain is adjusted to remain relatively stable in the face of wide changes in its perfusion pressure. However, when humans assume the upright position, gCBF, the TCD determined MCA \(V_{\text{mean}}\), and the NIRS determined cO2Hb decrease. Such reductions in indices of gCBF take place even though the cerebral perfusion pressure remains within what is considered to be its autoregulatory range. The \(P_{aCO2}\) has a pronounced influence on CBF and when assuming the upright position, \(P_{aCO2}\) and the \(P_{ETCO2}\) decrease. Hypocapnia induces a decrease in gCBF by vasoconstriction and the postural decrease in gCBF is at least partially caused by the postural decline in \(P_{aCO2}\).

The sensitivity of the CBF to CO₂ is expressed as percentage change per mmHg \(P_{aCO2}\) (the CO₂-reactivity of the brain) and it is quantified non-invasively by relating changes in MCA \(V_{\text{mean}}\) to those in \(P_{ETCO2}\). In the normocapnic range, MCA \(V_{\text{mean}}\) changes ~3.5 % per mmHg \(P_{ETCO2}\). During the transit from the supine to the upright position, \(V_{\text{E}}\) increases and the following reduction in \(P_{ETCO2}\) seems to explain the decrease in MCA \(V_{\text{mean}}\). However, when standing up \(Q\) declines and its distribution over the lungs changes with an alteration in \(V_{\text{E}}/Q\) ratio. The postural decrease in \(P_{ETCO2}\), therefore, would be likely to overestimate the decrease in \(P_{aCO2}\). The aim of this study was to examine whether the postural decline in \(P_{aCO2}\) accounts for the concomitant postural decrease in MCA \(V_{\text{mean}}\).

Methods

Thirteen healthy non-smoking subjects (4 women; aged 26 (range 21-38) years; weight 75 (range 50-88) kg; height 182 (range 162-194) cm) participated in the study. All subjects received verbal and written explanation of the objectives and techniques of measurements, as well as risks and benefits associated with the study and subsequently provided written informed consent in accordance with the Helsinki Declaration (the Copenhagen Ethical Committee KF 01-120/96). None of the subjects used any cardiovascular medication.

Protocol

At least 2 hours after a light meal without caffeine-containing beverages, the subjects presented in a room with an ambient temperature of 22°C. After instrumentation they remained supine for at least 30 min before 5 min of supine baseline recordings were obtained. Then the subjects stood up and remained in the free standing position for 5 min.

Measurements

The subjects were instrumented with electrocardiogram electrodes, non-invasive blood pressure measurement and \(P_{ETCO2}\). Systemic hemodynamics were calculated as described on page 13. Arterial blood samples to determine \(P_{aCO2}\) and \(P_{aO2}\) were drawn 2 and 1 min prior to standing up and after 2 and 4 min standing (see page 15 and 16). To ascertain that changes in MCA \(V_{\text{mean}}\) relate to cerebral blood flow, in 7 subjects, the postural changes in both MCA \(V_{\text{mean}}\) and cO2Hb were followed as described on page 13 to 15.
Blood pressure (A BP), heart rate (HR), stroke volume (SV), cardiac output (Q), systemic vascular resistance (SVR) of 13 subjects in the supine and upright positions. Values are mean ± S.E.M. * Different from supine (P < 0.05)

Statistical analysis
The signals of ABP, the envelope curve of the TCD spectrum from the MCA, cO2Hb, P_{ET}CO_2 and a marker signal were A/D converted at 100 Hz. The ventilatory gas analysis was recorded for each breath and data were stored for off-line analysis. MABP and MCA V_{mean} were the integral over one heart beat and HR was the inverse of the interbeat pressure interval. Beat-to-beat data were transformed to equidistantly resampled data at 1 Hz (ventilatory data at 0.25 Hz accounting for respiratory rate by polynomial interpolation). P_{a}CO_2 samples were compared with P_{ET}CO_2, averaged over the 30 to 10 s prior to blood sampling. Both in the supine and upright positions, P_{a}CO_2 and P_{ET}CO_2 were expressed as the average of the two determinations. Data are expressed as mean±s.e.m. or mean and range when indicated. Changes within groups were examined by Friedman's repeated measures of analysis of variance on ranks with the Dunnet adjustment to control for the family-wise Type I error-rate. Changes between groups were examined with the Student's t test when data fitted a normal distribution and otherwise with the Mann-Whitney rank sum test. A P-value < 0.05 was considered to indicate a statistically significant difference.

Table 3.1.1 Carbon dioxide and cardiovascular variables

<table>
<thead>
<tr>
<th></th>
<th>SUPINE</th>
<th>UPRIGHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic ABP (mmHg)</td>
<td>124±3</td>
<td>127±2</td>
</tr>
<tr>
<td>Mean BP (mmHg)</td>
<td>80±2</td>
<td>88±3*</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>62±2</td>
<td>74±3*</td>
</tr>
<tr>
<td>HR (min⁻¹)</td>
<td>65±3</td>
<td>88±2*</td>
</tr>
<tr>
<td>SV (%)</td>
<td>100</td>
<td>65±3*</td>
</tr>
<tr>
<td>Q (%)</td>
<td>100</td>
<td>87±3*</td>
</tr>
<tr>
<td>SVR (%)</td>
<td>100</td>
<td>128±5*</td>
</tr>
<tr>
<td>P_{ET}CO_2 (mmHg)</td>
<td>40.2±0.7</td>
<td>35.8±0.7*</td>
</tr>
<tr>
<td>P_{a}CO_2 (mmHg)</td>
<td>40.8±0.4</td>
<td>38.3±0.9*</td>
</tr>
</tbody>
</table>

Blood pressure (ABP), heart rate (HR), stroke volume (SV), cardiac output (Q), systemic vascular resistance (SVR) of 13 subjects in the supine and upright positions. Values are mean ± s.e.m. * Different from supine (P < 0.05)

Results
P_{a}CO_2 and P_{ET}CO_2
From the supine to the upright position in 13 subjects, mean and diastolic BP, HR and SVR increased while SV and Q decreased (Table 3.1.1; all P< 0.05). In the supine position the P_{a}CO_2 was 40.8±0.4 mmHg and P_{ET}CO_2 was 40.2±0.7 mmHg. The changes in P_{a}CO_2 and P_{ET}CO_2 were correlated (ΔP_{ET}CO_2 = –2.75 + 0.84 ΔP_{a}CO_2; R² = 0.71) (Figure 3.1.1) but the reduction in P_{ET}CO_2 vs. P_{a}CO_2 upon standing was larger (–4.4±0.5 vs. –2.5±0.6 mmHg; P < 0.05; Table 3.1.1).
Relative to the supine position, the \( \frac{V_F}{Q} \) ratio increased by 49±14% in the upright position due to an increase in \( V_F \) from 7.4±0.5 to 10.1±1.0 L·min⁻¹ and a decrease in \( Q \) of −15.1±3.8% (all \( P < 0.05 \)) (Figure 3.1.2). Posture did not affect the \( S_aO_2 \) or \( P_aO_2 \) (Table 3.1.2). The upright posture also resulted in a decrease in cerebral perfusion as \( cO_2Hb \) declined –7.2±2.2 \( \mu \)mol·l⁻¹ (\( P < 0.05 \)) and MCA \( V_{mean} \) by –16.4±3.2% (from 65.3±3.8 to 54.6±3.3 cm·s⁻¹; \( P < 0.05 \)).

Thus during standing MCA \( V_{mean} \) decreased 5.5% per mmHg reduction in \( P_aCO_2 \).

Discussion
We measured MCA \( V_{mean} \), \( P_aCO_2 \) and \( P_{ET}CO_2 \) during the transition from the supine to the standing position and confirmed that the MCA \( V_{mean} \) declines with \( P_aCO_2 \). The new finding is that when assuming the upright position, the postural decrease in MCA \( V_{mean} \) seems to be explained by the reduction in \( P_{ET}CO_2 \) (a CO₂ reactivity of 3.4 %·mmHg⁻¹) but that the larger reduction in \( P_{ET}CO_2 \) than in \( P_aCO_2 \) illustrates that \( P_{ET}CO_2 \) cannot be applied to estimate the cerebral CO₂ reactivity during change in body position. Accordingly, the postural decrease in MCA \( V_{mean} \) seems to be larger than can be accounted for by the reduction in \( P_aCO_2 \).

The \( P_aCO_2 \) has a dominant influence on gCBF and the CO₂ reactivity of the brain is quantified as the slope of the CBF – \( P_aCO_2 \) relationship.²¹⁹ Since in supine humans, \( P_{ET}CO_2 \) follows \( P_aCO_2 \)²²⁶ and changes in gCBF are followed by MCA \( V_{mean} \), the CO₂ reactivity of the brain is reported as the slope of the MCA \( V_{mean} – P_{ET}CO_2 \) relationship.¹¹⁴ ¹⁶¹ The CO₂ reactivity of the brain is then reported as ~3.5 %·(mmHg \( P_{ET}CO_2 \))⁻¹.¹⁴¹ and in accord with the postural reductions in MCA \( V_{mean} \) (-16%) and \( P_{ET}CO_2 \) (4.5 mmHg).³⁶ The MCA \( V_{mean} – P_{ET}CO_2 \) relationship is non-linear with a lower sensitivity of MCA \( V_{mean} \) to changes in CO₂ in hypocapnia compared with hypercapnia¹¹⁴ further supporting that the postural decrease in MCA \( V_{mean} \) cannot be accounted for by the cerebral CO₂ reactivity alone. However, there are other influences than \( P_aCO_2 \) on gCBF when posture is changed.
In the upright position \( V_E \) increases related to the gravitational pull of the abdominal contents on the diaphragm with an increase in \( V_t \) and pulmonary dead space. More importantly, the hydrostatic pressure gradient down the lung affects pulmonary perfusion. When standing up air expired from the basal alveoli is diluted by that from the relatively underperfused apical alveoli. Thus, the premise of a stable \( V_t/Q \) ratio is not met when humans assume the upright position and changes in \( P_{ET\text{CO}_2} \) overestimate those in \( P_{a\text{CO}_2} \) (Figure 3.1.1).
Changes in end-tidal (P$_{ET}$CO$_2$) and arterial carbon dioxide (P$_a$CO$_2$) and oxygen (P$_a$O$_2$) tension and saturation (S$_a$O$_2$) of the blood, middle cerebral artery blood velocity (MCA V mean), regional cerebral tissue oxygenation, ventilation (V E) and cardiac output (Q) of 7 subjects assuming the upright position. Values are mean ± S.E.M. All upright values differ significantly from supine (P < 0.05).

<table>
<thead>
<tr>
<th>SUPINE</th>
<th>UPRIGHT</th>
<th>CHANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>P$_{ET}$CO$_2$ (mmHg)</td>
<td>40.3 ± 0.4</td>
<td>35.5 ± 0.7</td>
</tr>
<tr>
<td>P$_a$CO$_2$ (mmHg)</td>
<td>39.7 ± 1.1</td>
<td>36.7 ± 1.2</td>
</tr>
<tr>
<td>MCA V mean (cm·s$^{-1}$)</td>
<td>65.3 ± 3.8</td>
<td>54.6 ± 3.3</td>
</tr>
<tr>
<td>cO$_2$Hb (μmol/L$^{-1}$)</td>
<td>-7.2 ± 2.2</td>
<td></td>
</tr>
<tr>
<td>P$_a$O$_2$ (mmHg)</td>
<td>106 ± 3</td>
<td>107 ± 6</td>
</tr>
<tr>
<td>S$_a$O$_2$ (%)</td>
<td>97.5 ± 0.2</td>
<td>97.9 ± 0.2</td>
</tr>
<tr>
<td>V E (L·min$^{-1}$)</td>
<td>7.4 ± 0.5</td>
<td>10.1 ± 1.0</td>
</tr>
<tr>
<td>Q (%)</td>
<td>100</td>
<td>84.9 ± 3.8</td>
</tr>
</tbody>
</table>

The ~5 mmHg decline in P$_{ET}$CO$_2$ with assumption of the upright position would seem to explain the ~15% decrease in MCA V mean. However, the postural decline in P$_{ET}$CO$_2$ overestimates the reduction in P$_a$CO$_2$ and the ~5% decrease in MCA V mean per mmHg decline in P$_a$CO$_2$ is too large to explain the postural reduction in MCA V mean. This conclusion is supported by remarkably similar data from Serrador et al. Blaber et al. demonstrated in healthy subjects during head-up tilt with P$_{ET}$CO$_2$ clamped at supine levels that MCA V mean was higher in the isocapnic compared with the eucapnic condition while also during isocapnic passive head-up tilt, MCA V mean declined ~15%. These observations support our finding that factors other than P$_a$CO$_2$ modulate the postural decrease in MCA V mean.

An influence of O$_2$ should be considered. Acute exposure to a high partial pressure of inspired O$_2$ increases brain tissue PPO$_2$, and decreases P$_a$CO$_2$ and gCBF. In the present study there was no effect of posture on arterial O$_2$ tension and saturation and we consider the contribution of O$_2$ minimal. The postural reduction in both MCA V mean and cO$_2$Hb has been attributed, at least in part, to cerebral vasoconstriction related to an increase in sympathetic tone. Van Lieshout et al. demonstrated in healthy subjects during lower body negative pressure as a model of postural stress, the reduction in steady-state MCA V mean together with the increase in transfer function gain of MABP to MCA V mean was initially interpreted to indicate a deterioration of cerebral autoregulation.

Assumption of the upright position imposes stress on the cardiovascular system. The gravitational displacement of blood away from the thorax to dependent regions of the body initiates orthostatic pooling of venous blood affecting the central blood volume with a reduction in Q and pulmonary blood supply. In healthy subjects during lower body negative pressure as a model of postural stress, the reduction in steady-state MCA V mean together with the increase in transfer function gain of MABP to MCA V mean was initially interpreted to indicate a deterioration of cerebral autoregulation. Van Lieshout et al.
demonstrated that the MCA $V_{\text{mean}}$ decreases in association with the postural reduction in $Q$ even though MABP was maintained, indicating a relationship between $Q$ and MCA $V_{\text{mean}}$ beyond the influence of ABP.\textsuperscript{265} Although ABP is the main short-term determinant of muscle sympathetic nerve activity in humans via the arterial baroreflex, muscle sympathetic nerve activity correlates with $Q$ and SV rather than with mean or diastolic blood pressure.\textsuperscript{37} Ogoh et al.\textsuperscript{192} examined the relationship between $Q$ and MCA $V_{\text{mean}}$ while manipulating $Q$ by lower body negative pressure and plasma volume expansion. They demonstrated that MCA $V_{\text{mean}}$ and $Q$ were linearly related both at rest and during exercise while phase and gain of the transfer function between MCA $V_{\text{mean}}$ and MABP were not altered indicating maintained cerebral autoregulation. Considering that a postural reduction in MCA $V_{\text{mean}}$ as in cO$_2$Hb in humans is the rule, these findings may be interpreted as being the result of the intrinsic adaptive responses of a functioning dCA to a sometimes critical postural reduction in $Q$ rather than to a malfunctioning of CA per se.\textsuperscript{97, 268}

A critical issue is to what extent the MCA $V_{\text{mean}}$ reflects volume flow. The MCA $V_{\text{mean}}$ is obtained from the frequency distribution of the Doppler shifts and it is assumed to represent flow velocity in the center of the vessel. As observed during craniotomy the vessel diameter does not change significantly during variations in ABP of a magnitude that surpasses the changes manifest in response to orthostasis.\textsuperscript{57} Accordingly orthostatic stress, as simulated by lower body negative pressure, does not alter the diameter of the MCA as assessed with magnetic resonance imaging (MRI)\textsuperscript{241} and changes in MCA $V_{\text{mean}}$ follow cerebral $^{133}$Xe clearance.\textsuperscript{19, 40, 91} Thus, the constancy of the MCA diameter during postural stress relates changes in $V_{\text{mean}}$ to those in CBF and cerebral oxygenation.\textsuperscript{268} The NIRS-determined cO$_2$Hb integrates the arterial O$_2$ content and the regional CBF, and as established for skeletal muscle, NIRS obtains information on tissue oxygenation and metabolism beyond that obtained by venous blood sampling.\textsuperscript{27, 60} To overcome the uncertainty of each of the methods used to evaluate changes in CBF we combined TCD and NIRS as they are based on different physical principles, assuming that concordant changes indicate a change in regional CBF.\textsuperscript{7, 90, 170, 215, 265} When assuming the upright position, the reduction in $P_{VT}$CO$_2$ overestimated the reduction in $P_c$CO$_2$. Although the reduction in $P_{VT}$CO$_2$ seems to explain the postural decrease in MCA $V_{\text{mean}}$ the ~40% smaller decline in $P_c$CO$_2$ makes it unlikely that the entire decrease in cerebral perfusion is explained by hyperventilation.
3.2

Transient influence of end-tidal carbon dioxide tension on the postural restraint in cerebral perfusion

R.V. Immink, J. Truijen, N.H. Secher and J.J. van Lieshout

Journal of Applied Physiology 2009(107)816-823
INTRODUCTION In the upright position gCBF is reduced maybe because $P_{aCO_2}$ decreases. We evaluated the time-dependent influence of a reduction in $P_{aCO_2}$ as indicated by the $P_{ETCO_2}$ on cerebral perfusion during head-up tilt (HUT).

METHODS MABP, $Q$, MCA $V_{mean}$, and dCA at supine rest and 70º HUT were determined during free breathing and with $P_{ETCO_2}$ clamped to the supine level.

RESULTS The postural changes in central hemodynamic variables were equivalent and the cerebrovascular autoregulatory capacity was not significantly affected by HUT or by clamping the $P_{ETCO_2}$. In the first minute of HUT, the decline in MCA $V_{mean}$ ($10\pm4$ vs. $3\pm4$ cm s$^{-1}$; mean±S.E.M.; $P < 0.05$) and $P_{ETCO_2}$ ($6.8\pm4.3$ vs. $1.7\pm1.6$ mmHg; $P < 0.05$) was larger during spontaneous breathing than during isocapnic HUT. However, after two minutes in head-up position, the reduction in MCA $V_{mean}$ was similar ($7\pm5$ vs. $6\pm3$ cm s$^{-1}$), although the spontaneous decline in $P_{ETCO_2}$ was maintained ($P < 0.05$ vs. isocapnic tilt).

CONCLUSION These results suggest that the potential contribution of $P_{aCO_2}$ to the postural reduction in MCA $V_{mean}$ is transient, leaving the mechanisms for the sustained restraint in MCA $V_{mean}$ to be identified.
Introduction

When upright, MCA $V_{\text{mean}}$ $^{164, 214}$ and $cO_2Hb$ $^{96}$ are lower than during supine rest indicating that gCBF is reduced. That is the case although the postural decline in MABP at the level of the brain is minimal because MABP at heart level increases. $^{96}$

A low $P_{aCO_2}$ reduces gCBF by cerebral vasoconstriction $^{163}$ independently of cerebral autoregulation, known as the $CO_2$ reactivity of the brain circulation. Accordingly, one explanation for the postural decline in gCBF is the concomitant reduction in $P_{ETCO_2}$ by an increase in pulmonary minute ventilation. $^{191}$ $Q$ also declines upon standing $^{95}$ and its distribution over the lungs changes $^{222}$ with an alteration in the $V_{E}/Q$ ratio $^{123}$ and an overestimate of the postural reduction in the $P_{CO_2}$ by $P_{ETCO_2}$. $^{12}$ $^{20}$ In supine humans $P_{ETCO_2}$ is an adequate reflection of $P_{ACO_2}$ but when the postural reduction in MCA $V_{\text{mean}}$ is related to $P_{ACO_2}$ rather than to $P_{ETCO_2}$, it explains only about half of the postural decline in MCA $V_{\text{mean}}$. $^{12}$ $^{240}$

No data are available on the effects of $P_{CO_2}$ on gCBF during adaptation to prolonged postural stress. We therefore evaluated the time dependent influence of $P_{ACO_2}$ as indicated by $P_{ETCO_2}$ to the decline in MCA $V_{\text{mean}}$ during a 70º HUT and testing the hypothesis that $P_{ACO_2}$ as indicated by $P_{ETCO_2}$ has an only temporary influence on the postural fall in cerebral perfusion.

Methods

Twenty healthy non-smoking subjects participated in this study at least two hours after a light meal without caffeine-containing beverages in a room maintained at 22º C. Following instrumentation, the subjects rested in a supine position on a tilt table to record baseline values after 10 min. The subjects received verbal and written explanation of the objectives of the study and techniques employed, including possible risks associated with the study and they provided written informed consent in accordance with the Declaration of Helsinki as approved by the Institutional Ethical Committee (MEC 01/147).

Arterial-to-end-tidal CO2 pressure gradient

The postural change in $P_{CO_2}$ and the $P_{ETCO_2}$ is correlated but the decrease in $P_{ETCO_2}$ overestimates that in $P_{CO_2}$ ($P_{ETCO_2} = -2.75 + 0.84 \Delta P_{CO_2}$). $^{123}$ Based on these data, we assumed that $P_{ACO_2}$ was clamped when the $P_{ETCO_2}$ was ~3 mmHg below the supine value. To verify that assumption, in 6 male subjects (28 (23 – 34) year), 72 (60 - 88 kg), 182 (173 - 194 cm)) $P_{ACO_2}$ was sampled 4 respectively 2 min before assuming the upright position and during the early postural adaptation associated with characteristic and marked changes in blood pressure and HR at 30, 60, 90 and 120 s (Figure 3.2.1A). $^{261}$ $^{281}$

We considered that invasive procedures increase the likelihood of (pre)vasovagal syncope during orthostatic stress $^{48}$ $^{179}$ $^{240}$ with changes in $Q$ and SVR preceding manifest syncope. $^{256}$ $^{268}$ In order to avoid exposing the subjects to these potentially confounding effects of invasive instrumentation, $P_{CO_2}$ was assessed non-invasively. To verify that approach, the steady-state arterial-to-end-tidal CO2 pressure gradient ($\Delta P_{A-E(T)CO_2}$) was determined twice in 4 male
subjects (26 (22 – 30 year), 74 (63 - 92 kg), 183 (171 - 188 cm)) both after 5 min of supine rest and during 70º HUT with free breathing and when blood pressure and HR had stabilized. Subsequently, the inspired $P_{\text{CO}_2}$ was increased by using a modified $P_{\text{ET}}\text{CO}_2$ clamping device (see below) until $P_{\text{a}}\text{CO}_2$ was equivalent to the supine value allowing for determination of $\Delta P(a-E\text{T})\text{CO}_2$ (Figure 3.2.1B).

For determination of $\Delta P(a-E\text{T})\text{CO}_2$, arterial blood samples were taken as described on page 15. $P_{\text{ET}}\text{CO}_2$ was followed by a capnograph (Datex Normocap 200) with the sample line mounted in the mouthpiece of the rebreathing device.

**Figure 3.2.1**
Panel A: Determination of the partial arterial to end-tidal carbon dioxide pressure difference ($\Delta P(a-E\text{T})\text{CO}_2$) directly after assuming the upright position (n=6). Panel B: Determination to what level the $P_{\text{ET}}\text{CO}_2$ should be increased in the upright position, by using the $CO_2$ clamping contrivance, to reach a partial arterial carbon dioxide pressure ($P_{\text{a}}\text{CO}_2$) that is comparable to the supine level (n=4). Panel C: Spontaneous vs. isocapnic tilt (n=10). White bars indicate spontaneous breathing. White to grey shaded bars indicate adjusting the clamping contrivance to create a $CO_2$ clamped situation. Grey bars indicate an adequate $CO_2$ clamped situation.

$P_{\text{ET}}\text{CO}_2$ clamping
To maintain the supine $P_{\text{a}}\text{CO}_2$ during tilt we used a modified contrivance clamp developed by Banzett et al. This method uses a functionally variable dead space to maintain alveolar ventilation by applying a self-regulating partial-rebreathing system that is independent of changes in breathing frequency and/or tidal volume and maintains $P_{\text{ET}}\text{CO}_2$ within ± 1 mmHg of the preset value. To reduce inspiratory pressure, the dimension of the flexible reservoir tube was modified to 7.5 cm ID by 100 cm stiff polystyrene tube and we added a T-junction in the inspiratory limb of the clamping device to switch between spontaneous breathing and isocapnia (Figure 3.2.2).

The mouthpiece and nose clip needed to clamp $P_{\text{ET}}\text{CO}_2$ were also used during spontaneous breathing to account for potential changes in breathing pattern and systemic hemodynamic...
variables. During spontaneous breathing, a valve closes the inspiratory limb of the clamp and allows for inhalation of room air. Prior to isocapnic tilt, the rebreathing loop device was opened when in the supine position. With the alveolar ventilation clamp in use, the amount of pressurized air provided was adjusted to just below supine minute ventilation. The PCO$_2$ was considered clamped when, in the supine position, $P_{ETCO_2}$ was equal to the value prior to HUT with spontaneous breathing (Figure 3.2.3).

**Figure 3.2.2**
Experimental set-up for the alveolar ventilation clamp. In the supine position, a continuous flow of pressurized air, adjusted to just below minute ventilation, supplies the alveolar ventilation clamp via a heater/humidifier. The pressurized air will be collected in a bag (black arrows). During expiration (gray arrows), the one way valve ($V_2$) closes and this will force the expiratory air into the rebreath tube. The air already present in the expiratory tube leaves the circuit via an one way valve ($V_2$). During inspiration, $V_1$ opens and $V_2$ closes and the collected pressurized air from the bag is inhaled. When the subject increases minute ventilation, the air pressure in the circuit tends to decrease, and a low pressure spring valve ($sV$) opens and carbon dioxide containing air from the rebreath tube (gray) is inhaled (dotted arrows). For spontaneous ventilation, a valve in $T_1$ closes the inspiratory limb of the circuit and the subject inhales room air (dashed arrow).
Representative example of the partial end-tidal carbon dioxide pressure ($P_{ETCO2}$) response in one subject to hyperventilation (black bar) during spontaneous breathing (Panel A) and with isocapnic clamp (Panel B).

**Spontaneous breathing vs. isocapnic tilt**

For determination of the time-dependent influence of a reduction in $P_{aCO2}$ on cerebral perfusion during HUT, 10 non-invasively instrumented subjects (3 women, 28 (range 21-36 year), 74 (59-85 kg), 184 (175-198 cm) were tilted 70° head-up during spontaneous breathing. Following instrumentation, the subjects rested in a supine position on a tilt table to record baseline values for 5 min. After 5 min in the head-up position, the subjects were returned to supine and rested for 20 min. Thereafter, the tilt was repeated with the postural reduction in $P_{ETCO2}$ offset by using the clamping device (isocapnic tilt; Figure 3.2.1C).

Arterial pressure, MCA $V$ and $P_{ETCO2}$ were monitored as described on page 13 to 15. Systemic hemodynamics are calculated as described on page 13. All signals were A/D converted at 100 Hz and stored on hard disk for off-line analysis. $P_{ETCO2}$ was followed by a capnograph with the sample line mounted in the mouthpiece of the rebreathing device. The inspiratory $P_{CO2}$ was increased to the preset $P_{ETCO2}$ until it was within 3 mmHg of the supine value by the clamping contrivance. Steady-state $P_{ETCO2}$ clamping was reached within 15 min and verified by maintained $P_{ETCO2}$ during hyperventilation. The cerebrovascular effects of $P_{aCO2}$ were quantified as CVRi, the ratio of MABP and MCA $V_{mean}$. Dynamic CA was determined as described on page 16 to 18.

**Statistical analysis**

Data were resampled at 0.1 Hz by polynomial interpolation, expressed as mean±S.E.M. and changes over time and between spontaneous breathing and isocapnic tilt were examined by two-way ANOVA for repeated measures. Post-hoc multiple comparisons were performed using the Holm-Sidak method. Differences in responses between body positions were examined by parametric or non-parametric tests where appropriate and a $P$ value <0.05 was considered to indicate a statistically significant difference.
Results

Effects of HUT on the arterial-to-end-tidal CO2 pressure gradient (Figure 3.2.1A; n=6)

In the supine position at 4 and 2 min prior to HUT, \(P_a\)CO2 was 43±1 and 42±1 mmHg, respectively, and \(P_{ET}\)CO2 was 39±1 and 40±1 mmHg. In the first 2 minutes following HUT, \(P_a\)CO2 decreased to 39±1, 40±1, 39±1 and 40±1 mmHg at 30, 60, 90 and 120 sec respectively whereas \(P_{ET}\)CO2 decreased from 38±1 mmHg after 1 min to 37±1 mmHg after 2 minutes (Figure 3.2.4).

Arterial-to-end-tidal CO2 pressure gradient during clamping (Figure 3.2.1B; n=4)

In the supine position, \(P_{ET}\)CO2 and \(P_a\)CO2 were 41±1 and 42±1 mmHg, respectively. During HUT with spontaneous breathing, \(\Delta P_{a-ET}\)CO2 increased from 1.1±0.4 to 3.8±0.7 mmHg with a \(P_{ET}\)CO2 of 34±2 mmHg and a \(P_a\)CO2 of 38±2 mmHg (\(P < 0.05\)). After adding CO2 to inspired air in the upright position to clamp \(P_a\)CO2 (41±2 mmHg), \(P_{ET}\)CO2 was 38±2 mmHg with a \(\Delta P_{a-ET}\)CO2 of 2.5±0.4 mmHg (Figure 3.2.5). The CO2 clamping procedure did not affect the \(P_a\)O2, \(S_a\)O2 or plasma pH.

Spontaneous breathing vs. isocapnic tilt (Figure 3.2.1C; n=10)

In the supine position, MABP was slightly lower than prior to isocapnic tilt (74±4 vs. 77±4 mmHg; \(P = 0.04\)) and that difference remained during HUT (87±4 vs. 90±4 mmHg; \(P = 0.04\)). The postural changes in HR (+21±4 vs. +20±4 min⁻¹), SV (-38±3% vs. -36±3%), \(Q\) (-20±3% vs. -16±3%) and SVR (+51±8% vs. +44±6%) after 2 min of HUT did not differ between spontaneous breathing and isocapnic tilt (Figure 3.2.6). Prior to HUT \(P_{ET}\)CO2 was 44±1 vs. 43±2 mmHg in the spontaneous breathing vs. the isocapnic conditions. After 1 min in the spontaneous breathing HUT position, \(\Delta P_{ET}\)CO2 stabilized at -6.8±4.3 mmHg.
isocapnic tilt, ΔP_{ETCO2} was -1.7±1.6 mmHg at 1 min, -3.1±1.4 mmHg at 3 min and stabilized after 5 min HUT at -2.3±0.8 mmHg (P < 0.05 vs. spontaneous breathing). Resting MCA V_{mean} was 64±5 cm s⁻¹ for both the spontaneous breathing and isocapnic tilted positions. After 1 min HUT, the postural reduction in MCA V_{mean} for spontaneous breathing was larger (10±4 vs. 3±4 cm s⁻¹; P < 0.05). However, from 2 min on, this difference in postural reduction was no longer present (8±1 vs. 7±1 cm s⁻¹; P = 0.29; Figure 3.2.6). Changes in CVRi were similar during spontaneous breathing (1.17±0.06 to 1.13±0.05 mmHg cm⁻¹s⁻¹) and isocapnic tilt (1.23±0.06 to 1.17±0.07 mmHg cm⁻¹s⁻¹). Unaltered MABP-MCA V_{mean} phase and gain across changes in ΔPCO₂ indicated maintained CA (Table 3.2.1 and Figure 3.2.7).

Discussion
This study determined the temporal contribution of the postural decrease in P_{ETCO2} on the decline in cerebral blood flow velocity. Isocapnic tilting limited the postural reduction in MCA V_{mean} only during the first minute of HUT as the postural decline in MCA V_{mean} was independent of P_{CO2} for the ~4 mmHg PCO₂ difference between the supine and the upright position. The data suggest that the postural decrease in MCA V_{mean} coincides with, but is not explained by a reduction in P_{CO2} indicating that other factors dominate the reduction in MCA V_{mean} during posture.

The MCA V_{mean} evaluated postural and PCO₂ related changes in cerebral perfusion assuming that changes in MCA V_{mean} are representative for those in rCBF. This was the case although transcranial Doppler monitors blood velocity rather than flow rate and changes in the diameter of the insonated vessel modulate velocity independently from flow. Yet, the large cerebral arteries are conduit rather than resistance vessels and changes in MAPB within the physiological range appear to have negligible effects on the diameter of the insonated artery. Observations during craniotomy reveal that the vessel diameter does not change during...
variations in MABP within a magnitude that surpasses the changes manifest in response to orthostasis.\(^8\) Also orthostatic stress, as simulated by lower body negative pressure, or changes in \(\text{PCO}_2\) do not alter the diameter of the MCA as assessed with magnetic resonance imaging\(^{241}\) and changes in MCA \(V_{\text{mean}}\) follow cerebral \(^{133}\text{Xe}\) clearance.\(^{19\text{b}, 237}\) Thus, MCA \(V_{\text{mean}}\) increases in proportion to gCBF \(^{133\text{Xe}}\) \(^{136\text{Xe}}\) \(^{237}\) and internal carotid flow,\(^{106}\) and constancy of the MCA diameter during postural stress relates changes in \(V_{\text{mean}}\) to those in gCBF.\(^{241}\)

### Table 3.2.1 Postural and carbon dioxide influence on dynamic cerebral autoregulation

<table>
<thead>
<tr>
<th>BREATHING</th>
<th>SPONTANEOUS</th>
<th>ISOCAPNIC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>supine</td>
<td>upright</td>
</tr>
<tr>
<td>MABP power ((\text{mm Hg·Hz}^2))</td>
<td>5.4 ± 1.6</td>
<td>15.1 ± 3.6*</td>
</tr>
<tr>
<td>(V_{\text{mean}}) power ((\text{cm·s}^{-1}·\text{Hz}^{-1}))</td>
<td>7.3 ± 2</td>
<td>20.5 ± 4.3*</td>
</tr>
<tr>
<td>Coherence</td>
<td>0.7 ± 0.1</td>
<td>0.8 ± 0.1*</td>
</tr>
<tr>
<td>Phase (degrees)</td>
<td>48 ± 6</td>
<td>34 ± 6</td>
</tr>
<tr>
<td>Gain ((\text{cm·s}^{-1}·\text{mm Hg}^{-1}))</td>
<td>1.1 ± 0.1</td>
<td>1.0 ± 0.1</td>
</tr>
<tr>
<td>CVRi ((\text{mm Hg·cm}^{-1}·\text{s}^{-1}))</td>
<td>1.17 ± 0.06</td>
<td>1.13 ± 0.05*</td>
</tr>
</tbody>
</table>

Low frequency variability of mean arterial pressure (MABP power), mean middle cerebral artery blood velocity (\(V_{\text{mean}}\) power), coherence, phase, gain and cerebrovascular resistance index (CVRi) in the supine position and during 70º head up tilt.

* \(P < 0.05\) vs. supine. Values are mean ± S.E.M.

**Posture and \(P_{\text{CO}_2}\)**

A tilt-induced reduction in MCA \(V_{\text{mean}}\) with \(P_{\text{ET}}\text{CO}_2\) clamped is reported.\(^{21}\) However, in that study inequalities in MCA \(V_{\text{mean}}\) between the control state prior to isocapnic tilt vs. spontaneous breathing tilt precluded quantification of the contribution of \(P_{\text{CO}_2}\) to the postural decrease in MCA \(V_{\text{mean}}\). A prerequisite for the present study was that the steady state hemodynamic condition was comparable for spontaneous breathing and isocapnic tilt. These requirements were fulfilled apart from a small expected difference in MABP that did not change with posture.\(^{258}\)

Association between the initial postural decline in \(P_{\text{ET}}\text{CO}_2\) and MCA \(V_{\text{mean}}\) was suggested by Cencetti et al.\(^{36}\) expressing \(P_{\text{ET}}\text{CO}_2\) as \(P_{\text{ET}}\text{CO}_2\). For the supine position, changes in \(P_{\text{ET}}\text{CO}_2\) correlated with those in \(P_{\text{ET}}\text{CO}_2\).\(^{286}\) However, in the upright position, ventilation increases with a reduction in lung perfusion and a gravitational blood pressure gradient over the lung.\(^{88}\) In upright humans, distribution of lung ventilation and perfusion by gravity\(^{226}\) overestimate the postural decrease in \(P_{\text{ET}}\text{CO}_2\) by the \(P_{\text{ET}}\text{CO}_2\).\(^{12\text{b}}\) \(^{20\text{b}}\) \(^{123\text{b}}\) \(^{240}\) Accordingly, applying the \(\Delta P_{\text{ET}}\text{CO}_2\) we considered \(P_{\text{ET}}\text{CO}_2\) to be clamped when \(P_{\text{ET}}\text{CO}_2\) decreased by 3 mmHg during posture.
Posture and critical closing pressure

Adaptation of gCBF to orthostatic stress is conceptually linked to critical closing pressure (CrCP). In the rabbit, the relationship between CrCP and intracranial pressure is linear and CrCP decreases with arterial hypotension. Kongstad and Grände demonstrated in the cat an increase in venous pressure not to influence tissue pressure for as long as venous pressure remains below tissue pressure. Only when pressures are equal the collapse of the outflow vein disappears and the two pressures increase in parallel. The implication is that for as long as there is a venous outflow resistance, the effect of venous pressure on intracranial pressure is
Accordingly, with the head at heart level, cerebral venous pressure rises linearly with end-expiratory airway pressure. However, when the head is elevated, cerebral venous pressure is affected only by a large increase in central venous pressure. Thus jugular venous collapse serves as a resistance to the transmission of central venous pressure to VP CRB and supports that in the upright position, a Starling resistor-type mechanism becomes operative. These observations are consistent with the cerebral venous outflow pressure and a variable independent of CA. In humans, CVP cannot be assessed directly and it remains uncertain whether a small decline in PA CO2 modifies CVP.

Figure 3.2.7 Averaged power spectra of mean arterial pressure (MAP) and middle cerebral artery mean blood velocity (MCA Vmean) and MAP to MCA Vmean coherence, phase and gain of 10 subjects ± S.E.M. during spontaneous breathing (black line) and isocapnia (grey line) in the supine position (upper panels) and upright (lower panels).
Posture and cerebral perfusion

CBF remains relatively stable over a range of blood pressure. Assumption of the upright position affects venous return and $Q$, whereas MABP at the level of the heart is maintained by a sympathetically mediated increase in SVR. In the upright position, the cerebral arteries are positioned above the heart and their perfusion pressure is reduced. Both the position of the cerebral circulation and the reduction in $Q$ challenge CBF, and although the postural reduction in cerebral perfusion may be limited by cerebral autoregulatory mechanisms, $\text{gCBF}$, MCA $V_{\text{mean}}$, and cerebral oxygenation decrease. CA is also affected by the basal vascular tone. Aaslid et al. demonstrated a relationship between $P_{\text{aCO}_2}$ and CA with a strong influence of $P_{\text{aCO}_2}$ on MCA $V_{\text{mean}}$ assumed to reflect changes in cerebral vascular smooth muscle tone. In the present study, CA was maintained across the changes in $P_{\text{CO}_2}$ associated with posture change. Autonomic neural control of the cerebral circulation is tonically active. Evidence for sympathetic control of the cerebral circulation in humans was identified by demonstrating that gCBF, and in parallel MCA $V_{\text{mean}}$, declines in response to trigeminal ganglion stimulation and increases following stellate ganglion blockade. A relationship between gCBF and $Q$ was found by demonstrating that both the MCA $V_{\text{mean}}$ and the NIRS determined cerebral oxygenation decrease in association with the postural reduction in $Q$. This reduction in cerebral perfusion takes place even though MABP increases, further indicating an important role of sympathetic activation for regulation of gCBF. In support, both MCA $V_{\text{mean}}$ and cerebral oxygenation increase when the standing position is supplemented by a leg muscle tensing manoeuvre that attenuates sympathetic activity by enhancing $Q$. Also, $Q$ and MCA $V_{\text{mean}}$ change concordantly with, respectively, volume expansion and depletion. Evidence for an influence of autonomic neural activity on cerebral hemodynamics in humans is the finding that norepinephrine plasma kinetic measurements across the brain reflect cerebrovascular sympathetic activity.

This study suggests that the partial contribution of $P_{\text{aCO}_2}$ to the postural reduction in cerebral perfusion is limited to the first minute of tilt. This finding indicates that after this first minute, other factors than $P_{\text{aCO}_2}$ dominate the postural reduction in MCA $V_{\text{mean}}$ and the postural reduction in $Q$ supports that cardiac output is likely to have an independent influence on cerebral perfusion.
3.3

A stellate ganglion block does not affect the postural reduction in cerebral perfusion
INTRODUCTION In the upright position, ABP is maintained by an increased HR and SVR as sympathetic activity increases. Despite a maintained ABP, gCBF assessed by MCA $V'$ and NIRS-determined $cO_2Hb$ decrease. It is unknown whether the modest orthostatic increase in sympathetic activity contributes to the postural decrease in gCBF. We therefore monitored systemic and cerebral hemodynamics in patients that assume the upright position before and after unilateral suppression of cerebral sympathetic activity by SGB.

METHODS In 11 chronic pain patients the postural response of beat-to-beat ABP and bilateral CVRi, $cO_2Hb$ and MCA $V'$ was quantified before and after SGB. Also bilateral dCA was determined in supine and standing position, before and after SGB.

RESULTS Both on the control side and the side that was to be blocked, the postural decrease in CVRi, $cO_2Hb$ and MCA $V_{mean}$ without and with SGB were comparable. Also, from supine to the upright position, the SGB did neither modify the power spectra for MABP or MCA $V_{mean}$ nor the MCA $V_{mean}$-to-MABP transfer function phase lead or gain.

CONCLUSION Suppression of cerebral sympathetic activity by SGB did not affect the cerebrovascular response to orthostatic stress suggesting that the orthostatic decrease in gCBF, MCA $V'$, and $cO_2Hb$ takes place independently of sympathetic activity.
Introduction
Cerebral autoregulation involves both fast and slow regulatory mechanisms that maintain gCBF. sCA describes that gCBF is maintained relatively constant within a cerebral perfusion pressure between ~50–150 and ~150 mmHg while dCA refers to the ability to restore gCBF in the face of a sudden change in blood pressure as for example during rapid thigh cuff deflation or calculated from spontaneous oscillations in blood pressure. Gravitational displacement of blood to the abdomen and the legs affects preload to the heart and cardiac output $Q$ is reduced. Increased HR and SVR maintain MABP as sympathetic activity raises and yet gCBF, MCA $V_{\text{mean}}$, and cO$_2$Hb decrease. The orthostatic decrease in gCBF has been attributed to the concomitant reduction in the $P_a$CO$_2$ but the limited reduction in $P_a$CO$_2$ cannot explain the attenuated MCA $V_{\text{mean}}$ after approximately 2 min of standing. Alternatively, the albeit modest increase in sympathetic activity while seated or standing could affect cerebral perfusion and oxygenation.

We took the opportunity to evaluate the potential role of sympathetic activation for regulation of gCBF during orthostatic stress provided by chronic pain patients for whom the treatment was supplemented by an unilateral SGB. SGB suppresses ipsilateral sympathetic activity to the arm, neck, and head. Thus, the patients were asked to stand up before and after the block while cerebral and central hemodynamic variables were monitored.

Methods
Eleven chronic pain patients (8 males, aged 44±4 years, length 183±3 cm, and weight 87±6 kg) scheduled to SGB agreed to participate in the study after oral and written informed consent and the study was approved by the Medical Ethical Committee of the Academic Medical Center in Amsterdam in accordance with the Declaration of Helsinki. The patients suffered from pain disorders in one arm (8), an eye (2), or the face (1). Besides the SGB, the patients were in treatment with oxycodone (4), pregabaline (3), buprenofine (2), amitriptyline (2), and clonazepam (1). Exclusion criteria for the study were age < 18 years, diseases known to influence cerebrovascular regulation including diabetes, severe hypertension, significant carotid artery stenosis or occlusion, or stroke. All patients refrained from alcohol and caffeine intake for at least 2 hours prior to the study.

Protocol
The patients were positioned supine in a quiet room with an ambient temperature of 22 °C and measurements were started two hours prior to the SGB. Following instrumentation and after obtaining 5-min baseline recording of variables, the subjects were asked to stand up and remain free standing for 10 min. The protocol was repeated within one hour following application of the unilateral SGB.

Instrumentation (Figure 3.3.1)
Before orthostatic testing, the subjects were instrumented with non-invasive blood pressure measurement (Nexfin) and systemic hemodynamics were calculated as described on page 13. $P_{\text{ET}}$CO$_2$, bilateral MCA $V$ and cO$_2$Hb and cHHb (with Artinis NIRS) were monitored as
Sympathetic Blockade

The SGB was performed with the patient supine and the neck slightly extended and the head somewhat rotated to the opposite side of the block (for six patients on the left side) while the mouth was open. The needle was inserted between the trachea and the vascular sheath at the level of the cricoid cartilage and Chassaignac's tubercle after application of a skin wheal for local anesthetic. The ganglion lies at the level of the 7th cervical vertebral body whereas the needle was inserted at the level of the 6th vertebra to avoid pleural piercing. The sternocleidomastoid muscle and carotid artery were retracted laterally as the index and middle finger palpated Chassaignac's tubercle. The skin and subcutaneous tissue were pressed firmly onto the tubercle to reduce distance between the skin and bone in an attempt to push the dome of the lung out of the path of the needle. The needle was directed towards the tubercle and subsequently medially and inferiorly towards the body of the 6th cervical vertebra. After the vertebral body was contacted, the needle was withdrawn 1 to 2 mm and relevant spread of radio contrast was confirmed by both antero-posterior and lateral views by fluoroscopy. A syringe with local anesthetic was then attached to the needle and aspiration ruled out intravascular placement. Then 3.5 to 5 ml 0.25% plain bupivacaine was injected supplemented by 25-μg fentanyl in 6 patients, 2.5 mg dexamethason in two patients, and 75-μg clonidine in one patient. Indications of successful blockade were hoarseness and a globus sensation developed in 5 patients (Horner -) and Horner’s syndrome in 6 patients (Horner +).

Data Analysis

The signals of ABP, the spectral envelopes of the MCA \( V \), the \( cO_2Hb \), \( cHHb \) and a marker signal were A/D converted at 100 Hz and stored on a hard disk for off-line analysis.

Dynamic cerebral autoregulation

dCA in the frequency domain was quantified with spectral analysis from a 2 minutes tracing of
beat-to-beat BP and MCA $V$ data as described on page 16 to 18.

**Results**

One patient was excluded from study analysis due to orthostatic intolerance after three minutes standing before the SGB.

*Postural systemic and cerebral hemodynamics*

When standing up, SV, $Q$, and $P_{ETCO_2}$ decreased, while HR, MABP, and SVR increased. (all $P < 0.05$; Table 3.3.1a and Figure 3.3.2). Prior to the block, INVOS determined $cO_2Hb$ was 64±7% on the control side and 66±8% on the side to be blocked (NS). After SGB, $cO_2Hb$ was 66±7% on the control side and 70±8% on the blocked side ($n=6$). The postural changes in systemic and cerebral hemodynamics prior to blockade and following SGB were comparable (Table 3.3.1a). Also the SGB did not affect the postural decline in MCA $V_{mean}$, $cO_2Hb$, $cHHb$ or CVGi. Separate analysis of the 6 patients who developed a Horner syndrome confirmed that the block did not affect the postural changes in central or cerebral vascular variables (Table 3.3.1b and Figure 3.3.3).

**Table 3.3.1a** Systemic and cerebral hemodynamics of all subjects ($n=10$)

<table>
<thead>
<tr>
<th></th>
<th>BEFORE BLOCKADE</th>
<th></th>
<th>AFTER BLOCKADE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SUPINE</td>
<td>UPRIGHT</td>
<td>SUPINE</td>
</tr>
<tr>
<td>MABP (mmHg)</td>
<td>80 ± 4</td>
<td>100 ± 5*</td>
<td>84 ± 5</td>
</tr>
<tr>
<td>$P_{ETCO_2}$ (%)</td>
<td>4.0 ± 0.9</td>
<td>3.8 ± 0.7*</td>
<td>3.9 ± 0.8</td>
</tr>
<tr>
<td>HR (min⁻¹)</td>
<td>71 ± 5</td>
<td>85 ± 4*</td>
<td>68 ± 4</td>
</tr>
<tr>
<td>SV (%)</td>
<td>100</td>
<td>65 ± 4*</td>
<td>100</td>
</tr>
<tr>
<td>$Q$ (%)</td>
<td>100</td>
<td>82 ± 5*</td>
<td>100</td>
</tr>
<tr>
<td>SVR (%)</td>
<td>100</td>
<td>156 ± 18*</td>
<td>100</td>
</tr>
<tr>
<td>MCA $V_{mean}$ (cm·s⁻¹)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bl-</td>
<td>48 ± 5</td>
<td>42 ± 4*</td>
<td>50 ± 6</td>
</tr>
<tr>
<td>bl+</td>
<td>48 ± 3</td>
<td>43 ± 2*</td>
<td>53 ± 6</td>
</tr>
<tr>
<td>$cO_2Hb$ (μMol)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bl-</td>
<td>-4.3 ± 1.5*</td>
<td>-3.5 ± 1.4*</td>
<td></td>
</tr>
<tr>
<td>bl+</td>
<td>-4.6 ± 1.9*</td>
<td>-3.3 ± 1.7*</td>
<td></td>
</tr>
<tr>
<td>$cHHb$ (μMol)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bl-</td>
<td>1.0 ± 0.6</td>
<td>2.1 ± 1.3</td>
<td></td>
</tr>
<tr>
<td>bl+</td>
<td>0.0 ± 0.8</td>
<td>1.4 ± 0.8</td>
<td></td>
</tr>
<tr>
<td>CVRi (mmHg·(cm·s⁻¹))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bl-</td>
<td>1.82 ± 0.19</td>
<td>2.40 ± 0.24*</td>
<td>1.88 ± 0.23</td>
</tr>
<tr>
<td>bl+</td>
<td>1.76 ± 0.18</td>
<td>2.32 ± 0.21*</td>
<td>1.77 ± 0.22</td>
</tr>
</tbody>
</table>

Mean arterial blood pressure (MABP), partial end-tidal carbon dioxide pressure ($P_{ETCO_2}$), heart rate (HR), percentage change in stroke volume ($SV$), cardiac output ($Q$), and systemic vascular resistance (SVR), and mean middle cerebral artery blood velocity (MCA $V_{mean}$), content of oxygenated ($cO_2Hb$) and deoxygenated ($cHHb$) hemoglobin in cerebral tissue and cerebral vascular resistance index (CVRi) on the control side (bl-) and the side to be blocked (bl+) in supine and upright position prior to and following SGB of all patients. Values are mean ± S.E.M; $n=10$; *$P < 0.05$. 

48
Figure 3.3.2
Postural changes in mean arterial blood pressure (MABP), partial end-tidal carbon dioxide pressure (PETCO₂), heart rate (HR), stroke volume (SV), Cardiac output (Q) and systemic vascular resistance (SVR) before (gray) and after stellate ganglion blockade (SGB) (black) in one subject. Mean middle cerebral artery blood velocity (MCA V̅ mean) and content of oxygenated hemoglobin in cerebral tissue (cO₂Hb) on the side to be blocked (gray) and blocked (black).
Dynamic cerebral autoregulation

SGB did not affect MABP or MCA $V_{\text{mean}}$ power spectrum, the MCA $V_{\text{mean}}$-to-MABP transfer function phase lead or gain and that was the case both in the supine (Figure 3.3.4) and upright (Figure 3.3.5) body positions (Table 3.3.2a) in both Horner – and Horner + patients (Figure 3.3.6).

Table 3.3.1b  Systemic and cerebral hemodynamics of the Horner subjects (n=6)

<table>
<thead>
<tr>
<th></th>
<th>BEFORE BLOCKADE</th>
<th></th>
<th>AFTER BLOCKADE</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SUPINE</td>
<td>UPRIGHT</td>
<td>SUPINE</td>
<td>UPRIGHT</td>
</tr>
<tr>
<td>MABP (mmHg)</td>
<td>78±6</td>
<td>95±5*</td>
<td>81±7</td>
<td>94±7*</td>
</tr>
<tr>
<td>$P_{\text{ET}}$CO$_2$ (%)</td>
<td>4.0±0.4</td>
<td>3.8±0.4*</td>
<td>3.7±0.4</td>
<td>3.7±0.3*</td>
</tr>
<tr>
<td>HR (min$^{-1}$)</td>
<td>72±8</td>
<td>86±7*</td>
<td>69±7</td>
<td>86±7*</td>
</tr>
<tr>
<td>SV (%)</td>
<td>100</td>
<td>67±6*</td>
<td>100</td>
<td>74±4*</td>
</tr>
<tr>
<td>Q (%)</td>
<td>100</td>
<td>80±6*</td>
<td>100</td>
<td>80±3*</td>
</tr>
<tr>
<td>SVR (%)</td>
<td>100</td>
<td>160±19*</td>
<td>100</td>
<td>132±11*</td>
</tr>
<tr>
<td>MCA $V_{\text{mean}}$ (cm·s$^{-1}$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bl-</td>
<td>51±4</td>
<td>46±5*</td>
<td>51±4</td>
<td>49±6*</td>
</tr>
<tr>
<td>bl+</td>
<td>51±4</td>
<td>46±5*</td>
<td>52±5</td>
<td>44±5*</td>
</tr>
<tr>
<td>cO$_2$Hb (μMol)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bl-</td>
<td></td>
<td>-5.2±2.2*</td>
<td></td>
<td>-5.5±1.6*</td>
</tr>
<tr>
<td>bl+</td>
<td></td>
<td>-5.8±2.5*</td>
<td></td>
<td>-5.4±1.8*</td>
</tr>
<tr>
<td>cHHb (μMol)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bl-</td>
<td></td>
<td>1.5±0.9</td>
<td></td>
<td>1.1±1.9</td>
</tr>
<tr>
<td>bl+</td>
<td></td>
<td>0.0±1.2</td>
<td></td>
<td>0.5±1.0</td>
</tr>
<tr>
<td>CVRi (mmHg·(cm·s$^{-1}$))</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bl-</td>
<td>1.68±0.27</td>
<td>2.11±0.26*</td>
<td>1.76±0.29</td>
<td>2.40±0.43*</td>
</tr>
<tr>
<td>bl+</td>
<td>1.69±0.29</td>
<td>2.07±0.28*</td>
<td>1.73±0.30</td>
<td>2.10±0.20*</td>
</tr>
</tbody>
</table>

Mean arterial blood pressure (MABP), partial end-tidal carbon dioxide pressure ($P_{\text{ET}}$CO$_2$), heart rate (HR), percentage change in stroke volume (SV), cardiac output (Q), and systemic vascular resistance (SVR), and mean middle cerebral artery blood velocity (MCA $V_{\text{mean}}$), content of oxygenated (cO$_2$Hb) and deoxygenated (cHHb) hemoglobin in cerebral tissue and cerebral vascular resistance index (CVRi) on the control side (bl-) and the side to be blocked (bl+) in supine and upright position prior to and following SGB of the patients who developed a Horner’s syndrome. Values are mean ± S.E.M; n=10; * P < 0.05.

Discussion

Assuming the upright position reduces Q and elicits sympathetic activation with a reduction in systemic vascular conduction maintaining arterial blood pressure. This study addressed whether the sympathetic activation in response to postural stress is manifested in the vascular conductance of the brain and in the cerebrovascular autoregulatory capacity. We found that suppression of the cerebral sympathetic activity by SGB did not affect the cerebrovascular conductance response to orthostatic stress suggesting that in humans the orthostatic decrease in CBF expressed as the decline in MCA flow velocity and cerebral cortical oxygenation takes place independently from sympathetic activity. The following discussion details the assumptions and evidence that underlie these conclusions.161
Figure 3.3.3
Averaged values (left: all subjects n=10, right: Horner group n=6) for mean middle cerebral artery blood velocity (MCA $V_{\text{mean}}$) and changes in oxygenated ($cO_2Hb$) and deoxygenated ($cHHb$) frontal lobe hemoglobin on the control side (grey) and the side to be blocked (black) when patients assume the upright position before and after cervical ganglion blockade (SGB).
The sympathetic innervation of cerebral vessels finds its origin in the hypothalamus and projects to the intermediolateral cell column of the spinal cord. From there, preganglionic neurons project to the stellate and superior cervical ganglion of the sympathetic trunk to synapse with postganglionic fibers that run rostrally together with the cerebral arteries. Although cerebral conductance vessels, like the MCA, have α- and β-adrenergic innervation, their influence remains a matter of debate. In our study, the SGB was performed in patients suffering chronic pain in the upper limb or the face. A successful SGB is traditionally ascertained by appearance of clinical symptoms like the Claude Bernard-Horner syndrome, hemifacial flushing, and a rise in skin temperature of the blocked arm and hand.

Figure 3.3.4 Average of 10 power spectra of mean arterial pressure (MAP) and mean middle cerebral artery flow velocity (MCA Vmean) before and after stellate ganglionic blockade.

Although cerebral conductance vessels, like the MCA, have α- and β-adrenergic innervation, their influence remains a matter of debate. In our study, the SGB was performed in patients suffering chronic pain in the upper limb or the face. A successful SGB is traditionally ascertained by appearance of clinical symptoms like the Claude Bernard-Horner syndrome, hemifacial flushing, and a rise in skin temperature of the blocked arm and hand.
A Horner’s syndrome (ptosis, miosis, and enophthalmus) is established when the injected local anesthetic spreads into cranial direction blocking the cervical sympathetic fibers. It should be noted that after a SGB, a Horner’s syndrome could be present without sympathetic denervation or rise in skin temperature of the upper limb that receives its sympathetic supply down to the level of the second thoracic vertebra. An earlier study addressing intra- and extracranial vessel diameter with MRI before and after SGB excluded 20% of their subjects who did not develop a Horner’s from analysis for that reason. In our study, a separate analysis of the Horner+ group did not reveal any differences.

**Figure 3.3.5**
Average of 10 power spectra of mean arterial pressure (MAP) and mean middle cerebral artery blood velocity (MCA Vmean), MAP-to-MCA Vmean transfer function coherence, phase, and gain in the upright position before (upper panels) and after (bottom panels) stellate ganglionic blockade. Gray is the control side and black the side that is (going to be) blocked.
Sympathetic activity and cerebral blood flow

Sympathomimetic agents like epinephrine, norepinephrine and phenylephrine applied directly to human pial artery segments lead to contraction. Intravenous norepinephrine lowers \( cO_2Hb, MCA V_{mean} \) and jugular bulb oxygen saturation, and equally \( \alpha \)-adrenergic stimulation by phenylephrine reduces \( cO_2Hb \).

Blocking of sympathetic activity with an agent like trimethaphan was reported to alter dCA as assessed with spectral analysis in the very low frequency area during steady state BP. The authors speculated that the autonomic neural control of the cerebral circulation is tonically active and likely plays a significant role in the regulation of beat-to-beat CBF in humans.

**Figure 3.3.6**

Individual curves of mean arterial blood pressure-to-mean middle cerebral artery blood velocity (MABP-to-MCA \( V_{mean} \)) transfer function phase difference in the upright position before and after cervical ganglion blockade (SGB) on the control side and the side to be blocked. Black lines: Horner + \((n=6)\); grey lines: Horner - \((n=4)\).
However, an earlier study using lower body negative pressure as a model to mimic orthostatic stress before and after systemic sympathetic blockade with trimethaphan did not find evidence for sympathetic activation under those circumstances.\textsuperscript{289} It has to be considered that in both studies the decrease in ABP elicited by systemic ganglion blockade was abolished by i.v. phenylephrine that in itself has an intrinsic effect on MCA $V$ and cO$_2$Hb.\textsuperscript{167}

Gierthmühlen et al. determined dCA by modulating blood pressure with thigh cuff release and head-up tilt in patients with a Horner’s syndrome due to an ischemic stroke in the dorsolateral medulla oblongata (Wallenberg’s syndrome) as a model of a permanent central sympathetic block. They found no evidence for sympathetic influence on dCA.

Our observation that SGB did not affect dCA, cO$_2$Hb and MCA $V_{\text{mean}}$, neither in supine position nor during orthostatic stress, is in accordance with earlier studies where the decrease in MCA $V_{\text{mean}}$ elicited by orthostatic stress, created with head up tilt\textsuperscript{84} or lower body negative pressure\textsuperscript{289} was not influenced when the sympathetic activity was blocked. One exception are data from an earlier study performed in supine subjects with unilateral MCA $V$ monitoring before and following cerebral sympathetic blockade by SGB.\textsuperscript{92} In that study MCA $V_{\text{mean}}$ declined with SGB, and this was attributed to vasodilatation.\textsuperscript{92}

SGB may increase carotid artery blood flow measured with HM-PAOSPECT\textsuperscript{263} or MRI\textsuperscript{188} both in healthy subjects and in patients with chronic pain. However, recently this observation was not confirmed in a study that quantified cerebral artery blood flow with MRI before and after SGB. This study showed diverging effects of SGB on extra- vs. intracranial arteries with an exclusive increase in MR signal intensity, suggesting an increase in blood flow, in extracranial vessels only whereas intracranial vessel diameter was maintained.\textsuperscript{138}

During dynamic exercise, larger changes in systemic hemodynamics are created, with an increase in MCA $V_{\text{mean}}$ and cO$_2$Hb.\textsuperscript{136} When in healthy subjects during exercise the normal increase in $\dot{Q}$ is artificially attenuated by $\beta$-adrenoceptor blockade, the increase in MCA $V_{\text{mean}}$ is also reduced.\textsuperscript{115} Yet the increase in MCA $V_{\text{mean}}$ is reestablished when the sympathetic activity to the brain is eliminated by SGB.\textsuperscript{113}

In summary, suppression of cerebral sympathetic activity by SGB did not affect the cerebrovascular response to orthostatic stress suggesting that the orthostatic decrease in gCBF, MCA $V$, and cO$_2$Hb takes place independently of sympathetic activity. Together these observations support the original statement by Bill and Lindner that under certain conditions stimulation of the sympathetic nerves to the brain causes a marked reduction in CBF, whereas under normal conditions the effect of such stimulation is practically nil.\textsuperscript{18}
Chapter 4

Microvascular Disease and the Cerebrovascular Response
4.1

Dynamic cerebral autoregulation in acute lacunar and middle cerebral artery territory ischemic stroke


Stroke 2005(35)2595-2600
INTRODUCTION We addressed whether dCA is affected in MCAS and LS.

METHODS MABP and MCA $V'$ were measured in 10 patients with large MCAS (National Institute of Health Stroke score; (NIHSS; 17±2; mean±S.E.M), in 10 with LS (score 9±1) and in 10 reference subjects (RS). dCA was evaluated in time (delay of the MCA $V_{\text{mean}}$ counter regulation during changes in MABP and frequency domains (cross-spectral MCA $V_{\text{mean}}$-to-MABP phase lead).

RESULTS In RS, latencies for MABP increments (5.3±0.5 s) and decrements (5.6±0.5 s) were comparable and low frequency MCA $V_{\text{mean}}$-to-MABP phase lead was 56±5º and 59±5º (left and right hemisphere). In MCAS, these latencies were 4.6±0.7 and 5.6±0.5 s in the non-ischemic hemisphere and not detectable in the ischemic hemisphere. In the unaffected hemisphere phase lead was 61±6º vs. 26±5º on the ischemic side ($P < 0.05$). In LS, no latency and smaller phase lead bilaterally (32±6 and 33±5º) conformed to globally impaired dCA.

CONCLUSION In large middle cerebral artery territory infarcts, dCA was impaired in the affected hemisphere. In lacunar ischemic stroke, dCA was impaired bilaterally, a finding consistent with the hypothesis of bilateral small vessel disease in patients with lacunar infarcts.
**Introduction**

gCBF is maintained by both fast and slow acting regulatory mechanisms spanning the prevailing demands on gCBF in everyday life. Static CA reflects the overall efficiency while dCA refers to the ability to restore CBF in the face of a sudden change in perfusion pressure, i.e. the delay of CA. Acute ischemic stroke is often associated with a temporarily elevated ABP returning to pre-stroke values within days. Adequate ABP management is of importance, considering CA impairment in penumbral tissue. Thus, in this setting, gCBF is likely to depend on cerebral perfusion pressure, or ABP. With global gCBF detected by cerebral $^{85}$Kr and $^{133}$Xe clearance, sCA in patients with acute ischemic stroke was demonstrated to be impaired. In patients with large unilateral MCAS, a transient ABP rise resulted in increased MCA $V_{l}$ on the affected side only, suggesting one-sided impaired sCA. In minor MCAS, dCA was found not to be relevantly disturbed. In contrast, bilateral dCA impairment was reported but without accounting for the type of stroke. This study determined bilateral dCA in two distinct subtypes of acute ischemic stroke, i.e. large MCA territory stroke and in lacunar infarcts of the basal ganglia and in reference subjects.

**Methods**

Ten patients with a first occurrence of MCAS and 10 patients with a first occurrence of LS were included in this study. Ischemic stroke was defined as a sudden onset of a non-convulsive and focal neurological deficit persisting for >24 hours without signs of a cerebral hemorrhage on computed tomography (CT) scan. Patients were excluded from the study in case of a diminished consciousness (Glasgow Coma Scale <10), an inadequate acoustic window, absence or insufficient quality of one of the MCA $V_{l}$ signals, atrial fibrillation or significant carotid stenosis (>70%). Following admission to the stroke unit stroke severity was quantified (NIHSS; maximal 42 point) and antihypertensive medication withdrawn (Table 4.1.1). An ischemic MCAS was diagnosed by neurological examination and CT scan. Six out of ten CT scans showed early signs of MCA infarction, and none revealed leukoaraiosis or hemorrhage. We diagnosed LS when a LS (pure motor stroke (in 4 patients), pure sensory stroke (1), sensorimotor stroke (1), ataxic hemiparesis (4) or dysarthria (none) was present. A CT served to exclude a hemorrhagic cause. An unilateral lacunar lesion was present in 6 out of 10 CT-scans made within three hours after hospital admission. Four patients had CT evidence of leukoaraiosis, suggestive of subcortical arteriosclerotic encephalopathy. In 4 patients no lacunar lesion was observed on CT-scan; on MRI-scanning made 3 days after admission in 2 of them a lacunar lesion infarct was present.

The RS had no history of cardiovascular disease and did not use any medication. Subjects, or a direct relative, received verbal and written explanation of the objectives and techniques of measurements and risks associated with the study. Written informed consent was provided in accordance with the Helsinki Declaration. The study protocol was approved by the Medical ethics committee of the Academic Medical Center, University of Amsterdam, The Netherlands (MEC 00/061).
Table 4.1.1  Subject characteristics

<table>
<thead>
<tr>
<th></th>
<th>References (n=10)</th>
<th>MCA Territory Stroke (n=10)</th>
<th>Lacunar Stroke (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (m:f)</td>
<td>5 : 5</td>
<td>5 : 5</td>
<td>8 : 2</td>
</tr>
<tr>
<td>Age (y)</td>
<td>57±2</td>
<td>59±5</td>
<td>63±3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>72±4</td>
<td>83±7</td>
<td>81±3</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>173±3</td>
<td>172±4</td>
<td>176±2</td>
</tr>
<tr>
<td>Infarct side (l:r)</td>
<td>6 : 4</td>
<td>4 : 6</td>
<td></td>
</tr>
<tr>
<td>NIHSS</td>
<td>17±2</td>
<td></td>
<td>9±1</td>
</tr>
</tbody>
</table>

History of:

- Hypertension: 6, 7
- Diabetes Mellitus: 3, 4
- Hyperlipidemia: 2, 7

Admission:

- HR (min⁻¹): 86±9, 78±5
- Systolic ABP (mmHg): 166±9, 178±16
- Mean ABP: 116±4, 121±11
- Diastolic ABP: 86±3, 93±9
- Glucose (mmol·l⁻¹): Total 5.2±0.4, 6.3±0.4
- Cholesterol (mmol·l⁻¹): Total 5.2±0.4, 6.3±0.4
- HDL 1±0.1, 1.2±0.1
- LDL 3.1±0.3, 3.4±0.4
- Triglycerids (mmol·l⁻¹): 2.1±0.4, 2.3±0.4

Medication:

- β-blocker: 2, 5
- ACE-inhibitor: 2, 1
- AT-II RA: 0, 2
- Diuretic: 2, 1
- Cholesterol lowering drug: 1, 4
- Glucose lowering drug: 3, 4

M:F, male – female ratio; L:R, left vs. right sided infarct; NIHSS, National Institute of Health Stroke Scale.

* P < 0.05 vs. lacunar stroke

The RS had no history of cardiovascular disease and did not use any medication.

Measurements were performed at the stroke unit between 8 and 11 PM within 72 hours after onset of stroke with the patients in supine position, in a quiet and dimly lit room to minimize arousal. RS were studied at the same time of the evening at least two hours after a light meal without caffeine-containing beverages. Recordings were obtained for at least 15 min. oscillometric blood pressure ABP was measured prior to the measurements as discussed on page 15. FinAP, bilateral MCA V and PaCO2 were monitored as described on page 15 and 17.
FinAP, MCA $V^\prime$ spectrum envelope, and $P_{\text{ET}}\text{CO}_2$ were A/D 100 Hz converted and stored. MABP and MCA $V_{\text{mean}}$ were the integral over one beat and heart rate was taken from pressure interval. MABP and MCA $V_{\text{mean}}$ data were interpolated and resampled for time domain dCA analysis. Dynamic CA in the time and frequency domain are assessed as presented on page 18 to 20.

Data were expressed as mean±S.E.M. or as median and range. Changes in systemic and cerebral hemodynamics were examined by Kruskal-Wallis non-parametric ANOVA. Significant changes were located with Wilcoxon signed rank test. Differences in dCA between the ischemic versus the nonischemic hemisphere, and patients versus RS were examined by non-parametric tests. $P < 0.05$ was considered to indicate statistically significance.

**Results**

**Subjects**

Age, weight and patient height did not differ between groups. On admission, NIHSS was higher in MCAS and ABP was comparable (Table 4.1.1). At the time of the study, ABP was lower in both groups (Table 4.1.2). In MCAS but not in LS, MCA $V^\prime$ tended to be higher in the ischemic hemisphere ($P = 0.08$).

**Time domain.**

In the 15 min tracings 2-10 episodes of spontaneous MABP increases and 2-9 decreases of comparable magnitude occurred in RS (18±3% and −12±1%), MCAS (17±2% and −16±4%) and LS (20±4% and −16±2%). In RS, CA latency was 5.3±0.5 s for MABP increments and 5.6±0.5 s for decrements (Figure 4.1.1). In MCAS these latencies were 4.6±0.7 and 5.6±0.5 s in the non-ischemic hemisphere and not detectable in the ischemic hemisphere. In LS, MCA $V_{\text{mean}}$ followed passively MABP in both hemispheres.

**Frequency domain**

In RS, LF MCA $V_{\text{mean}}$ to MABP phase lead was 56±5º (left hemisphere) and 59±5º (right hemisphere). In MCAS, phase lead was lower at the ischemic (26±6º; range 10-50º; $P < 0.05$) vs. non-ischemic side (61±6º; range 17-73º) with phase lead > 50º in 6 patients, and with 50º phase lead in 1 patient. In LS, LF phase lead was reduced bilaterally (non-ischemic: 32±6º; range 5-49º vs. ischemic hemisphere: 33±5º; range 6-54º; $P < 0.05$), and gain did not differ between the hemispheres (Figure 4.1.2).

**Discussion**

This study determined dCA capacity in the time and frequency domain in two main subtypes of acute ischemic stroke, large middle cerebral artery territory stroke and lacunar stroke. The main finding is that in acute MCAS, dCA is affected at the ischemic side only, while in acute LS, dCA is impaired bilaterally.

CA characterizes cerebral artery ability to modulate arterial wall smooth muscle tone, maintaining gCBF. The latency in dCA as derived from spontaneous MABP decreases...
provides confirmatory information regarding impaired CA as well as produced data akin to rapid thigh-cuff deflation as stimulus for dCA.160

**Figure 4.1.1**
Grey circles (all panels): percentage increase or decrease in finger arterial blood pressure (FinAP); upper panel: percentage changes in left (open circles) and right (closed circles) mean middle cerebral artery blood velocity (MCA Vmean); middle and lower panel: ischemic (open circles) and non-ischemic (closed circles) hemisphere. Reference subjects (RS), middle cerebral artery territory stroke (MCAS) and lacunar stroke (LS). Data are mean ± S.E.M.
CA in stroke is controversial. In large MCAS, a transient rise in BP by phenylephrine raises MCA $V_{\text{mean}}$ on the affected side only, indicating unilaterally impaired sCA.\textsuperscript{236} Several\textsuperscript{5} \textsuperscript{178} \textsuperscript{199} but not all\textsuperscript{46} reports suggest global sCA impairment. So far, global bi-hemispheric dCA impairment in acute and subacute stroke with preserved sCA has been reported without obvious differences between stroke subtypes.\textsuperscript{46} \textsuperscript{47} \textsuperscript{55} In subsequent studies, dCA appeared impaired bilaterally\textsuperscript{55} and to remain so for at least 1-2 weeks\textsuperscript{47} although this was not confirmed in minor MCAS.\textsuperscript{218} MCA territory infarcts are likely to result from embolism or large cerebral artery atherothrombosis with a considerable penumbral tissue volume. The present study extends the observations of unilaterally impaired static CA in MCAS\textsuperscript{236} to unilateral impairment of dCA.

<table>
<thead>
<tr>
<th>Table 4.1.2</th>
<th>Blood pressure and middle cerebral artery blood velocity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Brachial BP $\text{(mmHg)}$</td>
</tr>
<tr>
<td></td>
<td>Non-ischemic</td>
</tr>
<tr>
<td>Reference</td>
<td>systolic</td>
</tr>
<tr>
<td></td>
<td>mean</td>
</tr>
<tr>
<td></td>
<td>diastolic</td>
</tr>
<tr>
<td>MCA Territory Stroke</td>
<td>systolic</td>
</tr>
<tr>
<td></td>
<td>mean</td>
</tr>
<tr>
<td></td>
<td>diastolic</td>
</tr>
<tr>
<td>Lacunar Stroke</td>
<td>systolic</td>
</tr>
<tr>
<td></td>
<td>mean</td>
</tr>
<tr>
<td></td>
<td>diastolic</td>
</tr>
</tbody>
</table>

Brachial and finger arterial blood pressure (FinAP) and mean middle cerebral artery blood velocity (MCA $V_{\text{mean}}$) reference subjects and in patients with MCA territory or lacunar stroke. \textsuperscript{*}P < 0.05 vs. reference.

In contrast to what was found in large MCAS, dCA was affected bilaterally in one-sided LS. Intracranial small artery occlusion is the probable cause in the majority of LS.\textsuperscript{80} The penumbral volume in LS is usually small and we consider dCA impairment in LS by the ischemic event itself unlikely.\textsuperscript{80} In syndromes with more extensive atherosclerosis of both extracranial and intracranial vessels such as longstanding diabetes, CA is impaired.\textsuperscript{174} Cerebral small vessel disease can produce isolated lacunar infarcts or diffuse white matter changes appearing as leukoaraiosis on CT or MR images\textsuperscript{90} \textsuperscript{108} which may explain why dCA in LS was affected on the non-ischemic side as well. We examined CA capacity in acute stroke patients. In a follow-up study of patients suffering from minor MCAS, CA was still abnormal on the affected side but preserved on the normal side more than 2 months after stroke onset.\textsuperscript{190} We did not assess CA capacity prior to LS, but we speculate that a globally impaired dCA was already present.

In this study, CT scanning was the primary imaging technique used on admission. More ischemic strokes show up on diffusion weighted imaging than on CT or conventional MRI in the first few hours. However, MR imaging can be difficult to use routinely in acute stroke and may not identify hyperacute intracerebral hemorrhage correctly while CT scans are superior for differentiating ischemic from hemorrhagic stroke.\textsuperscript{90} \textsuperscript{276} In addition, lacunar syndromes are
highly predictive for small deep infarcts on MRI. For that reason MR brain imaging has even been considered redundant in the setting of a lacunar syndrome if supported by a CT that excludes non-ischemic causes of stroke.\textsuperscript{248} An inherent difficulty of both CT and MRI is the ability to differentiate between acute and chronic lesions. In spite of the problem of relating lacunar syndromes to certain locations of lacunae,\textsuperscript{235} our finding that CA capacity was impaired also in the contralateral ('healthy') hemisphere in LS remains unchallenged.

Critical for the interpretation of the data is to what extent MCA $V_{\text{mean}}$ reflects volume flow. The MCA $V_{\text{mean}}$ is assumed to represent flow velocity in the center of the vessel and when flow is laminar, MCA $V_{\text{mean}}$ follows $^{133}$Xe determined CBF.\textsuperscript{40} Thus, constancy of vessel diameter links changes in MCA $V$ to those in gCBF. When non-laminar blood flow in the affected cerebral arteries is considered, MCA $V_{\text{mean}}$ may change out of proportion to flow and therefore the analysis was restricted to normally shaped Doppler signals.\textsuperscript{9} CA was assessed after discontinuation of antihypertensive treatment but a remaining biological effect cannot be excluded. However, also with β-blockade, angiotensin converting enzyme inhibition or angiotensin-receptor antagonist treatment integrity of CA has been confirmed.

![Image](image-url)
We did not create different steady state ABP levels and quantification of sCA as established by Schwartz et al. was not carried out. Impairment of sCA by pharmacological manipulation also affects dCA and we therefore consider that the impaired dCA found in this study suggests impairment of sCA as well.

### Table 4.1.3
Variability in blood pressure and middle cerebral artery blood velocity

<table>
<thead>
<tr>
<th></th>
<th>MABP variability (mmHg·Hz²)</th>
<th>MCA V&lt;sub&gt;mean&lt;/sub&gt; variability ([cm·s⁻¹]·Hz²)</th>
<th>Coherence (k)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>non-ischemic</td>
<td>ischemic</td>
<td>non-ischemic</td>
</tr>
<tr>
<td>VLF</td>
<td>8.5±2.4</td>
<td>6.0±1.3</td>
<td>6.1±1.4</td>
</tr>
<tr>
<td>LF</td>
<td>4.0±0.8</td>
<td>2.1±0.4</td>
<td>2.2±0.5</td>
</tr>
<tr>
<td>HF</td>
<td>0.8±0.2</td>
<td>1.2±0.3</td>
<td>1.3±0.3</td>
</tr>
<tr>
<td>VLF</td>
<td>13.8±3.9</td>
<td>5.5±2.0</td>
<td>6.5±1.6</td>
</tr>
<tr>
<td>LF</td>
<td>5.0±1.7</td>
<td>1.7±0.3</td>
<td>2.3±0.5</td>
</tr>
<tr>
<td>HF</td>
<td>3.5±0.9</td>
<td>2.9±0.8</td>
<td>2.1±0.4</td>
</tr>
<tr>
<td>VLF</td>
<td>31.1±13.3*</td>
<td>6.9±2.7</td>
<td>9.3±3.9</td>
</tr>
<tr>
<td>LF</td>
<td>4.5±1.1</td>
<td>1.2±0.2</td>
<td>1.6±0.4</td>
</tr>
<tr>
<td>HF</td>
<td>2.0±0.5</td>
<td>1.1±0.3</td>
<td>1.2±0.5</td>
</tr>
</tbody>
</table>

MAP, blood pressure; MCA V<sub>mean</sub>, mean middle cerebral artery blood velocity; VLF, very low frequency; LF, low frequency; HF, high frequency; *: P<0.05 vs. reference

### Conclusion
In large middle cerebral artery territory infarcts, dCA was impaired in the affected hemisphere only. In lacunar ischemic stroke, dCA was impaired bilaterally. The latter finding is consistent with the hypothesis of bilateral small vessel disease in patients with lacunar infarcts.
4.2

Dynamic cerebral autoregulatory capacity is affected early in type 2 diabetes mellitus


Clinical Science 2008(115)255-262
INTRODUCTION  Type 2 diabetes is associated with an increased risk of endothelial dysfunction and microvascular complications with impaired autoregulation of tissue perfusion. Both microvascular disease and cardiovascular autonomic neuropathy may affect cerebral autoregulation. We tested the hypothesis that in absence of cardiovascular autonomic neuropathy, cerebral autoregulation is impaired in subjects with type 2 diabetes with microvascular complications but intact in subjects without complications.

METHODS  Dynamic cerebral autoregulation and the steady state cerebrovascular response to postural change were studied in subjects with type 2 diabetes with (DM+) and without (DM-) microvascular complications in absence of cardiovascular autonomic neuropathy and in reference subjects (RS). The relationship between spontaneous changes in MCA $V_{\text{mean}}$ and MABP was evaluated using frequency domain analysis.

RESULTS  In the LF region (0.07-0.15 Hz), the phase lead of the MABP-to-MCA $V_{\text{mean}}$ transfer function was 52±10° in RS, reduced in DM- (40±6°; $P < 0.01$ vs. CTRL) and impaired in DM+ (30±5°; $P < 0.01$ vs. DM-) indicating less dampening of blood pressure oscillations by affected dCA. The steady state response of MCA $V_{\text{mean}}$ to postural change was comparable for all groups (-12±6% in RS vs. -15±6% in DM- vs. -15±7% in DM+). HbA1c and duration of diabetes but not blood pressure were determinants of transfer function phase.

CONCLUSION  Dysfunction of dCA in subjects with type 2 diabetes appears to be an early manifestation of microvascular disease prior to the clinical expression of diabetic nephropathy, retinopathy or cardiovascular autonomic neuropathy.
Introduction

Blood flow to the brain is influenced by regional changes in neural activity and by global regulatory mechanisms including CA. Maintenance of cerebral perfusion during physiological challenges is secured by both fast- and slow-acting autoregulatory mechanisms. Although acute changes in ABP are transmitted to the cerebral circulation, under normal conditions gCBF tends to return to its baseline value within a few seconds. This short-term control is usually referred to as dCA. Static CA considers the net change in gCBF resulting from a manipulated change in cerebral perfusion pressure under steady-state conditions. In patients with moderate hypertension, CA protects the brain from regional hyperperfusion. However, with severe hypertension or ischemic stroke, impairment of CA leads to loss of control of cerebral perfusion, and gCBF becomes a function of arterial pressure, so-called pressure dependency. Type 2 diabetes is associated with hypertension and an increased risk of endothelial dysfunction and microvascular complications with impaired autoregulation of tissue perfusion. In subjects with long-standing type 1 diabetes with orthostatic hypotension due to cardiovascular autonomic neuropathy and microvascular complications including diabetic nephropathy and retinopathy, CA is impaired. Impairment of CA in subjects with diabetes is attributed to both cardiovascular autonomic neuropathy and microvascular endothelial dysfunction associated with cerebral small vessel disease. Despite sympathetic innervation of cerebral arteries, the role of the autonomic nervous system in the control of gCBF remains controversial. We hypothesized that in subjects with type 2 diabetes and manifest microvascular complications but without symptomatic cerebrovascular disease, CA capacity may become impaired in absence of cardiovascular autonomic neuropathy. We further hypothesized that in subjects with type 2 diabetes who have no signs of microvascular disease or cardiovascular autonomic neuropathy, CA capacity is maintained. To test these questions we set out to evaluate the dynamic component of CA capacity and the steady state cerebrovascular response to a postural change in subjects with type 2 diabetes and microvascular complications but without symptomatic cerebrovascular disease and cardiovascular autonomic neuropathy (DM+). Frequency domain analysis evaluated the relationship between transcranial Doppler (TCD) determined beat-to-beat changes in MCA V and spontaneous BP oscillations. Subjects with type 2 diabetes without microvascular complications (DM-) and healthy control subjects served as RS.

Methods

Subjects and study design

Thirty subjects participated in the study. Ten subjects with complicated type 2 diabetes (DM+, aged 61±8 years, 6 male), ten subjects with uncomplicated type 2 diabetes (DM-, aged 54±8 years, 5 male) and ten age- and gender matched RS, aged 61±16 years, 4 male) were studied. Each subject received verbal and written information about the study objectives, measurement techniques, and the risks and benefits associated with the investigation. All subjects gave their written informed consent as approved by the AMC Medical Ethical Committee and experiments were performed in accordance with the Declaration of Helsinki. DM+ and DM-
Subjects had been diagnosed with type 2 diabetes according to the WHO criteria\textsuperscript{10} and were receiving treatment with insulin and/or oral antidiabetic agents. Selection criteria for the group DM+ included microvascular complications such as diabetic nephropathy (clinically defined as persistent urinary albumin excretion rate of \textgreater 300 mg/24h or albumin/creatinine ratio \textgreater 2.5 mg/mmol (men) or \textgreater 3.5 mg/mmol (women) in the presence of diabetic retinopathy and in the absence of clinical or laboratory evidence of other kidney or renal tract disease),\textsuperscript{211, 212} retinopathy (diagnosed by an ophthalmologist), and symptoms or signs of diabetic polyneuropathy.\textsuperscript{26, 227} Subjects without these complications were designated as DM-. Exclusion criteria included history of stroke, TIA, clinical manifestation of cardiovascular disease or heart failure, uncontrolled hypertension (BP > 160/100 mmHg), orthostatic hypotension, cardiovascular autonomic neuropathy, use of medication with potential influence on autonomic cardiovascular function, and poor metabolic control (HbA\textsubscript{1c} > 9.5\%). Prior to inclusion in the study, all subjects underwent cardiovascular autonomic function testing. Parasympathetic control of HR was evaluated by quantifying time-course and magnitude of HR responses to active standing and the Valsalva maneuver.\textsuperscript{63, 257, 279} Sympathetic cardiovascular control was assessed by the ABP responses to active standing and the Valsalva maneuver.\textsuperscript{26, 280} The presence of two or more abnormal test results was considered to reflect presence of cardiovascular autonomic neuropathy.\textsuperscript{26, 293} After a light breakfast, subjects reported to the laboratory at 8:00 a.m. and were studied in a room at 22 °C. They abstained from caffeinated beverages. Subjects were placed in the supine position for instrumentation. After obtaining systemic and cerebrovascular variables in the supine resting position, the subjects were asked to stand up for 5 min. FinAP, MCA \textit{V'} and \textit{P}_{ET,CO_2} were monitored as discussed on page 15 and 17. An automated non-invasive ABP measuring device (HEM-705CP, Omron, Kyoto, Japan) was used to calibrate the FinAP measurements (see page 15).

\textbf{Data Analysis}

The signals of ABP, spectral envelope of MCA \textit{V’}, ECG, and \textit{P}_{ET,CO_2} were analog/digital converted at 100 Hz and stored on a hard disk for off-line analysis. Beat-to-beat values for MCA \textit{V'}\textsubscript{mean} and MABP were derived as the integral over one beat divided by the corresponding beat interval and HR was the inverse of the interbeat pressure interval. MABP at the MCA level was calculated from MABP measured at heart level and the vertical finger-to-TCD probe distance.\textsuperscript{96} Cerebrovascular resistance index (CVR\textsubscript{i}) was the ratio of MABP at brain level (MABP\textsubscript{brain}) and MCA \textit{V'}\textsubscript{mean}. The Gosling pulsatility index of the MCA was taken as an index of cerebral microangiopathy expressed as the amplitude of MCA \textit{V’} divided by time-averaged MCA \textit{V’}.\textsuperscript{139}

\textbf{Cerebral autoregulation}

The steady state response of MCA \textit{V'}\textsubscript{mean} to a postural change in relation to MABP\textsubscript{brain} and frequency domain CA were assessed as discussed on page 18.
Table 4.2.1  Subjects characteristics

<table>
<thead>
<tr>
<th></th>
<th>RS</th>
<th>DM-[n=10]</th>
<th>DM+[n=10]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (m:f)</td>
<td>4:6</td>
<td>5:5</td>
<td>4:6</td>
</tr>
<tr>
<td>Age (y)</td>
<td>61±6</td>
<td>54±8</td>
<td>61±8</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.3±3.6</td>
<td>28.3±8.1</td>
<td>29.8±4.0</td>
</tr>
<tr>
<td>ABP (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>113±17</td>
<td>133±14</td>
<td>137±13</td>
</tr>
<tr>
<td>Diastolic</td>
<td>74±11</td>
<td>73±11</td>
<td>76±7</td>
</tr>
<tr>
<td>Duration of disease (y)</td>
<td>8±3</td>
<td>16±10</td>
<td></td>
</tr>
</tbody>
</table>

Microvascular complications

|                      |        |           |           |
| Retinopathy          | 0      | 6         |           |
| Nephropathy          | 0      | 6         |           |
| Polyneuropathy       | 0      | 6         |           |

Oral hypoglycaemic agents

|                      |        |           |           |
| Insulin              | 5      | 8         |           |

Plasma glucose (mmol/L)

|                      |        |           |           |
| HbA1c (% Hb)         | 7.2±0.8| 8.0±1.1   |           |

Albumin/creatininratio (mg/mmol)

|                      | 0.80±0.65 | 8.38±12.89 |

Medication

|                      |        |           |           |
| ACE inhibitor        | 0      | 1         | 6         |
| Diuretic             | 0      | 4         | 5         |
| AT I RA              | 0      | 1         | 2         |
| β-blocker            | 0      | 2         | 0         |
| Calcium channel blocker | 0  | 2         | 6         |
| Statin               | 0      | 5         | 9         |

Abnormal autonomic function tests

Parasympathetic function tests

|                      |        |           |           |
| HR response to Valsalva | 0    | 0         | 0         |
| HR response to standing | 0    | 0         | 0         |

Sympathetic tests

|                      |        |           |           |
| ABP response to Valsalva | 0    | 0         | 0         |
| ABP response to standing | 0    | 0         | 0         |

RS, reference subjects; DM-, patients without complications; DM+, patients with complications; BMI, body mass index; BP, blood pressure; HbA1c, glycated hemoglobin; ACE, angiotensin converting enzyme; AT I RA, angiotensin II receptor antagonist; HR, heart rate. Data are mean±SD.

Statistics

Data are presented as mean±SD. When data fitted a normal distribution as indicated by Kolmogorov-Smirnov analysis, an unpaired Student t-test was used and a Mann-Whitney rank sum test was applied when data were not normally distributed. Differences among the 3 groups
were identified by ANOVA. A multivariate, stepwise regression model was constructed with MABP-to-MCA \( V_{mean} \) transfer function phase as the dependent variable and duration of diabetes, systolic and diastolic ABP, BMI, actual plasma glucose and HbA1c as the independent variables, with forward entry and removal. \( P < 0.05 \) was considered to indicate a statistically significant difference.

**Results**

**Subject Characteristics**

Cardiovascular autonomic function test results were without abnormalities. None of the subjects experienced symptoms of orthostatic intolerance or other signs of cerebral hypoperfusion. There were no differences among groups with regard to BMI, age, gender ratio, plasma glucose levels, or systolic and diastolic ABP (Table 4.2.1). In the DM+ group, duration of diabetes tended to be longer (16±10 vs. 8±3 yr in DM-; \( P = 0.14 \)) and HbA1c value tended to be higher (8.0±1.1 vs. 7.2±0.8 % in DM-; \( P = 0.09 \)).

**Table 4.2.2** Static cerebral autoregulation capacity

<table>
<thead>
<tr>
<th></th>
<th>Supine</th>
<th>Standing</th>
<th>∆</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MABPmean (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RS</td>
<td>93±14</td>
<td>102±18‡</td>
<td>+6%</td>
</tr>
<tr>
<td>DM-</td>
<td>94±12</td>
<td>101±10‡</td>
<td>+7%</td>
</tr>
<tr>
<td>DM+</td>
<td>97±10</td>
<td>108±11‡</td>
<td>+11%</td>
</tr>
<tr>
<td><strong>MABPmax (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RS</td>
<td></td>
<td>77±18‡</td>
<td>-18%</td>
</tr>
<tr>
<td>DM-</td>
<td></td>
<td>76±10‡</td>
<td>-19%</td>
</tr>
<tr>
<td>DM+</td>
<td></td>
<td>83±11‡</td>
<td>-14%</td>
</tr>
<tr>
<td><strong>MCA ( V_{mean} ) (cm/s)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RS</td>
<td>58±18</td>
<td>51±17‡</td>
<td>-12%</td>
</tr>
<tr>
<td>DM-</td>
<td>59±16</td>
<td>50±13‡</td>
<td>-12%</td>
</tr>
<tr>
<td>DM+</td>
<td>55±8</td>
<td>47±8‡</td>
<td>-15%</td>
</tr>
<tr>
<td><strong>CVRi (mmHg·cm⁻¹·s⁻¹)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RS</td>
<td>1.60±0.42</td>
<td>1.52±0.62</td>
<td>-5%</td>
</tr>
<tr>
<td>DM-</td>
<td>1.59±0.42</td>
<td>1.53±0.56</td>
<td>-4%</td>
</tr>
<tr>
<td>DM+</td>
<td>1.76±0.33</td>
<td>1.77±0.48</td>
<td>0%</td>
</tr>
<tr>
<td><strong>PET( CO_2 ) (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RS</td>
<td>42.2±2.6</td>
<td>39.0±3.3‡</td>
<td>-7%</td>
</tr>
<tr>
<td>DM-</td>
<td>40.6±2.8</td>
<td>38.1±2.7‡</td>
<td>-6%</td>
</tr>
<tr>
<td>DM+</td>
<td>41.2±2.2</td>
<td>38.9±2.7‡</td>
<td>-6%</td>
</tr>
</tbody>
</table>

**Pulsatility index**

<table>
<thead>
<tr>
<th></th>
<th>Supine</th>
<th>Standing</th>
<th>∆</th>
</tr>
</thead>
<tbody>
<tr>
<td>RS</td>
<td>0.93±0.23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM-</td>
<td>0.87±0.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM+</td>
<td>0.96±0.23</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RS, reference subjects; DM -, patients without complications; DM +, with complications; MABP, mean arterial blood pressure; MCA \( V_{mean} \), middle cerebral artery mean cerebral blood flow velocity; CVRi, cerebral vascular resistance index; \( PET\( CO_2 \), partial end-tidal carbon dioxide pressure. † \( P < 0.05 \) versus supine, ‡ \( P < 0.01 \) versus supine. Values are mean ± SD for 10 subjects per group.
MCA $V_{\text{mean}}$ Response to Postural Change

At rest prior to standing, baseline cerebro- and cardiovascular variables were comparable between groups, whereas pulsatility index and $P_{\text{ETCO}_2}$ did not differ (Table 4.2.2). With standing, CVRi did not change and the postural reduction in MABP at brain level and in MCA $V_{\text{mean}}$ was comparable among groups (Figure 4.2.1).

Dynamic Cerebral Autoregulation

Spectral analysis and MABP-MCA $V_{\text{mean}}$ transfer function data are given in Table 4.2.3. In the LF region (0.07-0.15 Hz), MABP power was lower in both DM- and DM+ compared with control subjects, whereas MCA $V_{\text{mean}}$ power was comparable between groups.

Table 4.2.3 Dynamic cerebral autoregulation control

<table>
<thead>
<tr>
<th></th>
<th>RS</th>
<th>DM -</th>
<th>DM +</th>
</tr>
</thead>
<tbody>
<tr>
<td>MABP power (mmHg²·Hz⁻¹)</td>
<td>9.7±7.5</td>
<td>4.7±2.9</td>
<td>3.3±2.4*</td>
</tr>
<tr>
<td>MCA $V_{\text{mean}}$ power (cm²·s⁻¹·Hz⁻¹)</td>
<td>3.5±2.5</td>
<td>3.8±3.8</td>
<td>4.2±8.6</td>
</tr>
<tr>
<td>Coherence (k)</td>
<td>0.76±0.11</td>
<td>0.79±0.12</td>
<td>0.73±0.12</td>
</tr>
<tr>
<td>Phase (degrees)</td>
<td>52±10</td>
<td>40±6**</td>
<td>30±5**§</td>
</tr>
<tr>
<td>Gain (%cm²·s⁻¹·%mmHg⁻¹)</td>
<td>1.21±0.28</td>
<td>1.47±0.73</td>
<td>1.44±0.42</td>
</tr>
</tbody>
</table>

*Averaged low frequency (0.07-0.15 Hz) transfer function gain, phase and coherence, DM -, patients without complications; DM +, with complications; MABP, mean arterial blood pressure; MCA $V_{\text{mean}}$, mean middle cerebral artery blood velocity.

* P < 0.05 versus RS, ** P < 0.01 versus RS, § P < 0.01 versus DM -. Values are mean ± SD for 10 subjects.
Coherence was > 0.5 in all groups. The transfer function phase between MABP and MCA $V_{\text{mean}}$ was 52±10° in RS subjects, lower in subjects with DM- (40±6°; $P < 0.01$ vs. RS) and reduced further in DM+ (30±5°; $P<0.01$ vs. DM-) (Figure 4.4.2). Phase vs. MABP power did not correlate in the three groups.

Table 4.2.4 Stepwise regression analysis of the determinant of transfer function phase in DM+ and DM-subjects

<table>
<thead>
<tr>
<th>In</th>
<th>Variable</th>
<th>SE of estimate</th>
<th>$R^2$-increment</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>HbA1c</td>
<td>5.75</td>
<td>0.47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>Duration of DM</td>
<td>5.09</td>
<td>0.60</td>
<td>0.005</td>
</tr>
<tr>
<td>No</td>
<td>BMI</td>
<td></td>
<td>0.396</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>ABP$_{\text{syst}}$</td>
<td></td>
<td>0.542</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>ABP$_{\text{dia}}$</td>
<td></td>
<td>0.639</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Plasma glucose</td>
<td></td>
<td>0.806</td>
<td></td>
</tr>
</tbody>
</table>

In, entering or removal of variables; Yes, variable is in stepwise model; No, variable is not in stepwise regression model; SE, standard error; ABP$_{\text{syst}}$, systolic blood pressure; BP$_{\text{dia}}$, diastolic blood pressure;

Representative examples of declining MCA $V_{\text{mean}}$-MABP phase lead are given in Figure 4.2.3. The larger gain in DM- and DM+ did not reach statistical significance. Plasma HbA1c and duration of diabetes, but not BMI, plasma glucose, systolic and diastolic BP contributed to a multiple linear regression model of the MABP-to-MCA $V_{\text{mean}}$ transfer function phase (Table 4.2.4).

Discussion

The present study provides novel information regarding the dCA in type 2 diabetes. The major finding was a significant impairment of dCA in subjects with type 2 diabetes and microvascular complications. This reduced dCA capacity was present in absence of signs or symptoms of cardiovascular autonomic neuropathy. Also, in contrast to our hypothesis, dCA efficiency was already reduced in subjects with type 2 diabetes in absence of clinical expression of established indicators of microvascular damage. At the same time the steady state response of MCA $V_{\text{mean}}$ to a postural change was unaffected in both DM- and DM+ groups. Together, these findings suggest impairment of dCA as an early manifestation of microvascular disease prior to cardiovascular autonomic neuropathy or clinical microvascular disease reflected by diabetic nephropathy and retinopathy. The following discussion details the assumptions and evidence that underlie these conclusions.

There are potential limitations of this study that need consideration. The lower age of DM- vs. DM+ questions the effect of age on cerebral autoregulation. However, in healthy subjects ageing does not affect dCA.34

The MCA $V_{\text{mean}}$ was chosen for evaluation of changes in gCBF assuming that changes in MCA $V_{\text{mean}}$ are representative of those in gCBF. TCD monitors blood velocity rather than blood flow and changes in the diameter of the insonated vessel by enhanced sympathetic activity
could modulate velocity independently of flow. However, large cerebral arteries, including the MCA, are conductance rather than resistance vessels and moderate sympathetic activation does not modify the lumbar diameter of a systemic conduit artery. Thus, the constancy of MCA diameter links changes in cerebral blood velocity to changes in flow.

Figure 4.2.2

Group-averaged low frequency (0.07-0.15 Hz) transfer function phase between MABP and MCA V_mean in reference subjects (RS; white), subjects with uncomplicated (DM-; grey) and complicated (DM+; black) type 2 diabetes. Values are mean ± SD.

Arterial blood pressure was comparable for RS and DM groups. Although dynamic and static components of CA capacity are affected in malignant hypertension, CA indices are unimpaired in uncomplicated hypertension in middle-aged humans rendering an effect of blood pressure level itself unlikely. In the DM groups, an effect of anti-hypertensive medication should be considered. However, integrity of CA and preservation of gCBF during treatment with β-blockade, calcium channel blocker and angiotensin converting enzyme inhibition or AT 1-receptor antagonist are confirmed. Thus, hypertensive elderly subjects, whether controlled or uncontrolled with anti-hypertensive medication, retain CA capacity.

In LS, dCA is impaired uniformly at both the non-ischemic and ischemic hemisphere. This is compatible with the notion that pre-existing generalized cerebral small vessel disease may affect CA. MCA V_mean LF power was comparable in all groups, whereas MABP LF power as input to the transfer function was lower in DM- compared to RS, and in DM+, the reduction reached statistical significance. This resulted in a higher gain in both DM- and DM+, reflecting proportionally less dampening of MABP oscillations compared to RS. Given a lower amplitude of a particular oscillation, there might be more influence of background noise in the determination of oscillation parameters. However, coherence between MABP and MCA V_mean was not statistically different for DM+, DM- and RS. Also, the expected increase in variance of the extracted parameters, gain and phase, was not observed. Moreover, MABP power and phase did not correlate. Therefore, we consider that the findings do not depend on signal noise, but reflect an inherent problem in DM+. The present study indicates that dCA becomes affected in subjects with type 2 diabetes prior to the occurrence of cerebral ischemic symptoms.
Impaired CA is associated with cardiovascular autonomic neuropathy. Moreover, when healthy humans are subjected to SGB with development of arterial hypotension, CA can no longer maintain MCA \( V_{\text{mean}} \). This has been attributed to removal of vasomotor effects of autonomic neural activity. The present study was designed to account for the influence of cardiovascular autonomic neuropathy by excluding patients with demonstrable cardiovascular autonomic dysfunction by standardized autonomic function tests. The mechanism underlying this early decrease in autoregulatory capacity in subjects with type 2 diabetes cannot be determined from the present study, but dCA capacity was reduced in absence of overt cardiovascular autonomic neuropathy.

To our knowledge this is the first study to establish a reduction of dCA efficiency in subjects with type 2 diabetes who have no clinical evidence of microvascular complications. The cerebral arterial pulsatility index is proposed as an indicator of cerebral microangiopathy in diabetes. An elevated pulsatility index of the MCA in complicated vs. uncomplicated type 2 diabetes and a close correlation with the duration of diabetes suggest that the pulsatility index reflects microangiopathic changes of cerebral vessels, but this was not substantiated in the present study where the pulsatility index did not differ across groups. The progressive reduction in phase lead of MCA \( V_{\text{mean}} \) to MABP correlated closely to the duration of diabetes suggesting that impairment of dCA is an early marker of microangiopathy in advance of established indicators for retino- and nephropathy.

A role for hyperglycemia regarding affected cerebral autoregulation should be considered.
However, in diabetic patients MCA $V_{\text{mean}}$ does not relate to either glucose or insulin plasma concentrations. Furthermore, hyperglycemic clamping does not affect dCA capacity both at rest and during exercise. The finding that the physiological postural reduction in MCA $V_{\text{mean}}$ in both DM- and DM+ was comparable to what is found in healthy subjects confirms the integrity of sCA. The present study documents that a reduced dCA capacity does not jeopardize cerebral perfusion when exposed to orthostatic stress. The finding that dCA appears to be a more vulnerable component of cerebrovascular control conforms to earlier observations that progressive impairment in CA first affects the latency and then the efficiency of the CA response.

Our findings are of concern for subjects with type 2 diabetes who have no clinical evidence for microvascular complications. Subjects with type 2 diabetes are advised to combine aerobic and resistance training. Similar to aerobic exercise, resistance training enhances insulin sensitivity but it also involves repeated straining-like maneuvers with abrupt ABP increments. The data of this study indicate that transmission of ABP surges to the cerebral vasculature is dampened less effectively in subjects with type 2 diabetes.

In conclusion, type 2 diabetes is associated with early impairment of dCA becoming manifest prior to the occurrence of diabetic nephropathy, retinopathy or cardiovascular autonomic neuropathy.
Chapter 5

Malignant Hypertension and the Cerebrovascular Response
5.1

Impaired cerebral autoregulation in patients with malignant hypertension


Circulation 2004(110)2241-2245
INTRODUCTION  In patients with a malignant hypertension immediate parenteral treatment with ABP lowering agents, such as intra-venous SNP, is indicated. In this study we evaluated static and dynamic CA during acute ABP lowering with SNP in these patients.

METHODS  In eight patients with MABP > 140 mmHg and grade III or IV hypertensive retinopathy at hospital admission, MCA $V'$ and ABP were monitored. Dynamic CA was expressed as the 0.1 Hz MCA $V'_{\text{mean}}$ to MABP phase lead and sCA as the MCA $V'_{\text{mean}}$ to MABP relationship during SNP treatment. Eight normotensive subjects served as a reference group.

RESULTS  In the patients the MCA $V'_{\text{mean}}$ to MABP phase lead was lower ($30^\circ\pm 8^\circ$ versus $58^\circ\pm 5^\circ$; mean ± s.e.m.; $P < 0.05$) while the transfer gain tended to be higher. During SNP treatment, target MABP was reached within 90 min in all patients. The MCA $V'_{\text{mean}}$ decrease was $22\pm 4\%$ together with a $27\pm 3\%$ reduction in MABP (from 166±4 to 121±6 mmHg; $P < 0.05$) in a linear fashion (averaged slope $0.82\pm 0.15$ % cm$^{-1}$ % mmHg$^{-1}$; $r=0.70\pm 0.07$).

CONCLUSION  In patients with malignant hypertension, dCA is impaired. A MCA $V'_{\text{mean}}$ plateau was not detected during the whole SNP treatment indicating loss of sCA as well. This study showed that during the whole rapid reduction in blood pressure with SNP, MCA $V'_{\text{mean}}$ decreases almost one on one with MABP.
Introduction
In patients with malignant hypertension immediate treatment with ABP reducing agents, such as intra-venous SNP or labetolol is indicated to limit cerebral, myocardial and renal damage.1 It is considered that in these patients with a MABP > 140 mmHg, the presence of grade III–IV retinopathy and occasionally hypertensive encephalopathy, reflecting cerebral hyperperfusion and edema, indicate compromised CA capacity.109–270 Based on this assumption it has become generally accepted that the initial reduction in ABP should not exceed ~25% of the presenting level within the first hours of treatment to prevent cerebral hypoperfusion.1–93,140,158,270 CA is defined as the intrinsic capacity of cerebral vasculature to maintain gCBF constant.155,234,268 When in normotensive subjects MABP decreases below ~60 mmHg, considered as the lower limit of CA, cerebral blood flow decreases proportionally with ABP. The majority of patients suffering of malignant hypertension have a history of chronic hypertension287 and in those patients the lower limit of CA has been shifted in proportion towards higher pressures.233,250 For obvious reasons the upper limit of cerebral autoregulation has not been determined in normotensive or hypertensive humans. In normotensive baboons it was located between 120 and 150 mmHg252 and between 155 and 170 mmHg in chronic hypertensive baboons.251 A moderate reduction of ABP with SNP in normotensive subjects does not influence gCBF107 but, to our knowledge, no human studies specifically tested the assumption that CA is impaired in patients with malignant hypertension. Therefore we determined CA in this group of patients prior to and during a decline in BP as elicited by SNP.

Methods
Eight consecutive patients fulfilling the WHO criteria for malignant hypertension, namely severely elevated blood pressure together with grade III (bilateral retinal hemorrhages or cotton wool exudates, 5 cases) or IV (III plus papilledema, 3 cases) hypertensive retinopathy according to the Keith, Wagener and Barker classification, were included in the study (Table 5.1.1).
Prior to hospital admission, three out of these eight patients were known with moderate hypertension treated with one or two anti-hypertensive drugs. Two of these three patients withdraw medication without consulting their general practitioner. One had untreated hypertension, one was normotensive and in the other three blood pressure was not documented.
At hospital admission three out of eight patients presented with symptoms of hypertensive encephalopathy (e.g. convulsions prior to hospital admission). Six had left ventricular hypertrophy, six had moderately elevated plasma creatinin levels (between 100 and 200 μmol·l⁻¹), and in one patient plasma creatinin level was considerably elevated (1050 μmol·l⁻¹). A cause of hypertension was identified in three patients: respectively, high dose corticosteroid treatment, a cortisol producing adrenal carcinoma, and deterioration of renal function with volume overload related to IgA nefropathy. In five patients extended testing including renal artery imaging did not identify a definite cause of the hypertension.
To decrease blood pressure, intravenous SNP infusion was started at 0.3 μg·kg⁻¹·min⁻¹. After 5
min it was increased to 0.5 µg·kg⁻¹·min⁻¹ and from then on, by 0.5 µg·kg⁻¹·min⁻¹ every 5 min until MABP had stabilized at ~25% below the presenting value. Eight normotensive healthy subjects matched for age, weight and length (Table 5.5.1) were included to estimate normal CA parameters.

**Table 5.1.1** Characteristics of reference subjects and patients

<table>
<thead>
<tr>
<th></th>
<th>RS</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>m:f</td>
<td>5:3</td>
<td>6:2</td>
</tr>
<tr>
<td>Age (y)</td>
<td>46 (25-64)</td>
<td>44 (24-54)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>177 (160-186)</td>
<td>175 (165-188)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76 (62-92)</td>
<td>76 (63-96)</td>
</tr>
<tr>
<td>HR (min⁻¹)</td>
<td>67 (55-85)</td>
<td>89 (55-106)*</td>
</tr>
<tr>
<td>ABP (mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>systolic</td>
<td>124 (101-146)</td>
<td>225 (180-260)*</td>
</tr>
<tr>
<td>mean</td>
<td>82 (73-94)</td>
<td>166 (147-187)*</td>
</tr>
<tr>
<td>diastolic</td>
<td>62 (54-69)</td>
<td>137 (130-150)*</td>
</tr>
<tr>
<td>maximal</td>
<td>96 (82-112)</td>
<td>97 (65-126)</td>
</tr>
<tr>
<td>MCAV (cm·s⁻¹)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>63 (54-74)</td>
<td>64 (37-85)</td>
</tr>
<tr>
<td>minimal</td>
<td>42 (35-50)</td>
<td>43 (30-56)</td>
</tr>
</tbody>
</table>

Male : female (m:f), arterial blood pressure (ABP), middle cerebral artery blood velocity (MCAV) and heart rate (HR) of eight normotensive reference subjects (RS) and eight patients with a hypertensive emergency prior to treatment. Values are mean (range), * P<0.01 vs. RS.

In the first six months of follow-up the patient with corticosteroid related malignant hypertension was well controlled (ABP 110/80 mmHg) with two anti-hypertensive drugs and tapering of corticosteroid dosage. Four patients were well controlled (ABP < 140/90 mmHg) with three or four anti-hypertensive drugs. In two others ABP was moderately elevated (ABP 150/90 mmHg and 160/100 mmHg) despite the use of three and five drugs, respectively.

All subjects, or a direct relative in case of encephalopathy, received verbal and written explanation of the objectives and techniques of measurements and risks and benefits associated with the study and provided written informed consent in accordance with the Helsinki Declaration. This study was approved by the Medical Ethical Committee of the Academic Medical Center, University of Amsterdam, the Netherlands (MEC 02/194).

**Measurements**

In the supine position, patients and RS were instrumented with electrocardiogram electrodes and transcranial Doppler as discussed on page 17. In the patients, IAP was monitored. For comparison between patients and reference subjects, FinAP was measured in both groups (page 15). Systemic hemodynamics, like HR, SV, Q and SVR were calculated as presented on page 12. MCAV (mean, page 15) mean IAP and mean FinAP (page 15) were the integral over one heart beat. Static and dynamic CA in the frequency domain are assessed as presented on page 18 to 20.
To assess the effect of SNP on cerebrovascular conductance, a cerebrovascular resistance index (CVRI) was calculated as discussed on page 17. SNP was administered using a perfusor (B. Braun Medical Inc.).

The signals of IAP, FinAP, spectral envelope of MCA $V'$ and a marker signal were A/D converted at 100 Hz and stored on a hard disk for off-line analysis. In the patients, all signals were monitored from 20 min prior to SNP infusion to one hour following the last increment of SNP dose. Measurements in the reference subjects were obtained in the supine position for 30 min. Changes in systemic and cerebral hemodynamics as elicited by SNP were expressed as averages of three minute episodes of mean IAP, HR, $Q$, SVR, MCA $V_{\text{mean}}$ and CVRI determined at three moments: prior to SNP treatment, midway treatment and when target ABP was reached.

Data were expressed as mean and range in tables and as mean±S.E.M. in figures. Changes in systemic and cerebral hemodynamics during SNP treatment were examined by Friedman ANOVA on ranks. sCA was analysed by non-parametric regression technique (Spearman rank order). Differences in dCA between reference subjects and hypertensive patients (unpaired) and before and after treatment (paired) were examined with Wilcoxon rank sum test and Wilcoxon signed rank test, respectively. $P < 0.05$ was considered to indicate a statically significant difference.

Results

Characteristics of patients and reference subjects

Patients did not differ from normotensive reference subjects in age, height and weight. ABP and HR at admission were higher in the patient group ($P < 0.01$), while MCA $V'$ was comparable (Table 5.1.1).

Cerebral autoregulation prior to treatment

Low frequency variability of mean FinAP and MCA $V_{\text{mean}}$ were comparable for patients and reference subjects with a smaller phase lead ($P < 0.05$) and a tendency toward a higher transfer gain in the patients (Table 5.1.2).

Cerebral autoregulation during treatment

Target mean IAP was reached within 90 min in all patients (Figure 5.1.1). With increasing dose of SNP, SVR declined (-43±5%) while HR (16±4 min^{-1}), SV (9±4%) and thus CO (31±8%) increased (Figure 5.1.2). Systolic IAP decreased from 225±8 to 182±6 mmHg, mean IAP from 166±4 to 122±6 mmHg and diastolic IAP from 137±6 to 102±6 mmHg. The CVRI did not increase significantly (9.5±5.3%).
Table 5.1.2 Dynamic cerebral autoregulation

<table>
<thead>
<tr>
<th></th>
<th>RS</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre SNP</td>
<td>During SNP</td>
</tr>
<tr>
<td>MABP power (mmHg^2·Hz^-1)</td>
<td>4.5 (1.5-10.4)</td>
<td>5.8 (1.4-15.8)</td>
</tr>
<tr>
<td>V^mean power (cm^2·s^-1·Hz^-1)</td>
<td>3.6 (1.1-9.8)</td>
<td>1.8 (1.1-4.9)</td>
</tr>
<tr>
<td>Coherence (k)</td>
<td>0.75 (0.54-0.84)</td>
<td>0.64 (0.49-0.76)</td>
</tr>
<tr>
<td>Phase (degrees)</td>
<td>58 (41-82)</td>
<td>30 (6-67)*</td>
</tr>
<tr>
<td>Gain (°·°^-1)</td>
<td>1.02 (0.48-1.37)</td>
<td>1.32 (0.93-1.87)</td>
</tr>
</tbody>
</table>

Low frequency mean blood pressure variability (MABP power), mean middle cerebral artery blood velocity variability (V^mean power), coherence and cross-spectral V^mean to MABP phase lead and gain of eight reference subjects (RS) and of eight patients with a hypertensive emergency prior to and during SNP treatment. Data are presented as mean (range). *P < 0.05 vs. reference subjects.

MCA V^mean decreased 22±4% together with a 27±3% reduction in MABP in a linear fashion (averaged slope 0.82±0.15, averaged r=0.70±0.07; Figures 5.1.3 and 5.1.4). With mean IAP stabilized, variability of mean FinAP and MCA V^mean, and the MCA V^mean to mean FinAP phase lead and transfer gain were not significantly different from values prior to SNP treatment nor from reference subjects (Table 5.1.2).

Discussion
The main findings of this study are that both dynamic and static CA are impaired in patients with malignant hypertension prior to and during treatment with sodium nitroprusside. The data of this study show that during a rapid reduction in ABP with SNP, MCA V^mean decreases almost one on one with MABP.
Limitations

The technique to monitor changes in arterial cerebral blood flow may raise discussion for several reasons. First, the MCA $V_{\text{mean}}$ is calculated from the frequency distribution of the Doppler shifts and it is assumed to represent flow velocity in the center of the vessel. Changes in MCA $V_{\text{mean}}$ however reflect changes in flow only when the diameter of the MCA remains constant during SNP treatment. Direct observations made during craniotomy have revealed that SNP did not affect the vessel diameter of the M1 segment of the MCA and therefore we consider that in this study changes in MCA $V_{\text{mean}}$ are proportional to those in flow.

Second, it is uncertain at which level of MABP the upper and lower limits of sCA are located in patients (admitted to the hospital) with malignant hypertension. In normotensive humans the lower limit of sCA is located around 60 mmHg. For obvious reasons the upper limit of sCA can not be studied in (normotensive) humans but in normotensive baboons it ranges between 120 and 150 mmHg. In humans with untreated severe chronic hypertension the lower limit of sCA is shifted rightwards to ~115 mmHg. Data on the upper limit of sCA are limited in that it has been determined only in 3 hypertensive baboons and found to be shifted rightwards (between 155 and 169 mmHg). We assume with MABP ~165 mmHg at admission in this study the pressure level located around the upper limit of sCA with dCA impaired prior to treatment with SNP. The finding that during treatment with IAP in the autoregulatory range MCA $V_{\text{mean}}$ decreased almost one on one with MABP conforms with impaired CA.
Third, in the reference subjects we did not determine MCA $V$ during a substantial decrease in BP as induced by SNP infusion and thus sCA was not evaluated. We consider that in healthy subjects a decline in MABP as induced by SNP of ~20% does barely affect MCA $V_{\text{mean}}$\textsuperscript{157} and cerebral blood flow\textsuperscript{107} while a reduction in mean IAP in the patients was associated with a significant decline in MCA $V_{\text{mean}}$. Also, in healthy subjects data on dCA reflect integrity of sCA\textsuperscript{260} and we assume in the reference subjects sCA as to be preserved.

**Static and dynamic cerebral autoregulation**

Autoregulation implies that blood flow is maintained at a normal level of approximately 60 ml per 100 gr brain tissue per minute despite changes in perfusion pressure.\textsuperscript{155} Impaired sCA, with loss of the more or less zero slope MABP – MCA $V_{\text{mean}}$ relationship, has been reported in ischemic stroke,\textsuperscript{236} severe head injury,\textsuperscript{44} and following cardiac arrest.\textsuperscript{255} Our findings suggest that sCA is impaired in patients with malignant hypertension as well.

Dynamic CA is quantified by the counter-regulatory capacity to maintain MCA $V$ during abrupt changes in blood pressure as induced by thigh cuff deflation\textsuperscript{3} or as evaluated by the transfer gain and phase lead of MCA $V_{\text{mean}}$ to MABP during imposed\textsuperscript{52} or spontaneous blood pressure oscillations.\textsuperscript{208, 290} Both during hypotension\textsuperscript{234} and hypertension\textsuperscript{166} this phase lead remains unaltered when compared with the normal situation. In the present study, the MCA $V_{\text{mean}}$ to MABP phase lead in patients with malignant hypertension prior to SNP treatment was significantly smaller than in the reference subjects and comparable to the phase lead found in patients with carotid artery obstruction.\textsuperscript{52} The tendency toward a larger transfer gain further supports a deteriorated dampening of blood pressure oscillations in patients with malignant hypertension.

**Figure 5.1.3**

Representative example of the decrease in mean middle cerebral artery blood velocity ($MCA\ V_{\text{mean}}$) during the decrease in mean intra arterial pressure (mean IAP) as induced by SNP in a patient with malignant hypertension. Every circle represents an average of 30 seconds. Regression coefficient of this patient:

\[ MCA\ V_{\text{mean}} = 0.81 \times \text{IAP} + 19.7; \ r=0.87. \]
Kety et al. observed that in chronically hypertensive patients global resting cerebral blood flow and cerebral oxygen consumption are not different from normotensive subjects but cerebrovascular resistance is elevated.\textsuperscript{144} SNP reduces systemic vascular resistance but when infused directly in the carotid artery it does not modify cerebrovascular resistance in healthy subjects.\textsuperscript{137} These findings, taken together with recent evidence that in normotensive subjects a reduction in MABP by SNP does not affect MCA\textsubscript{mean},\textsuperscript{157} suggest that when blood pressure is reduced pharmacologically, MCA\textsubscript{mean} is secured by CA mediated cerebral vasodilatation rather than a direct SNP induced pharmacological effect on the cerebral vasculature. The present data demonstrate a systemic vasodilatation during SNP treatment with a considerable increase in cardiac output, yet leaving the cerebrovascular conductance index unaltered. One may speculate that the linear relation between MABP and MCA\textsubscript{mean} during treatment with SNP reflects a preferential blood flow to the (low resistance) systemic vascular bed versus the (high resistance) cerebrovascular bed.

In conclusion, in patients with malignant hypertension dCA is impaired. A decrease in cerebral artery blood velocity together with arterial blood pressure in a linear fashion during SNP treatment also indicates impairment of sCA. This study confirms the contention that CA is compromised in patients with malignant hypertension.
5.2

Cerebral hemodynamics during treatment with sodium nitroprusside versus labetalol in malignant hypertension

R.V. Immink, B.J.H. van den Born, G.A. van Montfrans, Y.S. Kim, M.W. Hollmann and J.J. van Lieshout

Hypertension 2008(52):236-240
INTRODUCTION  In patients with malignant hypertension immediate lowering of ABP is indicated to prevent further organ damage. Because CA capacity is impaired in these patients, a pharmacologically induced decline of ABP reduces gCBF with the danger of cerebral hypoperfusion. We compared the reduction in TCD determined MCA V during ABP lowering with SNP with that to labetalol.

METHODS  In fifteen patients, fulfilling World Health Organization criteria for malignant hypertension, beat-to-beat MABP, SVR, MCA V mean and CVRi were monitored during treatment with SNP (n=8) or labetalol (n=7).

RESULTS  The reduction in MABP with SNP (-28±3%; mean±S.E.M.) and labetalol (-28±4%) was similar. With labetalol, both systemic and cerebral vascular resistance decreased proportionally (-13±10% and -17±5%) whereas with SNP, the decline in SVR was larger than that in CVRi (-53±4% and -7±4%). The rate of reduction in MCA V mean was smaller with labetalol than with SNP (0.45±0.05 % cm·s⁻¹·% mmHg⁻¹ versus 0.78±0.04 % cm·s⁻¹·% mmHg⁻¹; P < 0.05).

CONCLUSION  SNP reduced SVR rather than cerebral vascular resistance with a larger rate of reduction in MCA V suggesting a preferential blood flow to the low resistance systemic vascular bed rather than the cerebral vascular bed.
Introduction

Malignant hypertension and hypertensive encephalopathy are hypertensive emergencies, characterized by a severe elevation of ABP and impaired CA.\textsuperscript{127} CA is defined as the capacity to maintain constancy of gCBF despite changes in MABP. Normally, CA is preserved for a range of MABP from approximately 60 to 150 mmHg, respectively the lower and upper limits of CA. In patients with moderate hypertension, the autoregulation curve is shifted towards higher ABP values, protecting the brain from hyperperfusion.\textsuperscript{166} However, in patients with malignant hypertension\textsuperscript{127} ABP is supposed to surpass the upper limit of CA with loss of control of cerebral perfusion. \textsuperscript{166} Under those circumstances gCBF becomes a function of ABP, so-called pressure dependency.\textsuperscript{252} Therefore, the initial reduction in ABP is restricted to \textasciitilde 25\% of the presenting level in order to avoid symptomatic hypoperfusion of the brain.\textsuperscript{66, 269, 270}

Of the therapeutic agents available, SNP and labetalol are commonly used for the initial parenteral treatment of malignant hypertension.\textsuperscript{140, 270} SNP, an arteriolar and venous vasodilator, is widely advocated as a first-line agent in the treatment of malignant hypertension.\textsuperscript{33, 66, 85} It is effective within seconds, and has a short half-life making it most suitable for an immediate and controlled reduction of ABP. Despite its superior pharmacokinetics, SNP has some disadvantages which may hamper its use. First, with SNP infusion intracranial pressure may rise,\textsuperscript{11} although in subjects with intact CA cerebral blood flow velocity is preserved.\textsuperscript{247} Second, there is a dose dependent risk of cyanide and thiocyanide toxicity.\textsuperscript{271} Labetalol, an \(\alpha\) - and \(\beta\)-adrenergic blocker, has a slower onset of action with a maximal hypotensive effect within 5 to 15 min.\textsuperscript{269} Its long half-life of 4 to 6 h limits the ability to promptly correct hypertension with cessation of the drug.\textsuperscript{139} In contrast to SNP however, ICP does not seem to increase and labetalol in therapeutic dosages is non-toxic.

Both agents reduce ABP effectively in patients with malignant hypertension\textsuperscript{66, 284} but their distinct effects on the cerebral and systemic circulation have not been investigated. We considered that in patients with malignant hypertension and failing CA an immediate reduction of ABP has to be achieved with the smallest reduction of cerebral perfusion possible. In this study we therefore set out to determine the effect of an immediate \textasciitilde 25\% reduction in MABP with SNP or labetalol on cerebral and systemic vascular resistance in patients with malignant hypertension.

Our earlier observations on gCBF during parenteral blood pressure lowering treatment were obtained with SNP.\textsuperscript{127} We now report the findings in a group of similar patients with malignant hypertension using labetalol parenterally administered, and compared cerebral and systemic hemodynamics in the two groups.

Methods

Fifteen patients fulfilled the WHO criteria for malignant hypertension, severely elevated ABP together with grade III (bilateral retinal hemorrhages or cotton wool exudates) or IV (III plus papilledema) hypertensive retinopathy according to the Keith, Wagener and Barker classification, were included in the study. The details of patients receiving SNP have been described previously.\textsuperscript{127}
Of the patients receiving labetalol, three had grade III and two a grade IV hypertensive retinopathy. The other two patients had no bilateral retinal abnormalities, but had clinical features of hypertensive encephalopathy. One patient was a 21 years old male who was on chronic ambulatory peritoneal dialysis because of renal failure due to SLE nephritis. He presented with a blood pressure of 228/140 mmHg and generalized seizures following withdrawal of antihypertensive medication on his own initiative. A CT-scan of the brain showed a decreased sign signal intensity in the parieto-occipital regions consistent with posterior leukencephalopathy. Treatment with diphantoine and labetalol terminated his convulsions and with adequate antihypertensive medical treatment his recovery was uneventful.

The other patient was a 19 years old refugee presenting with headache, vomiting and blurred vision. Her prior history was unremarkable; data on her previous BP were not available. On physical examination she had a BP of 237/163 mmHg and unilateral optic nerve edema on fundoscopic examination. Laboratory findings revealed a Coombs negative microangiopathic hemolysis and renal insufficiency (serum creatinine 212 µmol·l⁻¹). BP control with labetalol resulted in the disappearance of symptoms, resolution of the microangiopathic hemolysis and partial improvement of renal dysfunction. Both patients had signs of left ventricular hypertrophy (LVH) on ECG according to the Sokolow-Lyon criteria.

Of the other five patients receiving labetalol, three were previously known with hypertension, one of these patients was prescribed anti-hypertensive medication which he had stopped before admission. The clinical presentation included hypertensive encephalopathy in one patient with lesions in the posterior-occipital region of the brain on CT-scan, dyspnoea due to congestive heart failure (2 patients) and headache with visual disturbances (2 patients). Four patients had LVH on the ECG. Two had a Coombs negative hemolysis with schistocytes in a peripheral blood smear and a platelet count of < 150·10⁹ l⁻¹ and four had a moderate to severe renal insufficiency (serum creatinine 242 to 599 µmol·l⁻¹) at presentation.

Written informed consent was provided in accordance with the Helsinki declaration. The study protocol was approved by the Medical Ethical Committee of the Academic Medical Center, University of Amsterdam, the Netherlands.

**Treatment**

With intravenous labetalol or SNP, MABP was reduced ~25% below the presenting value. The order of the open label administration of the two drugs was not randomized because the admittance rate of patients with proven malignant hypertension in the Netherlands is fairly small. The first 8 patients were treated with SNP and described in an earlier report. SNP infusion was started at 0.3 µg·kg⁻¹·min⁻¹, increased to 0.5 µg·kg⁻¹·min⁻¹ after 5 min and from then on, by 0.5 µg·kg⁻¹·min⁻¹ every 5 min (with a maximum of 5 µg·kg⁻¹·min⁻¹). In the present study 7 patients were treated with labetalol administered in boluses of 0.5 mg·kg⁻¹ every 8 min with a maximum of 200 mg. When the desired MABP reduction was achieved, a continuous infusion of 20 mg·hr⁻¹ was started.
Table 5.2.1 Patient characteristics and blood pressure on admission

<table>
<thead>
<tr>
<th></th>
<th>SNP</th>
<th>Labetalol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Age (y)</td>
<td>44±5</td>
<td>40±5</td>
</tr>
<tr>
<td>Gender (m:f)</td>
<td>6:2</td>
<td>5:2</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>175±5</td>
<td>172±5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76±5</td>
<td>73±5</td>
</tr>
<tr>
<td>ABP (mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>225±5</td>
<td>227±5</td>
</tr>
<tr>
<td>Diastolic</td>
<td>137±3</td>
<td>133±4</td>
</tr>
</tbody>
</table>

Arterial blood pressure (ABP); sodium nitroprusside (SNP) Mean±S.E.M.

*Measurements*

Patients were instrumented with electrocardiogram electrodes. Intra arterial blood pressure was monitored as discussed on page 15. Systemic hemodynamics like HR, SV, $Q$ and SVR were calculated as presented on page 15. The MCA $V$ was measured as discussed on page 17. The CVRi was expressed as the ratio of MABP and MCA $V_{\text{mean}}$.

*Data Analysis*

Data were expressed as mean±S.E.M. Changes in cerebral blood flow were tracked by MCA $V_{\text{mean}}$ and integrity of CA is reflected by constancy of MCA $V_{\text{mean}}$ despite changes in MABP. For assessment of sCA see page 15. To compare sCA between groups MABP and MCA $V_{\text{mean}}$ were expressed as percentage change of pretreatment values. Dynamic CA in the frequency domain was determined as presented at page 19.

*Statistical Analysis*

Changes in systemic and cerebral hemodynamics during treatment were examined by Friedman ANOVA on ranks. Differences in CA between labetalol and SNP treatment (unpaired) and before and after treatment (paired) were examined with Wilcoxon rank sum test and Wilcoxon signed rank test, respectively. A value of $P < 0.05$ was considered to indicate a statically significant difference.

*Results*

Patient characteristics, systolic and diastolic blood pressure (Table 5.2.1) and MCA $V_{\text{mean}}$ ($64±6$ vs. $58±8$ cm·s$^{-1}$) did not differ between SNP and labetalol. The MCA $V_{\text{mean}}$ to MABP phase difference was equally affected for SNP ($30±8^\circ$) and labetalol ($26±9^\circ$) with comparable coherences ($0.64±0.04$ and $0.59±0.05$ respectively).
Table 5.2.2  Hemodynamic variables before and after treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>SNP</th>
<th>LABETALOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>MABP (mm Hg)</td>
<td>155±6</td>
<td>166±7</td>
</tr>
<tr>
<td>HR (min⁻¹)</td>
<td>87±7</td>
<td>99±8</td>
</tr>
<tr>
<td>SV (%)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Q (%)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>SVR (%)</td>
<td>57±5*</td>
<td>87±10*</td>
</tr>
<tr>
<td>MCA Vmean (cm·s⁻¹)</td>
<td>64±6</td>
<td>50±5*</td>
</tr>
<tr>
<td>CVRi (mmHg·(cm·s⁻¹))</td>
<td>2.59±0.26</td>
<td>3.17±0.38</td>
</tr>
</tbody>
</table>

Mean arterial radial blood pressure (M-ABP), heart rate (HR) and percentage change in stroke volume (SV), cardiac output (Q), systemic vascular resistance (SVR), mean middle cerebral artery blood velocity (MCA Vmean) and cerebral vascular resistance (CVRi) before and after treatment with sodium nitroprusside (SNP) or labetalol. Mean±S.E.M, * P < 0.05 vs. before treatment, † P < 0.05 vs. after treatment with SNP.

Target BP was reached within 60 min in all patients. Changes in systemic and cerebral hemodynamics are given in Table 5.2.2. The reduction in MABP with SNP (28±3%) and labetalol (28±4%) was comparable. SVR and CVRi declined to the same extend (-13±10% and -17±5%) during treatment with labetalol, whereas with SNP the decrease in SVR (-53±4%) was larger than the decrease in CVRi (-7±4%: P < 0.05; Figure 5.2.1). The rate of reduction in MCA Vmean with labetalol was smaller compared to SNP (0.45±0.05 versus 0.78±0.04 % cm·s⁻¹·% mmHg⁻¹: P < 0.05; Figure 5.2.2).

Figure 5.2.1
Percentage change in systemic vascular resistance (black bars) and cerebral vascular resistance index (grey bars) during a decrease in blood pressure with sodium nitroprusside (SNP) and labetalol. (Mean±S.E.M. * P < 0.05) Note that with SNP, SVR decreases and CVRi tends to increase whereas with labetalol both SVR and CVRi decline proportionally.
**Discussion**

In patients with malignant hypertension the therapeutic challenge is to reduce ABP without jeopardizing the cerebral circulation against the background of impaired CA. In this study the reduction in MABP with SNP and labetalol was comparable, but the decline in MCA $V_{\text{mean}}$ with labetalol versus SNP was less significant for a given reduction in ABP. This could be attributed to different effects of the two agents on the systemic and cerebral vascular beds. With labetalol, SVR decreased proportionally to cerebral vascular resistance with a relatively small rate of reduction in MCA $V_{\text{mean}}$. In contrast, SNP reduced systemic rather than cerebral vascular resistance resulting in a preferential blood flow to the systemic vascular bed with a considerable reduction in MCA $V$ per unit blood pressure. A deviation of blood flow with SNP has been reported earlier for the coronary circulation in patients with coronary artery disease where SNP treatment moved blood flow away from the ischemic myocardium to the coronary arteries.$^{38,175}$

**Malignant hypertension and cerebral autoregulation**

CA is defined as the intrinsic capacity of cerebral vasculature to maintain constant gCBF. Maintenance of cerebral perfusion during physiological challenges is secured by both fast- and slow-acting autoregulatory mechanisms.$^{260}$ Although acute changes in ABP are transmitted to the cerebral circulation, under normal conditions gCBF tends to return to its baseline value within a few seconds.$^{3}$ $^{205}$ This short-term control is usually referred to as dCA. Static CA considers the net change in gCBF resulting from a manipulated change in cerebral perfusion pressure under steady-state conditions.$^{3}$ $^{127}$ $^{260}$ When either SNP$^{157}$ or labetalol$^{198}$ is administered to normotensive subjects, gCBF remains unaltered conforming maintained integrity of CA.$^{155}$ When ABP decreases below $\sim 60 \text{ mmHg}$ in normotensive subjects, that is below what is considered the lower limit of CA, gCBF decreases proportionally with ABP.$^{155}$ The majority of patients with malignant hypertension have a history of chronic hypertension,$^{287}$ and in those patients the lower limit of CA has been shifted in proportion towards higher pressures.$^{250}$
obvious reasons the upper limit of CA has not been determined in normotensive or hypertensive humans. It was located between 120 and 150 mmHg in normotensive baboons and between 155 and 170 mmHg in baboons with experimental renovascular hypertension. In the present study MABP on admission was approximately 160 mmHg and assumed to be located around, or just above, the upper limit of the CA plateau. With intact CA, during treatment more or less constancy of MCA \( V_{\text{mean}} \) is expected between ~160 to ~115 mmHg, i.e. within the CA range. Instead, the observation that either with SNP or labetalol, MCA \( V_{\text{mean}} \) decreased linearly with MABP suggests serious impairment of sCA.

Considerations
Critical for the interpretation of the data is to what extent MCA \( V_{\text{mean}} \) reflects volume flow. The MCA \( V_{\text{mean}} \) was calculated from the frequency distribution of the Doppler shifts and assumed to represent maximal flow velocity in the center of the vessel. Changes in MCA \( V_{\text{mean}} \) however reflect changes in flow only as long as the diameter of the MCA remains constant during SNP or labetalol treatment. Direct observations made during craniotomy have revealed that SNP does not affect the vessel diameter of the MCA. Also, constancy of MCA diameter was demonstrated for a range of pressures. Therefore we considered that in this study changes in MCA \( V_{\text{mean}} \) were proportional to those in flow.

Improvement of symptoms of hypertensive encephalopathy or visual disturbances takes place after several days to weeks. The study period was too short to notice such improvement although some patients reported a relief of headache within the study period. Another potential limitation was that the order of the open label administration of the two drugs was not randomized. Our earlier observations on MCA \( V_{\text{mean}} \) during parenteral blood pressure lowering was with SNP. We now report the findings in a group of similar patients with malignant hypertension using labetalol intravenously, and compared cerebral and systemic hemodynamics in the two groups. Generally the admittance rate of patients with malignant hypertension in the Netherlands is fairly small and for practical reasons a sequential drug protocol was used. In spite of this study design patient groups were fully comparable for anthropomorphic data.

Base-line cerebral and cardiovascular variables before treatment were not statistically different but neither fully identical. Importantly, base-line Doppler derived flow velocity does not reveal volume flow whereas in this study MCA \( V_{\text{mean}} \) before drug treatment did not differ significantly between groups. For methodological reasons we restricted the interpretation by considering only changes in MCA \( V_{\text{mean}} \) with reference to base-line when comparing the circulatory effects of both drugs. More importantly, the dCA capacity prior to treatment and the magnitude of ABP reduction were almost identical leaving the main findings of this study unchallenged.

Clinical perspective
Both sodium nitroprusside and labetalol reduce blood pressure adequately in patients with malignant hypertension. However, the underlying systemic hemodynamic mechanism are different. The use of labetalol resulted in a proportional reduction in systemic and cerebral vascular resistances. Sodium nitroprusside, on the other hand, reduced systemic rather than
cerebral vascular resistance with a larger rate of reduction in middle cerebral artery blood velocity suggesting a preferential blood flow to the low resistance systemic vascular bed rather than the cerebral vascular bed.
SUMMARY
The oxygen supply to the brain depends on the arterial $O_2$ content and a resting $gCBF$ of approximately 50 to 60 ml·100 g⁻¹·min⁻¹. The cerebral oxygen uptake of ~3 ml·100 g⁻¹·min⁻¹ accounts for 15% to 20% of total body basal metabolic rate. It underscores that the brain, among all tissues, is the least tolerant to ischemia; an interruption of blood supply to the brain for no more than a few seconds results in loss of consciousness. Therefore it is crucial that the cerebral blood flow is guaranteed at all times. In this thesis the regulation of the cerebral blood flow during changes in systemic hemodynamics in health and disease is discussed.

Chapter 1 summarizes the history of CA. Until the mid 19th century the Monro-Kellie doctrine continued to consider the human brain circulation as a system of rigid tubes where in every experimental condition the cerebral circulation passively follows the change in the systemic arterial and venous pressures. Around 1850, Burrows suggested that also intrinsic regulatory mechanisms are present. The introduction, by Kety and Schmidt in 1945, of a method to quantify $gCBF$ in humans using a nitrous oxide wash out technique, proved that CBF barely changed despite fluctuations in MABP between ~60 and ~150 mmHg. In the last quarter of the 20th century, the possibilities created by new monitoring devices that deliver non-invasive derivatives of $gCBF$ as presented in chapter 2, like $cO_2Hb$ with NIRS and TCD derived MCA $V_{mean}$, have moved the concept of CA forward. As powerful as CA may be, it does not have an infinite gain, an intrinsic property shared by all biological control systems. From the first change in arterial pressure as a surrogate of cerebral perfusion pressure it takes several seconds to recognize the result of action of CA as a controller and still $gCBF$ is not maintained exactly constant when blood pressure changes as it does continuously. Rather CA operates by its capacity to dampen the transmission of arterial pressure fluctuations to the brain vasculature.

Chapter 3 attempts to identify why both $MCAV$ and $cO_2Hb$ decrease during standing up despite the fact that blood pressure remains in what is designated as the CA range. At first, a decline in $P_{aCO_2}$ upon standing is a known fact with the potential to reduce CBF by hypocapnia induced cerebral vasoconstriction. Thus far, there was debate on whether the postural decrease in CBF is to be attributed to this decline in the $P_{aCO_2}$ with the unspoken premise of an infinite gain of CA. In the majority of studies the $P_{aCO_2}$ is usually monitored as the $P_{ETCO_2}$. It is true that during steady state conditions, i.e. stable pulmonary blood flow, changes in the $P_{ETCO_2}$ tracks changes in the $P_{aCO_2}$. However, we challenged the validity of the $P_{ETCO_2}$ as a measure for $P_{aCO_2}$ when changing the position of the body. In Chapter 3.1 we monitored the $P_{aCO_2}$, $P_{ETCO_2}$, the $V_i/Q$ ratio, MCA $V$ and $cO_2Hb$ in healthy subjects who assumed the upright position. During the transit from supine to upright, $V_i$ increased and the following reduction in $P_{ETCO_2}$ seems to explain the decrease in MCA $V_{mean}$. However, when standing $Q$ declines and at the same time the flow distribution across the lungs changes with an alteration in $V_i/Q$ ratio. We suggest that due to this phenomenon the postural decrease in the $P_{aCO_2}$ is overestimated by the $P_{ETCO_2}$ and therefore explains the postural decrease in MCA $V$ and $cO_2Hb$ only in part at the most.

Chapter 3.2 studies this effect into some detail by considering the effects of clamping the partial $P_{aCO_2}$ during head-up tilt by using a custom made rebreathing device. After one minute...
upright the postural decrease in MCAV was exactly the same as when the same subjects were passively tilted head-up while breathing freely. Based on these two studies we suggest that the postural decrease in the $P_aCO_2$ has only a minor effect on the postural decrease in MCAV (and cO$_2$Hb).

**Chapter 3.3** addresses whether systemic sympathetic activation in response to active postural stress is manifested also in the cerebral circulation, which could explain the postural decline in cerebral perfusion and oxygenation in healthy humans. To that purpose, in chronic pain patients the cerebral sympathetic activity in one hemisphere was blocked by injecting local anesthetics around the superior cervical ganglion. Following superior cervical ganglion blockade, subjects assumed the upright position while following the ensuing changes in cerebral perfusion and cortical oxygenation. Suppression of cerebral sympathetic activity by SGB did not affect the cerebrovascular conductance response to orthostatic stress and neither CA efficacy, suggesting that in humans the orthostatic decrease in CBF takes place independently of sympathetic activation.

**Chapter 4** is concerned with the integrity of dCA during cerebral ischemia and stroke in microvascular disease. In **chapter 4.1** middle cerebral artery blood velocity was monitored bilaterally in the acute phase of a first lacunar or cortical ischemic stroke to study the effect of acute ischemia on dCA efficacy and thus MCAV. Dynamic CA was impaired unilaterally in cortical stroke but bilaterally in lacunar stroke. Considering the larger volume of ischemic brain tissue in cortical vs. lacunar stroke this finding was somewhat unexpected. Penumbra size and etiology of the two stroke types are different in that cortical strokes result mainly from embolism or large cerebral artery artherothrombosis while lacunar strokes more often occurs in subjects with small vessel disease. Therefore, we speculated that in subjects suffering lacunar stroke, CA was already impaired prior to the cerebrovascular incident due to pre-existing microvascular damage. In **chapter 4.2** we made an attempt to test this hypothesis in part by assessing CA in subjects with type II diabetes with and without end organ damage. There appeared to be a positive relationship between severity of end organ damage and CA impairment.

**Chapter 5** describes the behavior of CA during extreme hypertension. In **chapter 5.1** patients were studied who had been admitted to the hospital because of symptoms related to malignant hypertension (i.e. a blood pressure above the upper limit of CA). In these patients immediate treatment with short-acting parenteral arterial blood pressure lowering agents is indicated to prevent further cardiac, renal, cerebral or retinal tissue damage. The classical teaching is that since CA capacity is impaired, the initial ABP reduction should not exceed 25% to prevent cerebral hypoperfusion. Here the premise is that within these 25% blood pressure reduction the relation between blood pressure and cerebral blood flow is such that flow remains when pressure is lowering. We found, however, that both static and dynamic CA before, during and directly after intravenous treatment with sodium nitroprusside had been seriously effected with the result that MCAV declined in proportion to arterial pressure, and an upper limit of autoregulation was not found. Chapter 5.2 compared the cerebrovascular effects of blood pressure lowering with sodium nitroprusside, a nitric oxide donor, and labetalol, a mixed α and
β-adrenergic antagonist. We found that dCA was affected equally in both groups but when hypertension was treated with labetalol vs. sodium nitroprusside the reduction in middle cerebral blood artery blood velocity for a given decrease in blood pressure was smaller, thus favouring labetolol as the drug of choice from the viewpoint of the brain.
GENERAL DISCUSSION

The dogma that cerebral autoregulation implies that cerebral blood flow does not alter despite changes in cerebral perfusion pressure between ~50 and ~150 mmHg was questioned by Hermes and Kontos as early as 1983. Rennie and Panerai postulated in 1998 that perfect autoregulation with a flat cerebral perfusion pressure-flow relation would require feedback gains much greater than what is normally found in biological systems.

Autoregulation is present in many tissues, for instance, the limits of static autoregulation in the coronary arteries correspond remarkably well to that of the arteries in the brain. A major difference is that the steady state oxygen saturation in the coronary sinus is ~20% while in the jugular bulb it is around 70%. Therefore, unlike the heart, that extracts almost all oxygen from the blood, the brain consumes only about one third. When the beating frequency of a heart increases and therefore its metabolism, it can keep up with the increased demand only by raising coronary blood flow. Evidence exists that this may be different for the brain.

At first, the metabolic theory of cerebral autoregulation states that a reduction cerebral blood flow results in local release of (a) chemical factor(s) that elicit(s) dilatation of cerebral vessels and therefore increase cerebral blood flow. Although not considered as an intrinsic component of cerebral autoregulation, for carbon dioxide the metabolic regulation is revealed by a 2 to 5% increase in cerebral blood flow per mmHg rise in the partial arterial carbon dioxide pressure. The second defence of the brain is the enhancement of oxygen and nutrients extraction from the blood. For instance, during propofol/fentanyl anesthesia mean middle cerebral arterial blood velocity decreases 50% but, jugular bulb venous saturation decreased by ~70%. Another example is exercise, when cerebral blood flow increases to meet the enhanced metabolic demand, until during exhaustive exercise cerebral blood flow starts to decrease by the progressive exercise-related hypocapnia with a reduction in jugular bulb saturation.

Determination of the arterial pressure – cerebral blood flow relationship in conscious humans continues to remain difficult. Deliberately induced changes in blood pressure considered as a surrogate of cerebral perfusion pressure are intrinsically accompanied by changes in systemic hemodynamics and brain vascular conductance. For instance reducing blood pressure pharmacologically with sodium nitroprusside results in a massive systemic vasodilatation. Whether the cerebral and systemic vessels dilate into a similar extent is, however, unknown. If not, a “cerebral steal” may preferentially direct blood flow into the low resistance systemic vascular bed rather than into the relatively high resistance cerebrovascular bed, resulting in a reduction in middle cerebral artery blood velocity. In addition, the reflex tachycardia in response to nitroprusside increases cardiac output. There is mounting evidence that changes in cardiac output affect middle cerebral artery blood velocity independently from arterial pressure. Vice versa, increasing blood pressure with an α-agonist e.g. phenylephrine induces a reflex bradycardia with a reduction in cardiac output. There is a ongoing discussion whether the cerebral vasculature has a sympathetic innervation and the increase in middle cerebral artery blood velocity in combination with a decreasing cerebral oxygenation with α-
stimulation may be explained by maintaining flow through a conductance vessel of smaller
diameter by cerebrovascular constriction\textsuperscript{195} in parallel with its effect on other vascular beds, or
flow may be reduced explaining the progressive reduction in cerebral tissue oxygenation.
This does not imply absence of counter-regulation against an increase in arterial blood pressure
by cerebral vasoconstriction. On the contrary, with fluids being virtually incompressible, this
mechanism is fundamental in preventing swelling of the brain within the rigid skull. In absence
of any control of the cerebrovascular pressure-flow relationship, an increase in intracranial
pressure would obstruct the inflow of arterial blood, jeopardizing cerebral metabolism.
Against this background and given some of the data presented in this thesis it is merely
inconsistent to hold to the traditional concept of cerebral autoregulation that “cerebral blood
flow remains constant despite changes in cerebral perfusion pressure”. It seems quite probable
that cerebral autoregulation rather represents “the phenomenon that defends the brain from
excessive perfusion resulting in high intracranial pressure levels and therefore a jeopardized
perfusion, but also preserves an adequate cerebral metabolism during changes in systemic
hemodynamics”. In fact, this definition diverges not that much from the definition of tissue
autoregulation in a more broad sense; “The capability of an organ to regulate its blood supply
in accordance with its metabolic needs”\textsuperscript{65} that was expressed by Lassen in his review published
in 1974.\textsuperscript{156} The implication is that the fundamental ideas on the regulation of cerebral blood
flow formulated ~ 40 years ago are still very relevant today.
SAMENVATTING

De zuursofvoorziening van de hersenen is afhankelijk van de hoeveelheid zuurstof in het bloed en de hoeveelheid bloed die naar de hersenen stroomt. De hersenen, die ongeveer 2% van het lichaamsgewicht uitmaken, verbruiken ongeveer 3 ml zuurstof per 100 gram hersenweefsel per minuut en dat is 15 tot 20% van al de zuurstof die in een lichaam wordt opgenomen. Dit, in combinatie met het feit dat hersenen heel slecht zonder zuurstof kunnen en dat een onderbreking van de bloedtoevoer van enkele seconden al leidt tot een verlies van bewustzijn, maakt het cruciaal dat de bloedtoevoer naar de hersenen te allen tijde gewaarborgd is.

In Hoofdstuk 1 wordt een chronologisch overzicht gegeven hoe over de regeling van de bloedtoevoer naar de hersenen gedacht werd. Tot het midden van de 19e eeuw stelde de Monro-Kellie doctrine dat de cerebrale circulatie altijd passief de bloeddruk die heerst in de systemische circulatie volgt. Rond 1850 suggereert Burrows dat er mogelijk toch intrinsieke regelmechanismen in de hersenen aanwezig kunnen zijn waarmee de diameter van vaten in de hersenen kan variëren. In 1945 werd door Kety en Schmidt een techniek geïntroduceerd waarmee, met behulp van een stikstofoxide uitwastechniek, werd aangetoond dat in mensen de hersenbloedstroom nauwelijks verandert gedurende variaties in de gemiddelde arteriële bloeddruk tussen de 50 en 150 mmHg. In het laatste kwart van de twintigste eeuw zijn twee nieuwe meettechnieken, te weten de hersenweefsel oxygenatie gemeten met een bijna infrarood spectroscope en de bloedstroomsnelheid in de middelste hersenslagader met een transcraniale Doppler, zoals in Hoofdstuk 2 beschreven, die per hartsimpuls iets kunnen zeggen over de hersenbloedtoevoer, geïntroduceerd. Met deze twee methoden werd de observatie van Kety en Schmidt ondersteund maar het werd ook duidelijk dat cerebrale autoregulatie niet perfect werkt. Het kost een aantal seconden voordat het met deze twee meettechnieken zichtbaar wordt dat de hersenbloedtoevoer een verandering in arteriële bloeddruk begint tegen te regelen. Het lijkt dat het vermogen tot cerebraal autoreguleren niet een perfect werkend systeem is maar de veranderingen in de bloedtoevoer naar de hersenen dempt tijdens fluctuaties in arteriële bloeddruk.

In Hoofdstuk 3 proberen we uit te zoeken waarom bij opstaan, ondanks het vermogen tot cerebraal autoreguleren en de nauwelijks veranderende bloeddruk, de bloedtoevoer naar de hersenen, de bloedstroomsnelheid in de middelste hersenslagader en de hersenweefsel-oxygenatie daalt. De eerste mogelijke verklaring ligt in de observatie dat de hoeveelheid koolzuur in het arteriële bloed daalt. Daling hiervan geeft een cerebrale vasoconstrictie terwijl een stijging een vasodilatatie geeft. Er is gesuggereerd dat dit de afname in de cerebrale bloedstroom veroorzaakt bij een perfect werkende cerebrale autoregulatie. In de meeste studies wordt de hoeveelheid koolzuur in het arteriële bloed bepaald door de hoeveelheid koolzuur in de uitgeademde lucht te meten. In de situatie dat de doorbloeding van de longen niet verandert klopt het veranderingen in hoeveelheid koolzuur in het arteriële bloed goed gevolgd worden door de veranderingen in de hoeveelheid koolzuur in de uitgeademde lucht. Echter, als mensen opstaan verandert de doorbloeding van de longen en wij denken dat dan de hoeveelheid
koolzuur in de uitgeademde lucht niet meer goed de hoeveelheid koolzuur in het arteriële bloed weergeeft.

In *Hoofdstuk 3.1* maten wij tijdens opstaan, naast de bloedstroomsnelheid in de middelste hersenarterie en de hersenweefseloxygenatie, de CO₂ concentratie in het bloed in een slagader en in de uitgeademde lucht, de hoeveel lucht die per minuut werd in- en uitgeademd en de hoeveelheid bloed die per minuut door het hart werd uitgepompt.

Conform eerdere studies vonden we dat tijdens opstaan het ademminuutvolume toename en de daling van de CO₂ concentratie in de uitgeademde lucht was zodanig dat dit de daling in de bloedtoevoer naar de hersenen kon verklaren. Echter opstaan gaf ook een daling van de hoeveelheid bloed die het hart uitpompt en de positieverandering beïnvloedde de distributie van dit bloed over de longen. De hoeveelheid koolzuur in de uitgeademde lucht daalde veel meer dan de hoeveelheid koolzuur in het arteriële bloed. We concludeerden dat de werkelijke daling van de CO₂ concentratie in het arteriële bloed te klein was om als enige de daling van de bloedtoevoer naar de hersenen te verklaren.

In *Hoofdstuk 3.2* beschrijven we een opstelling waarmee we tijdens positieveranderingen de arteriële CO₂ concentratie op hetzelfde niveau kunnen houden als liggend. We vonden dat na één minuut staan met een CO₂ concentratie op het liggende niveau, de afname van de stroomsnelheid in de middelste hersenslagader hetzelfde is als dezelfde proefpersonen overeind zijn gezet zonder dat de CO₂ concentratie constant werd gehouden. Na deze studie concludeerden we dat bij opstaan de veranderingen in CO₂ slechts een minimaal effect hebben op de afname van de cerebrale bloedstroom en andere oorzaken voor de daling van de bloedtoevoer naar de hersenen moeten worden overwogen.

In *Hoofdstuk 3.3* analyseerden we of de toename van de systemische sympatische activiteit die optreedt bij opstaan de daling in de cerebrale bloedstroom veroorzaakt. Hiervoor hebben wij, in patienten met chronische pijn in een arm of het aangezicht, de bloedstroomsnelheid in de middelste hersenslagader en de hersenweefseloxygenatie gemeten terwijl de pijn behandeld werd door lokale verdovingsvloeistof rond een zenuwknoop in de nek te spuiten waarvan bekend is dat de sympatische activiteit naar één hersenhelft geblokkeerd. We vonden dat blokkering van deze zenuwknoop de daling in de cerebrale bloedstroomsnelheid en hersenweefseloxygenatie niet beïnvloedt. Bij opstaan dalen deze parameters van de hersenperfusie na blokkade even veel als voor blokkade. We concludeerden dat de toename van de sympatische activiteit bij gaan staan niet de veroorzaker is van de daling in hersenperfusie.

In *Hoofdstuk 4* werd gekeken naar het vermogen van cerebraal autoreguleren in patienten met vaatlijden in de eerste dagen na een beroerte. In *Hoofdstuk 4.1* maten we bloedstroomsnelheid in beide middelste hersenslagaders binnen 3 dagen na het ontstaan van twee typen beroerte, te weten corticale infarcten en lacunaire infarcten. We vonden dat het vermogen tot autoreguleren bij de corticale infarcten alleen was aangedaan in de hersenhelft waar het infarct was opgetreden terwijl bij de lacunaire infarcten in beide hersenhelften de autoregulatie gestoord was. Dit was een onverwachte vinding aangezien corticale infarcten veel groter zijn dan lacunaire maar mogelijk speelde het verschil in oorzaak van ontstaan van een beroerte een rol. Corticale infarcten ontstaan met name door het vastlopen van bloedstolsels,
die bijvoorbeeld waren gevormd door hartritmestoornissen, terwijl patiënten met vaatlijden vaker de kleinere lacunaire infarcten krijgen. Wij hypothetiseerden dat de in twee hersenhelften aangedane cerebrale autoregulatie bij patiënten met een lacunair infarct, veroorzaakt werd door losgeloosde microtrombi die gepaard gaan met microvascular vaatlijden en dus al manifest was voordat de beroerte optrad.

In **Hoofdstuk 4.2** testten we deze hypothese door de cerebrale autoregulatie te kwantificeren in patiënten met suikerziekte type II die wel of geen bijkomende schade aan de perifere bloedvaten hadden die door de suikerziekte veroorzaakt wordt. We vonden een positieve relatie tussen de ernst van het vaatlijden en de mate waarvan de cerebrale autoregulatie was aangedaan.

In **Hoofdstuk 5** beschrijven we de cerebrale autoregulatie bij patiënten met een extreem hoge bloeddruk. In **Hoofdstuk 5.1** kwantificeerde we het vermogen van cerebrale autoregulatie in patiënten die werden opgenomen op de medium care afdeling met symptomen passend bij een maligne hypertensie. In deze patiëntengroep, met een bloeddruk die boven het cerebrale autoregulatieplateau lag, werd onder invasieve bloeddrukbeelden via een infuus een zeer snel werkend bloeddrukverlagend middel, nitroprusside, toegediend om hersenoedeem en verdere vaat- en organeschade aan organen zoals de ogen, de nieren en het hart te voorkóomen. De gedachte is dat, wegens de verstoorde cerebrale autoregulatie, de bloeddruk in de eerste uren niet meer dan 25% mag dalen om zuurstoftekort in de hersenen te voorkomen. Wij vonden dat het vermogen tot cerebraal autoreguleren bij deze patienten ernstig gestoord was en dat de stroomsnelheid in de middelste hersenslagader bijna één op één daalde met de bloeddruk.

In **Hoofdstuk 5.2** hadden we bij patiënten met maligne hypertensie de daling in de cerebrale bloedtoevoer tijdens de acute behandeling met nitroprusside, een vaatverwijder, vergeleken met een acute bloeddrukverlaging met labetalol, een α- en β-adrenerge antagonist. We vonden dat voor behandeling de cerebrale autoregulatie in beide groepen even ernstig was aangedaan maar dat bij dezelfde daling in bloeddruk, tijdens behandeling met labetalol de cerebrale bloedtoevoer minder daalde dan als nitroprusside werd gebruikt. Mogelijk is ten aanzien van een beter gepreserveerde hersenperfusie, labetalol te prefereren boven nitroprusside bij behandeling van maligne hypertensie.
DANKWOORD

Beste Han (prof. van Lieshout). Via Rudolf van Olden, Michaela Diamant, Gert van Montfrans, Bart Vogel en Mark Harms kwam ik met jou in contact. Na in 1998 een paar keer op je kleine kamerjuffje op F4 te zijn geweest wist ik het; van jou wil ik leren hoe je onderzoek doet. Er waren mensen die voorspelden dat het lang zou gaan duren. Al deze mensen hadden gelijk maar dat lag zeker niet alleen aan jou. Ik maak alles af waar ik aan begin maar doe er alleen wat langer over. (7 jaar VWO, 9 jaar geneeskunde, 11 jaar rijbewijs, enz). Wat de afraders mij niet vertelden was dat ik je promovendi altijd beschermt, hoeveel je weet, hoeveel tijd je in iemand steekt, hoeveel je praat als ik langskwam, hoe simpel een oplossing kan zijn, hoeveel we gelachen hebben, hoe je goede onderzoeks vragen stelt, hoe je goed moet meten, dat jij tijdens metingen langskomt om te kijken hoe het gaat, hoe belangrijk goed schrijven is (het clamp-stuk heeft 120 versies gehad in 8 jaar en ja, iedere versie was weer net iets beter). Al met al heeft het misschien 12 jaar geduurd, zijn we door een aantal mensen voor een ‘folie a deux’ uitgemaakt, maar ondanks af en toe wat gevloek beiderzijds, heb ik wel het idee dat het boekje enige mate van kwaliteit heeft gekregen.

Beste Antoon (prof. Moorman). Sinds het emeritaat van prof. Wesseling in 2000 was het toendertijd genaamde ODP 32 professorloos. Zodoende was ik ook eigenlijk altijd promotorloos. In januari 2012 toen de laatste eindjes aan elkaar werden geknoopt ben ik met Han bij je langs geweest. Je praktische en duidelijke manier van denken heeft het eindtraject zeker versneld.

Beste John (Karemaker), wonend in een uithoek van de afdeling M01 in het AMC. Zodanig was je schoolbord al, net als in alle andere kamers in de gang. Bij gebruik van het schoolbord werden je didactische capaciteiten nog beter dan ze al waren. De meest lastige dingen kon je mij, als gewone onderzoeker die later gewoon een clinicus zou worden, zo uitleggen dat ik het idee had dat ik het (even) begreep. Tijdens mijn werk vandaag de dag heb ik dagelijks plezier van de dingen die je mij hebt verteld. Heel veel dank dat jij nog een jaar extra financiering hebt kunnen regelen toen de Hartstichting niet meer wilde.

Beste Gert van Montfrans, ik benijd je om je uiterlijk stressloze levensstijl. Daarnaast is je kritische manier van lezen en gevoel voor stijl heel erg waardevol geweest voor iemand die schrijven niet als grootste hobby heeft. Nog altijd ben ik benieuwd hoe die “hut” op de berg in Frankrijk eruit ziet waar je regelmatig naar toe gaat. Heel veel dank dat jij mij had uitgekozen om onderzoek te gaan doen in toendertijd nog ODP 32 en dat je op een gegeven moment Bert-Jan en mij in contact hebt gebracht.

Beste Wim, dank voor alle tijd die je in mij gestoken hebt. Laten we het simpel houden, jij bleek onmisbaar. Als jij er niet geweest was om allerlei rare matlab-programma’s te schrijven voor vragen die ik had, was dit boekje er nooit geweest. Aangezien ik toch wel bij de digibeten hoor, waren de handleidingen vaak langer dan de programma’s zelf. Alle kamergenoten en collega promovendi die er in 12 jaar zijn geweest en waar mee gegeten is, borrels mee gedronken zijn, Domburg-uitjes zijn geweest heel veel dank. Als je 12 jaar over een promotie doet zijn dit er teveel om op te noemen.
Beste Michael, we kennen elkaar nu zo'n 35 jaar. Volgens mij zijn we totaal verschillend in karakter, doen en laten, werk, talenten en wat dan ook. Misschien wel een VVD - PvdA kabinet al weet ik dan niet wie wie is. Buiten de onvoorwaardelijke vriendschap en steun is ook jou wetenschappelijke inbreng in dit boekje onmisbaar gebleken. Hoofdstuk 3.2 was er nooit gekomen als jij er niet was geweest om met lijm en Wavin-buizen een CO2-clamp te bouwen.

Lieve Karina, In het najaar van 2004 begonnen we samen als AGNIO op de anesthesiologie en een paar maanden later zijn we in opleiding gekomen. Ook wij hebben een totaal andere achtergrond maar je naar buiten toe altijd vrolijke karakter, je daaronder verscholen grappig (cynische) (zelf)spot met vaak verhelderende redeneringen maken het altijd een feest om dingen met je te doen.

Lieve papa, van heel jongs af aan wist ik al dat ik in de geneeskunde zou eindigen. Grootmoeder gaf mij voor mijn vijfde verjaardag een door haar zelf genaaide doktersjas (met veel zakken) kado. Ik hoop dat ik iets van je doorzettingsvermogen, nieuwsgierigheid en drang tot redeneren waarom iets is zoals het is heb meegekregen.

Lieve mama, omdat jij bij iedere ouderavond op school weer ging uitleggen dat het niet alleen met domheid te maken heeft als je voor een taalproefwerk niet hoger kan halen dan een 4, is het gelukt om door het VWO te komen. Met name door de combinatie van jullie twee heb ik al vroeg bedacht dat je bij inspanningen altijd het doel voor ogen moet houden. Soms moeten daar wat omwegen voor genomen worden en worden mensen daar ongeduldig door maar, het eindpunt blijft altijd in zicht en wordt altijd bereikt.

In 12 jaar tijd is een hoop gebeurd. Van alleen op drie hoog in Amsterdam Oud-West hebben we met z'n vieren op de mooiste plek van de Rivierenbuurt gewoond (met de beste buren die we ons konden voorstellen). Lieve Tiets dit boek is nu af maar twee nieuwe hoofdstukken zijn begonnen met werken in Zwolle en wonen in Amersfoort. Ik weet zeker dat het met jou daar weer net zo leuk zal worden als in Amsterdam. Werken is leuk maar thuiskomen is leuier om dan de onverschoeibare vrolijkheid van de kinderen te zien. Hun zien opgroeien en met z'n allen leuke dingen doen als naar het strand gaan (in Noordwijk of Domburg) lekker eten, voetballen, fietsen, treinen bouwen, enz, enz is zoveel mooier dan avonden werken of in een ziekenhuis zitten.
References

(14) Banzett RB, Garcia RT, Moosavi SH. Simple contrivance "clamps" end-tidal PCO2 and PO2 despite rapid changes in ventilation. J Appl Physiol 2000(88)1597-600.


