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Cerebral hemodynamics in stroke and traumatic brain injury

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Cerebral Hemodynamics in Stroke and Traumatic Brain Injury

The interplay between blood pressure, cerebral
perfusion, body position and autoregulation

M.J.H. Aries

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The interplay between blood pressure, cerebral
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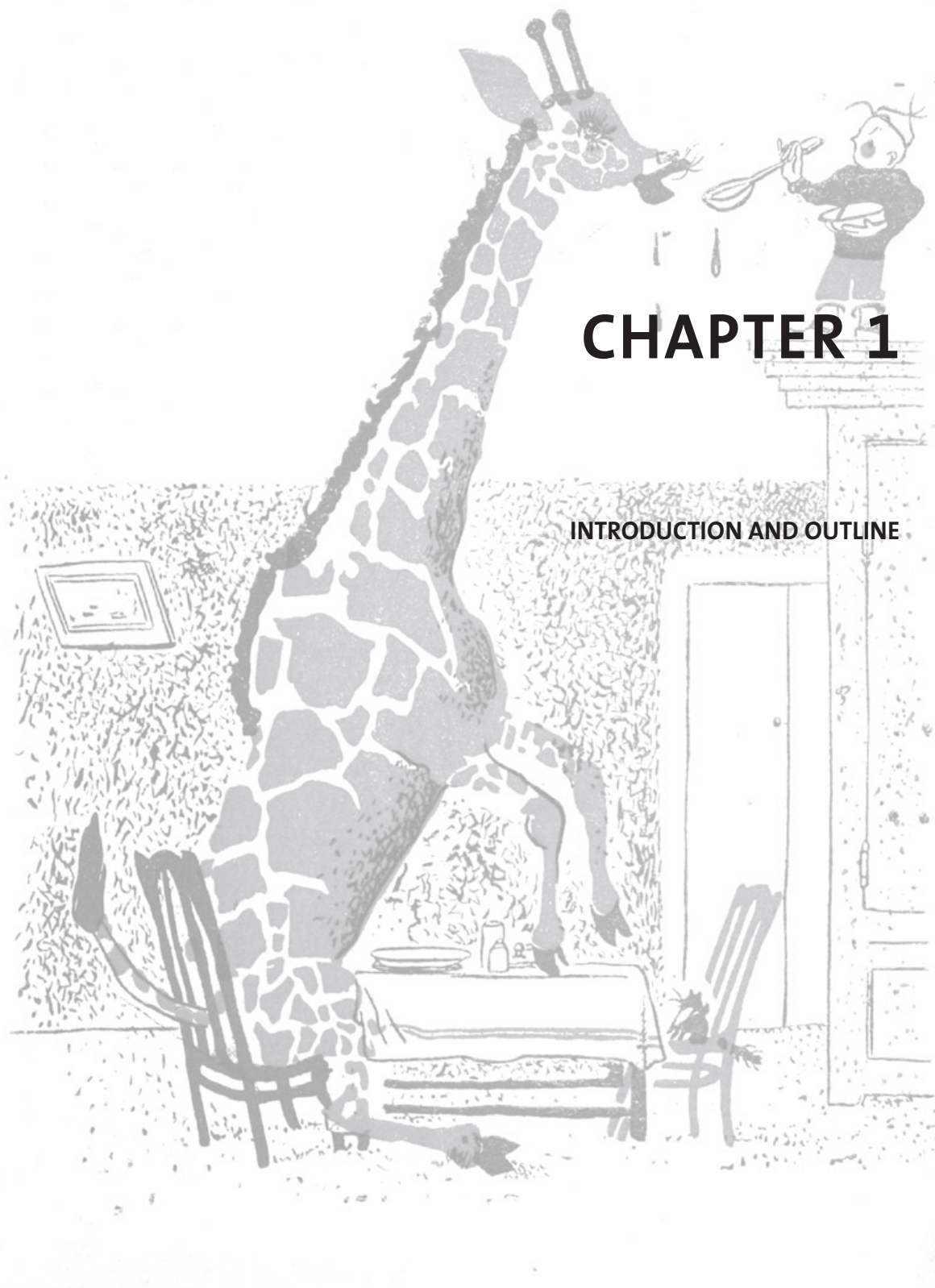
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CHAPTER 1

INTRODUCTION AND OUTLINE

INTRODUCTION

Stroke unit care

Acute stroke ranks second after ischemic heart disease as a cause of lost disability-adjusted life-years in high-income countries and as a cause of death worldwide. In Western societies, about 80% of strokes are caused by focal cerebral ischemia due to sudden arterial occlusion.¹ Intravenous administration of recombinant tissue plasminogen activator within 4.5 hrs after the onset of stroke increases the probability of a favorable outcome.² After this initial recanalization therapy, patients are frequently admitted to a ward during their initial illness where they can receive care (called post-acute care) in a variety of ways and in a range of settings.

Traditionally, the care of stroke patients was provided within departments of general (internal) medicine, neurology or geriatrics where they would be managed alongside a range of other patient groups. Organised inpatient care is a term used to describe the focusing of care for stroke patients in hospital under a multidisciplinary team who specialise in stroke management.³ An updated Cochrane systematic review in 2007 concluded that acute stroke patients are more likely to survive, return home and regain independence if they receive organised stroke unit care. This is typically provided by a coordinated multidisciplinary team operating within a 'discrete stroke unit', which can offer close physiological monitoring and a substantial period of rehabilitation if required.⁴

A major focus for stroke unit care is to prevent and limit ongoing brain damage and to provide the best conditions for natural brain recovery. Optimal oxygenation, perfusion, nutrition, glycemic control, and temperature homeostasis are indicated, as in generally ill patients. In addition, specific protocols (mostly based on observational studies) exist for the acute stroke period.⁵ For acute ischemic stroke, treatment is focused on 'penumbral salvage'. Initially after arterial occlusion, a central core of very low perfusion is surrounded by an area of dysfunction caused by metabolic and ionic disturbances but in which structural integrity is preserved (called the ischemic penumbra). In the first minutes to hours, therefore, clinical deficits do not necessarily reflect irreversible damage. Depending on the rate of residual cerebral blood flow (CBF) and the duration of ischemia, the penumbra will eventually be incorporated into the infarcted region if reperfusion is not achieved.⁶ The cerebral circulation has developed several specialised features to cope with the high metabolic demands of the (recovering) brain and the devastating consequences of cerebral ischemia (cerebral autoregulation). It is suggested that specialized stroke unit care with close monitoring of hemodynamic parameters (ideally including CBF) may be important in penumbral salvage.⁷⁻⁹

Which determinants of stroke unit care are important, is largely unknown but close observation for a critical period is suggested as one of the determinants. Failure of homeostatic mechanisms and susceptibility to complications (e.g., venous thrombosis and infections) during the acute phase of stroke are common. Supportive care on the stroke unit is therefore crucial. However, evidence supporting interventions at the stroke unit aiming

to “correct” deranged physiology is lacking; even simple measures such as supplementary hydration and oxygen therapy are of unproven benefit. The role of blood pressure (BP) control in the immediate phase after stroke is unclear.^{5, 10}

Traumatic brain injury care

Traumatic brain injury (TBI) constitutes a major health and socio-economic problem throughout the world. It is the leading cause of mortality and disability among young individuals in high-income countries.¹¹ Approximately, 10 to 15% of patients with TBI have serious injuries and are unconscious, requiring specialist care with mechanical ventilation and intensive monitoring. Severe TBI is a heterogeneous disorder with different forms of presentation. The nature, intensity, direction and duration of the external forces determine the pattern and extent of damage (primary damage). Ischemic damage is often superimposed on the primary damage and can be widespread or more perilesional (secondary damage). Over the past 10 years, much of the treatment of TBI has evolved towards standardized approaches, mostly focused on severe head injury.¹¹ Approaches to TBI management focus mainly on prehospital emergency care, admission care and intensive care management. It is recognized that no single treatment can be uniformly appropriate across the wide range of conditions within TBI, and this vision would support the search for more individualized treatment options.

Severe TBI patients with depressed level of consciousness and structural damage on brain CT are treated with sedation and mechanical ventilation. Clinical monitoring is therefore difficult. Special monitoring and treatment (non-surgical, surgical or combination) protocols for these patients have been developed over time. Treatment is focused on avoiding hypotension, decreasing cerebral metabolism and reducing brain swelling and raised intracranial pressure (ICP). Different concepts (like ‘Lund’ or ‘optimal perfusion’) have been launched over the years and all claim improved outcomes. Despite their differences, all these concepts have some important fundamental similarities.¹² They all emphasize to improve and optimize the CBF and microcirculation and aim especially at the conditions for a tissue enclosed within rigid walls. Cerebral autoregulation plays an important protective role against the danger of hypoxia at low perfusion pressure, and the risk of brain edema at higher arterial pressure.^{11, 13}

Cerebral vasoregulation

The brain is capable of adapting cerebral vascular resistance in order to compensate or reduce the effects of BP on CBF. This effect is known as cerebral vasoregulation or autoregulation.¹⁴ Consequently, it’s incorrect to assume that changes in CBF always parallel changes in BP. In the past, easily performed measurements of BP were used as surrogate markers of changes in CBF, because the (mostly radio-active isotope based) techniques to evaluate cerebral vasoregulation available at that time were not easily applicable clinically.⁸ This has changed with the development of techniques like non-invasive bedside transcranial Doppler (TCD) and

near-infrared spectroscopy (NIRS) in the eighties and the evolution of complex intracranial signal analysis, like ICP and brain tissue oxygen tension (PbtO₂).¹⁵ There is growing evidence that information from cerebral vasoregulation is crucial for correct interpretation of the impact of several interventions or events on the stroke or intensive care unit. Some simple or unnoticed events might be potentially dangerous for vulnerable brain tissue. Examples are early patient upright positioning and early mobilization on the stroke unit, nocturnal peripheral cerebral desaturations in stroke patients with obstructive sleep apnea (OSA) and estimating individual and flexible (optimal) BP targets during critical periods on the stroke or intensive care unit.

Early upright positioning and mobilization

Different guidelines recommend by consensus that patients should sit in and out of their bed and become mobile as soon as their clinical condition permits. Intuitively, early mobilisation may reduce immobility associated complications of stroke (muscle wasting, thrombosis, pressure sores, pneumonia) but there is limited evidence to support the practice.^{5,10} The Very Early Rehabilitation Trials (AVERT) are currently assessing the value of early mobilisation in a multicentre randomised controlled trial but funding problems oppose short term answers.¹⁶ A recent study showed that 60% of surveyed stroke specialists had concerns about early stroke mobilisation.¹⁷ These concerns regard cerebral hypoperfusion in the context of orthostatic hypotension and/or impaired cerebral vasoregulation/ autoregulation.

In this thesis we aimed to study aspects of the complex interplay between BP, cerebral perfusion, body position and cerebral vasoregulatory/autoregulatory status in the (sub) acute phase of stroke and TBI. Our aims originated from practical (clinical) questions with the objective to improve study methods, therapies and patient outcome.

AIMS

This thesis addresses three primary questions:

1. How does arterial BP react to postural changes (decubitus, supine, sitting and standing position) in acute stroke and critically ill patients. Is there a correlation between postural BP responses and outcome after stroke.
2. What are the effects of in-bed-mobilization on estimates of cerebral perfusion and neurological status in the acute phase after stroke.
3. How can the bedside monitoring of estimates of cerebral autoregulation or vasoregulation be improved in stroke and traumatic brain injury patients.

These general aims have been translated in a series of experiments, retrospective analyses and background studies which are presented in the subsequent chapters of this thesis.

Chapter 2 provides a further clinical background for the evaluation of cerebral hemodynamics in patients with stroke, subarachnoid hemorrhage (SAH) and TBI. We describe the application of different techniques and methods to measure CBF, cerebral blood flow velocity (CBFV), ICP and NIRS. The (historical) concept of cerebral vasoregulation/autoregulation is explained and the currently available methods to test and quantify cerebral vasoregulation or autoregulation in clinical practice are described.

Chapter 3 provides background information about clinical studies using the application of TCD to measure CBFV in ischemic stroke patients in the (sub) acute phase. This review addresses the question whether vasoregulation or autoregulation is impaired and to identify the effects of the disease on cerebral perfusion.

Chapter 4 introduces the passive cyclic leg raising as a new maneuver to induce large fluctuations in BP and CBFV, aimed at improving variability and reproducibility of dynamic cerebral autoregulation estimates. Specifically, we tested a bedside method that doesn't require patient cooperation. This study was done in healthy volunteers.

Chapter 5 introduces BP as one of the major vital parameters monitored in the stroke unit. The accuracy of indirect BP measurement is strongly influenced by the position of both the patient and the BP cuff during the measurement. Acute stroke patients are often nursed in lateral decubitus positions. The effect of these alternating body positions in relation to affected body side on the outcome and reliability of indirect (oscillometric) BP readings in acute stroke patients is studied.

Chapter 6 describes whether the results, presented in chapter 5, could be replicated in critically ill patients on the intensive care with continuous invasive BP monitoring.

Chapter 7 continues research into postural BP measurements in acute stroke patients. In this chapter the effects of early upright positioning and mobilisation (supine, sitting and active standing) in the (sub) acute phase of ischemic stroke on both BP and functional outcome were examined.

Chapter 8 describes the application of continuous non-invasive BP, TCD and NIRS recordings during in-bed-mobilisation of acute stroke patients. These hemodynamic changes are related to neurological status, functional outcome and autoregulatory capacity to investigate the safety of early mobilisation.

Chapter 9 describes whether bilateral frontal NIRS can be used for nocturnal monitoring of cerebral oxygenation in acute stroke patients. Changes are related to co-registered non-invasive continuous BP and peripheral oxygen saturation measurements.

Chapter 10 introduces the development of accurate methods for assessment of the relationship between cerebral perfusion pressure (CPP) and cerebral vasoregulation/

autoregulation in severe TBI patients. In this chapter we investigated the relationship between slow fluctuations of BP and ICP pulse amplitude (a new index called PAX) using a moving correlation technique to reflect the global state of cerebral vasoreactivity and compared it to the well known index of pressure reactivity (PRx) as a moving correlation coefficient between averaged values of BP and ICP. Global cerebral vasoreactivity status was related to patient outcome.

Chapter 11 describes the development of an automated methodology for the continuous updating of 'optimal CPP' for patients after severe TBI injury, using continuous monitoring of cerebrovascular pressure reactivity (methods described in chapter 10). We validate the 'optimal CPP' algorithm by determining the association between outcome and the deviation of actual CPP from calculated 'optimal CPP'.

Chapter 12 provides a summary and discussion of the findings in this thesis.

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CHAPTER 2

CEREBRAL VASOREGULATION: CLINICAL PERSPECTIVES?

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ABSTRACT

- Cerebral perfusion deficits after brain damage, caused by a cerebrovascular accident (CVA), subarachnoid hemorrhage (SAH) or severe traumatic brain injury (TBI), may be detected earlier and may be better understood with neuromonitoring techniques.
- Due to their unique properties, cerebral arterioles keep cerebral perfusion more or less constant. This process is called cerebral vasoregulation or autoregulation and can be measured with different techniques, which will be discussed in this article.
- In current clinical guidelines on treatment of stroke, SAH and TBI, impaired cerebral vasoregulation is often assumed. However, there is a need to measure cerebral vasoregulation status at the individual level, with follow-up over time.
- Some neuromonitoring techniques inform the clinician about subtle local regulation disorders ('snapshot' assessment). Other techniques are suitable for the global long-term monitoring of vasoregulation (continuous 'monitoring' measurement) with results serving as feedback for treatment interventions and prognostification.
- Appropriate use in clinical practice requires standardization of the methods available for monitoring of cerebral vasoregulation.

INTRODUCTION

Advanced neuromonitoring techniques enable us to detect, study and understand altered cerebral blood flow (CBF) after initial damage after a stroke, subarachnoid hemorrhage (SAH) or severe traumatic brain injury (TBI).^{1,2} Perfusion disorders directly disrupt the supply of oxygen and glucose to the highly demanding brain. In addition, impaired washout of emboli, break through edema and hemorrhage are associated.³ The cerebral arterioles possess unique properties to optimally regulate cerebral perfusion, a process referred to as cerebral vasoregulation. Several local and systemic factors are involved in cerebral vasoregulation such as arterial CO₂ tension, sympathetic nervous system activity, metabolic demand, respiration, and cerebral venous drainage. However the adaption of the arterioles to blood pressure (BP) changes has been studied most frequently (cerebral autoregulation).^{1,4} Under the influence of, for example, (chronic) hypertension, sudden vessel occlusion, vasospasms or cerebral swelling, the failure of cerebral vasoregulation causes perfusion deficits with significant neuronal dysfunction and ultimately cell death. With early recognition and treatment of these perfusion disorders, the neurological outcome of patients may improve.

Cerebral vasoregulation can be studied in many different ways. Often the response of the cerebral perfusion on slow BP changes is studied (cerebral autoregulation). Another technique is to (artificially) increase the arterial CO₂ tension to assess what is called cerebral vasoreactivity.

In healthy individuals, spontaneous, slow changes in BP are present. With functional cerebral vasoregulation, cerebral perfusion remains constant despite these slow systemic BP fluctuations. Also sudden BP changes or volume shifts (within certain limits), for example after orthostatic challenges, do not affect cerebral perfusion significantly in healthy individuals. It is suggested that cerebral arterioles compensate for these BP reductions by active vasodilatation. BP increase is anticipated by vasoconstriction.⁴ It is generally accepted that cerebral vasoregulation works well in the wide range of mean BP values between 40 and 150 mmHg. In patients with chronic hypertension these limits are likely shifted to higher values.⁵ With impaired vasoregulation due to a cerebrovascular event or brain swelling, cerebral perfusion is directly dependent on systemic BP values.^{6,7} In this situation even small BP changes may have serious consequences (neuronal dysfunction and cell death) caused by (prolonged and unnoticed) periods of hypoperfusion or hyperperfusion.¹ Local factors, such as increased intracranial pressure (ICP), vasospasm or ischemia, may directly affect the perfusion in areas at risk. The (global) pressure within the skull can be measured by inserting an ICP probe or (external) ventricular drain. The cerebral perfusion pressure (CPP) is calculated as the BP minus the ICP. With ICP monitoring, intracranial space occupying lesions are more easily detected in sedated patients, but also effects of (aggressive) therapy can be examined.⁸

In current clinical guidelines, impaired cerebral vasoregulation is often assumed to be present in stroke, SAH and TBI patients. Consistent with this assumption, protocols advocate

strict limits for BP, ICP and ventilation (CO_2) to optimize cerebral perfusion and oxygenation. For example, based on retrospective studies, protocols advice to keep CPP between 50-70 mmHg for TBI patients during their intensive care unit (ICU) stay.⁹ Targeted adjustment of BP, ICP or intracranial volume (through evacuation of hematoma, cerebral spinal fluid (CSF) drainage or decompressive craniectomy) may improve cerebral perfusion. Research in this area is ongoing. Recent examples are the discontinuation of antihypertensive drugs in the acute phase after stroke, review of triple-H therapy with SAH, and the effects of decompressive craniectomy on TBI outcome.¹⁰⁻¹² Measuring and taking into account the individual cerebral vasoregulation may form the missing link between the limited impact of these interventions on neurological outcome at the group level.^{13,14} In this paper, we discuss current ways to measure cerebral vasoregulation and its clinical applicability.

Cerebral vasoregulation and cerebral perfusion: static research

Before the introduction of the transcranial Doppler (TCD) ultrasound technique, the cerebral perfusion was measured by calculating the washout of nitrous oxide (N_2O) or the decay of radioactive isotopes.^{1,2,15} With these invasive methods absolute values for the regional cerebral perfusion are obtained, related to the actual BP level (with a reasonable spatial resolution). By repeating the measurement (which takes a few minutes) on another BP level, information is obtained about the adaptation of arterioles to large BP increase or decrease. This steady state adjustment mechanism is called 'static vasoregulation or autoregulation' and classically displayed as the cerebral perfusion at different BP levels ('Lassen autoregulation curve'). Such relative perfusion changes can often be interpreted more reliably inter-individually than the absolute perfusion values.¹⁶

The Lassen autoregulation curve has a plateau with an upper and a lower limit where the cerebral perfusion follows the BP passively (Figure 1a).^{15,17,18} The discussion about its exact shape and which factors (except BP) influence the configuration of the curve, is still ongoing.¹⁹ Complete curves are only obtained in groups of individuals, offer limited follow-up over time (temporal resolution of minutes), require potentially dangerous BP interventions (with adrenaline, nitroprusside infusions) and generate information mainly about the extremes (the limits) of the vasoregulation. Nowadays, the static vasoregulation curve is often only reproduced on two BP levels (Figure 1b).^{14,20}

Using the positron emission tomography (PET) technique with radio-active oxygen before and after strong arteriolar vasodilatation (with the drug acetazolamide) is an attractive alternative method to perform static measurements. An important advantage of this technique is that not only is the cerebral blood volume (C^{15}O gas) and perfusion (H_2^{15}O) measured, but also is information on the local oxygen consumption ($^{15}\text{O}_2$ gas) obtained. Therefore, a statement about impaired vasoregulation in brain regions, which shows increased oxygen consumption besides reduced perfusion and volume after vasodilatation, is more convincing.¹⁶

Figure 1a

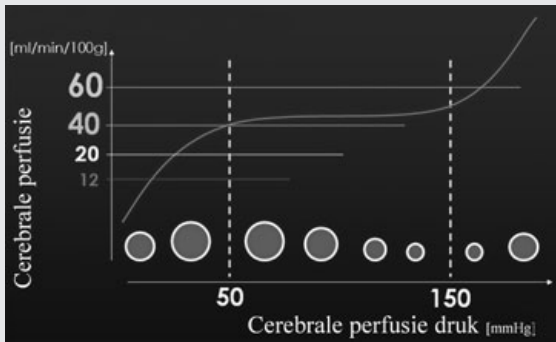
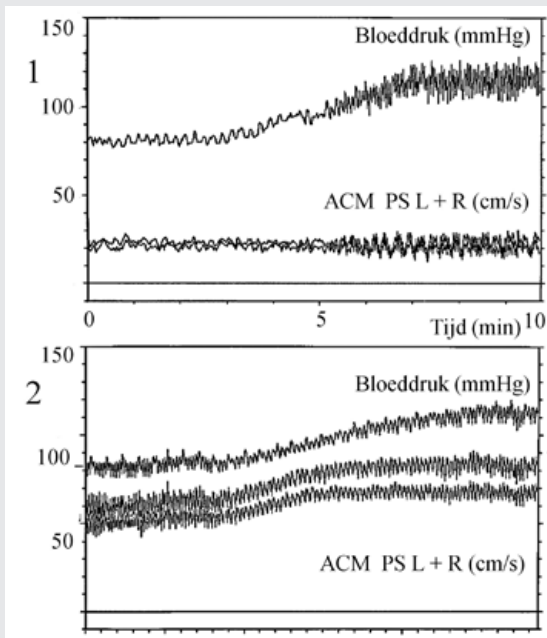


Figure 1b



Within the limits of an intact 'static' vasoregulation/autoregulation (50-150 mmHg) changes in the average blood pressure (BP), have no or only minor influence on the cerebral perfusion. This curve - with a plateau between 50-150 mmHg - is cited in the literature as the 'Lassen autoregulation curve'.¹⁵ Within this plateau the cerebral arterioles guarantee constant cerebral perfusion by vasoconstriction and vasodilatation. Outside the limits of vasoregulation, perfusion is unpredictable and follows BP changes passively (Figure 1a). With impaired vasoregulation, the cerebral perfusion (or surrogates like cerebral blood flow velocity) increases bilaterally with induced hypertension after infusion of adrenaline (Figure 1b, lower image).²⁰ ACM PS L + R indicates middle cerebral artery flow velocity left + right.

Cerebral vasoregulation and cerebral perfusion: dynamic research

TCD measurements (in which the flow velocity in the large intracranial arteries is measured) in combination with continuous BP measurements allow analysis of both the effectiveness and the speed of the cerebral vasoregulation bedside and over a prolonged period. This is called the 'dynamic cerebral vasoregulation or autoregulation'. In one of the first studies decreases in BP were induced by sudden deflation of bilateral tight cuffs. The BP drop of a few seconds made it possible to quantify the cerebral flow rate recovery in the middle cerebral artery (as a surrogate for global hemispheric perfusion) and compare it to a static vasoregulation method.^{20,21} The dynamic vascular response is probably complete after 10-15 seconds, indicating that arterioles are able to counter slower BP fluctuations.²² Faster BP fluctuations - as with every heart beat - are not compensated (also known as the high pass filter principle of cerebral vasoregulation).¹⁸ The discussion whether dynamic and static vasoregulation are established by different mechanisms, or that they are both manifestations of the same physiological control system, is ongoing.^{17,18,20}

In the literature, in addition to the cerebral perfusion also other intracranial signals are used for studying the dynamic vasoregulatory status. Examples are the near-infrared spectroscopy (NIRS) signal, which represents (mostly) the superficial intracranial venous system, local brain tissue oxygenation (PbtO₂) and the ICP signal derived from a monitoring or CSF draining system.²³⁻²⁵ The latter is often available in severe SAH and TBI patients.¹⁷ The basic principle of these dynamic measurements remains the same: a sudden (large) transient BP or volume change as the input signal and the resulting change in the intracranial compartment as output signal.¹⁷

Techniques for measuring and analyzing static and dynamic vasoregulation

Table 1 shows the different techniques that are currently available or in development for displaying the cerebral vasoregulation. Clear differences are present regarding the spatial and temporal resolution, radiation exposure, usability in different patient categories, overall availability, cost and robustness, as well as interpretation of the obtained signals.^{2,7} Overall it seems possible to classify the techniques into ones that are useful for intensive long-term monitoring ('monitoring assessment') and others that allow a single, short but thorough evaluation ('snapshot assessment'). For the nuclear (PET) and radiological (CT and MRI) techniques, the temporal resolution is still too low for dynamic measurements. Developments in this area are in progress. Simultaneous recording of continuous (noninvasive) BP are still missing.²⁶

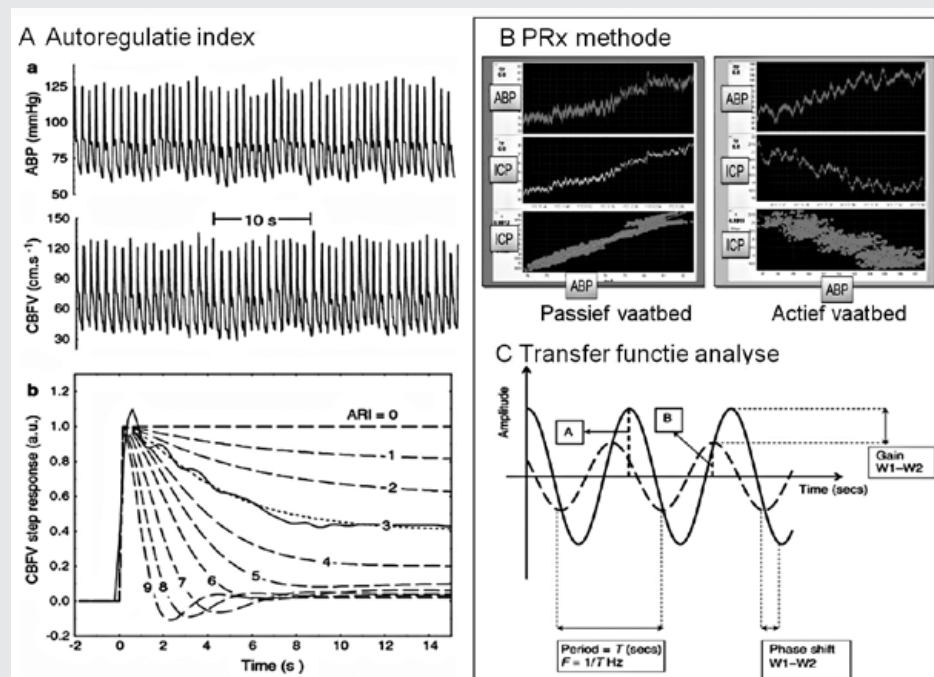
In the past, several models have been developed to quantify vasoregulation. For detailed information we refer to recent review articles.^{17,18,22,27} For both static and dynamic vasoregulation, these models are mainly linear with BP as 'input' and cerebral perfusion (or other intracranial signals) as 'output'. The input signal is often a well-controlled hemodynamic stimulus (for 'snapshot assessment') or spontaneous slow BP fluctuations (for long-term 'monitoring assessment'). In Figure 2, some examples of the different analysis techniques

Table 1

Methods	Techniques	Spatial/temporal resolution (S/T)	Pro's and Con's of techniques (P/C)	(Clinical) Applications
Absolute or relative perfusion measurements with isotopes or contrast agents (exogenous or endogenous)	Nuclear research (PET/SPECT/CT) Perfusion MR imaging with gadolinium contrast agent (exogenous contrast) MR with arterial spin labeling technique (endogenous contrast) BOLD MR imaging (indirect perfusion measurement) Perfusion CT with iodinated contrast	S: good to excellent T: poor (nuclear research), moderate (CT and MRI perfusion), promising (MRI arterial spin labeling technique/ BOLD MRI technique)	P: anatomical images (including vessels)/possibility to measure (local) oxygen metabolism (nuclear techniques) C: radiation exposure (nuclear/CT)/allergic reactions, nephropathy and vasodilatation by contrast agents (CT/MR) /absolute values are sometimes not reliable calculated/ not bedside/low experience (MR)/ indirect signals (MR)	Snapshot evaluation Only in specialized centers (nuclear techniques) Especially in research setting
Continuous relative perfusion measurements (flow velocity)	Transcranial Doppler (TCD) ultrasonography	S: bad (large basal cerebral arteries with flow territories) T: very good	P: cheap/noninvasive/easy to combine with other techniques/ readily available/harmless C: no absolute perfusion measurements/ in 10% of patients no bone window/ technique is user dependent	Snapshot evaluation Intermittent monitoring (hours) Ward/stroke unit/operating room/ intensive care
Relative (local) cerebral oxygenation	Venous oxygen saturation (SiVO ₂) 'near-infrared' spectroscopy (NIRS) Cerebral (local) oxygenation (PbtO ₂)	S: poor (PbtO ₂), moderate (SiVO ₂ and NIRS) T: moderate (PbtO ₂ : minutes), good (SiVO ₂ and NIRS)	P: minimally invasive/noninvasive (NIRS) C: complex signal (NIRS) / invasive (PbtO ₂ and SiVO ₂) / mixed intra-extracranial venous circulation contribution (SiVO ₂) / difficult to relocate (PbtO ₂)	Long term monitoring Intensive care (PbtO ₂ / SiVO ₂ / NIRS) Ward/stroke unit/operating theatre (NIRS)
Intracranial pressure	Intracranial pressure monitoring CPP calculation	S: very limited (global pressure) T: very good	P: stable robust signal/easy to combine with other techniques/ simultaneous therapeutic CSF drainage possible C: invasive measurement	Long term monitoring Intensive care

PET 'Positron Emission Tomography'; SPECT 'Single Photon-Emission-CT'; CT 'Computer Tomography'; MR Magnetic Resonance; BOLD MR 'Blood Oxygen Level-Dependent MR'; S Spatial resolution; T Temporal resolution; P Pro; C Con

Figure 2



This figure illustrates some common 'dynamic' autoregulation models currently available in stroke, subarachnoid hemorrhage (SAH) and traumatic brain injury (TBI). The autoregulation index (ARI) is calculated by measuring the perfusion change induced after a sudden BP or volume change or (as in this example) with spontaneous BP fluctuations (Figure 2Aa). The response curve is compared with ten hypothetical curves, constructed from a mathematical model where different elements involved in the cerebral vasoregulation are simulated (Figure 2Ab).^{18, 20} A value of 0 represents absence of autoregulation and 9 the fastest and most effective autoregulation response. In this example, the patient has an ARI of 3 (suggesting impaired vasoregulation). CBFV indicates cerebral blood flow velocity; ABP, arterial blood pressure; ICP, intracranial pressure.

With the PRx method the correlation coefficient between spontaneous slow mean BP fluctuations and the mean ICP is calculated and averaged over a longer period. A positive correlation indicates that slow BP fluctuations are followed by cerebral blood volume and subsequent ICP changes in the same direction. This is suggestive of a 'passive' vascular bed and impaired cerebral vasoregulation (scatterplots, figure 2b).¹⁷ With transfer function analysis different frequencies in the BP (continuous waveform with amplitude 'A') and perfusion (interrupted waveform with amplitude 'B') signals are decomposed with mathematical functions. Provided there is sufficient coherence between the input (BP) and output (cerebral perfusion) signals, the ability of arterioles to filter (spontaneous or induced) slow BP frequencies (< 0.25 Hz) can be measured. With this method, the vasoregulation can be expressed in terms of 'gain' (damping effect 'W1-W2'), and 'phase' (speed of vasoregulation 'W1-W2') (Figure 2c).^{18, 22, 27}

are displayed. Studies comparing different vasoregulation methods show moderate to good agreement.^{28, 29} Reproducibility of most dynamic methods, quantified by intraclass correlation coefficients (ICCs), is disappointing and more work is needed to understand the determinants of variability and reproducibility in vasoregulatory parameters.^{30, 31}

Cerebral (CO₂) vasoreactiviteit versus cerebral autoregulation

Besides BP, arterial CO₂ tension has a major impact on the cerebral arterioles and therefore perfusion. Hypercapnia causes vasodilatation with increased perfusion, hypocapnia causes vasoconstriction with decreased perfusion.⁴ This (slow) metabolic vasoregulation - also called the cerebral vasoreactivity - can be simply tested by breathing instructions or inhalation of a 5-8% CO₂ gas mixture. However there is no consensus how the exact protocol should be and how to improve the (especially long term) reproducibility.³² CO₂ changes are also accompanied by systemic BP changes of approximately 10%.³³ Instead of CO₂, the drug acetazolamide can also be used as a potent vasodilator. The degree of vasodilatation after inhalation of the CO₂ mixture or acetazolamide infusion has a clear clinical prognostic value, possibly apart from an impairment in the cerebral autoregulation. A diminished CO₂ vasoreactivity is associated with an increased risk of (delayed) ischemia in patients with severe carotid stenosis or SAH with vasospasm.^{34,35} Several studies show an impaired autoregulation with hypercapnia and conversely, an improvement with hypocapnia.³⁶ Therefore, concomitant CO₂ registration should not be omitted in vasoregulation studies.

Cerebral vasoregulation in routine clinical practice

Intact cerebral vasoregulation protects the brain against acute or chronic perfusion disorders. Some of the above mentioned techniques are suitable for the clinician to detect subtle (asymptomatic) local regulatory disorders ('snapshot assessment') (Table 1). Abnormalities are possible additional (early) risk factors for endothelial or arteriolar dysfunction and cardiovascular disease, in accordance with impaired CO₂ vasoreactivity in patients with significant carotid stenosis.³⁵ Other techniques are more suitable to follow-up vasoregulation over time, e.g. to perform continuous monitoring in patients admitted to the ICU or stroke unit where information besides having prognostic value also can serve as feedback for treatment interventions (improving arteriolar function or not).³⁷ Figure 3 shows that it is possible to retrieve an 'optimal CPP' level at population level (severe TBI patients) using a long-term monitoring method (PRx) using the signals BP and ICP. It is suggested that around this 'optimal' CPP value the cerebral arterioles are capable of keeping CBF constant with the largest reserve (Figure 3a). Also in the individual TBI patient, this value can be calculated continuously and might thus be of great support for ICU management decisions (figure 3b). A retrospective TBI study showed that on average deviation from this calculated 'optimal CPP' target value was associated with poor outcome.³⁷

For both the 'snapshot' and 'monitoring' vasoregulation methods clear protocols and normal values are lacking at the moment. Promising retrospective studies have already demonstrated a clear independent relationship between impaired vasoregulation and poor outcome or complications after TBI and SAH.^{38,39,40}

Figure 3a

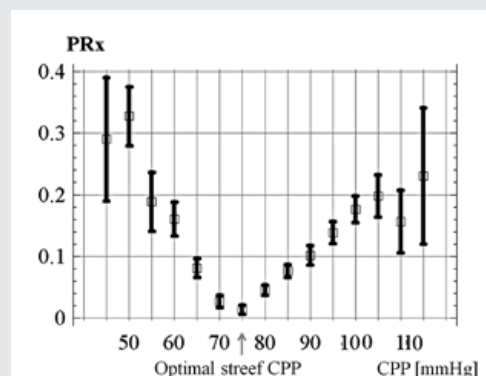
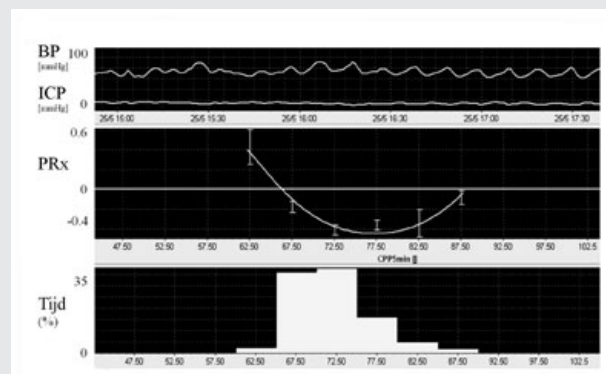


Figure 3b



In this figure the cerebrovascular pressure index PRx – representing the correlation coefficient between mean BP and mean ICP – is plotted against the CPP for a large cohort of severe traumatic brain injury (TBI) patients with continuous long term ICP monitoring ($n = 327$). From this graph an optimal target CPP value for the whole TBI group can be estimated (retrospectively), e.g. the CPP value where vasoregulation is thought to work ‘optimal’ (represented by the lowest PRx value) (Figure 3a). Also for the individual patient (at present from retrospective data) such a vasoregulation curve can be generated (and updated) from a sequential monitoring session of 4 hours (Figure 3b). This information can assist the clinician in determining individual treatment goals, suited to the disease condition at that time.^{37, 43} ICP indicates intracranial pressure; CPP, cerebral perfusion pressure; PRx, pressure reactivity index; BP, blood pressure.

Requirements for use of cerebral vasoregulation in clinical practice

To implement vasoregulation measurements in neurological practice within a reasonable time period, a number of requirements have to be fulfilled. Firstly, in a research context the most practical techniques and methods have to be selected with easy to interpret intracranial signals, focused per clinical question (roughly ‘snapshot’ or ‘monitoring’). Secondly, normal values for vasoregulation in various disease states have to be determined,

taking into account patient factors (such as age, sex and vascular risk factors) and acceptable reproducibility. Thirdly, combinations of intracranial signals (e.g. TCD and NIRS or ICP and PbtO₂) have to be tested taking into account changes in cerebral metabolism, brain function (electroencephalography) or (vascular) anatomy.⁴¹ Fourthly, repeated, potentially dangerous (input) challenges such as hypotension or hypercapnia risking ischemia and increased ICP should be avoided. This implies the development of dynamic vasoregulation methods, preferably with simple interventions (breathing instructions, or repetitive postural changes) or use of spontaneous slow BP fluctuations.²⁷ However, breathing instructions are not possible in aphasic or comatose patients, there are concerns regarding high 'between-subject' variability and spontaneous BP fluctuations >10 mmHg are not always present.⁴² Finally, the exact influences of various physiological parameters and (surgical and non-surgical interventions) on the cerebral vasoregulation have to be investigated (for example, influence of CO₂ tension or barbiturate coma).

CONCLUSION

Early recognition and treatment of vasoregulation disorders seems crucial in efforts to improve the neurological outcome of patients with acute or chronic vessel occlusions, sudden hemorrhages, contusions, brain swelling or increased ICP. In this overview we describe the different vasoregulation evaluation options presently available. Standardization and selection of methods will facilitate the implementation of vasoregulation methods in clinical practice. In the near future, patient at risk for (subtle) perfusion disorders can be identified, who would benefit directly from application of vasoregulation-oriented therapies.

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CHAPTER 3

CEREBRAL AUTOREGULATION IN STROKE: A REVIEW OF TRANSCRANIAL DOPPLER STUDIES

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ABSTRACT

Background and Purpose

Cerebral autoregulation may become impaired after stroke. To provide a review of the nature and extent of any autoregulation impairment after stroke and its course over time, a technique allowing repeated bedside measurements with good temporal resolution is required. Transcranial Doppler (TCD) in combination with continuous blood pressure measurements allows noninvasive continuous bedside investigation with high temporal resolution of both the dynamic and the steady-state components of cerebral autoregulation. Therefore, this review focuses on all TCD studies on cerebral autoregulation in the setting of documented ischemic stroke.

Methods

PubMed and EMBASE were searched for studies of stroke, autoregulation and TCD. Studies were either acute phase (<96 hours after index stroke) or chronic phase (>96 hrs after index stroke) autoregulation studies. Quality of studies was studied in a standardised fashion.

Results

Twenty-three studies met the inclusion criteria. General agreement existed on cerebral autoregulation being impaired, even after minor stroke. Bilateral impairment of autoregulation was documented, particularly after lacunar stroke. Studies showed progressive deterioration of cerebral autoregulation in the first five days after stroke and recovery over the next three months. Impaired cerebral autoregulation as assessed by TCD was related to neurological deterioration, the necessity for decompressive surgery and poor outcome. Synthesis of the data of various studies was, however, limited by studies not meeting key methodological criteria for observational studies.

Conclusions

TCD in combination with continuous blood pressure measurement offers a method with a high temporal resolution feasible for bedside evaluation of cerebral autoregulation in the stroke unit. TCD studies have shown impairment of cerebral autoregulation in various subtypes of ischemic stroke. To improve the synthesis of data from various research groups there is urgent need for standardization of methodology of TCD studies in cerebral autoregulation.

INTRODUCTION

It is generally accepted that cerebral autoregulation may become impaired after stroke.¹ Autoregulation impairment in the presence of moderate to severe ischemia may render penumbral tissue particularly vulnerable to alterations in cerebral perfusion. It may be crucial in the survival of ischemic penumbra, especially during interventions in the stroke unit such as blood pressure (BP) manipulation or mobilisation, and, as such, may confound trials of interventions in the stroke unit. Important research questions concern the reasons for cerebral autoregulation impairment, the nature of and extent to which autoregulation becomes impaired, and how impairment progresses over time. Autoregulation is hypothesized to become impaired by damage to cerebral arterioles and capillaries during ischemia or other chronic insults (like hypertension).² Cessation of blood flow then rapidly initiates a related series of processes that effects endothelial cell and receptor dysfunction and smooth muscle activation, all leading to impaired vasoregulator function.³ The primary focus of this review is on the nature and extent of cerebral autoregulation impairment and its course over time. For this, a definition of autoregulation and a description of various evaluation methods is required.

Cerebral autoregulation is the inherent ability of blood vessels to keep cerebral blood flow (CBF) relatively constant over a wide range of systemic BP levels by means of complex myogenic, neurogenic, and metabolic mechanisms. The CBF depends on vascular conductance and arterial BP. Cerebral vascular tone is sensitive to arterial CO₂.⁴ In response to a variation in perfusion pressure, an adaptation in cerebrovascular resistance will cause CBF to return to its baseline.⁵⁻⁸

Evaluations of cerebral autoregulation have traditionally been performed under steady-state conditions: a measurement of CBF was obtained at a constant baseline BP and constant CBF, followed by another steady-state measurement after manipulation of BP. This 'static' autoregulation was supposed to be intact if CBF was maintained at or near the baseline level despite BP changes.^{9,10} The group of Stirling used such 'classic' steady-state methods to demonstrate different dysautoregulation responses to various anatomical ischemic locations, various risk factors and duration after stroke.¹¹ Drawbacks of single steady-state evaluations are the vulnerability to confounding by spontaneous non-BP-related variability, such as CO₂ changes,¹² the time-consuming nature of procedures, the need for invasive pharmacological interventions, and the lack of information on any period of hypoperfusion possibly preceding the eventual return to stable perfusion.^{6,7}

More recent developments, such as transcranial Doppler ultrasonography (TCD) and servo-controlled finger photoplethysmography have offered the advantage of investigating beat-to-beat dynamics of the pressure-flow relationship of the cerebral circulation and of differentiating between fast and slow response mechanisms.^{6,7} This 'dynamic' approach uses the induced or spontaneous rapid changes in BP as an autoregulatory stimulus and compares BP and CBF velocity (CBFV) during the whole autoregulatory process (dynamic pressure autoregulation).^{5, 6, 13} Obviously, TCD can be used to study both CBFV responses to steady-state changes in BP (static pressure autoregulation),^{14, 15} and the autoregulatory

reserve and adaptability after, for example CO₂ inhalation or breathing maneuvers (chemical vasomotor autoregulation or cerebrovascular reactivity).¹² Although, Stirling Meyer found no correlation between the degree of static pressure dysautoregulation and impairment of chemical vasomotor autoregulation in stroke patients,¹⁶ many authors today interpret the isolated assessment of chemical vasomotor autoregulation as a steady-state method (i.e., measurement at 2 static levels of CO₂).¹⁷

Contrasting with the classical static autoregulation, no uniform method exists to provoke, measure, analyze and report dynamic or chemical vasomotor autoregulation. Recently, some excellent articles provided an overview of the different methods to provoke hemodynamics and quantify pressure autoregulation using TCD.^{6-8,18,19} TCD studies are highlighted in this review because TCD studies allow evaluation of both the steady-state and dynamic components of cerebral autoregulation, and because TCD together with finger photoplethysmography stands out as a technique with excellent temporal resolution allowing non-invasive continuous bedside monitoring of CBFV and BP, and thus autoregulation.

The central question of this review is what the nature and extent of autoregulation impairment after stroke is as measured by TCD is. All 3 study approaches to cerebral autoregulation are considered: static pressure, dynamic pressure, and chemical vasomotor or combination autoregulation studies.

MATERIALS AND METHODS

Study identification

Cochrane Collaboration methodology for meta-analysis reviews modified for observational studies (www.equator-network.org) was used.²⁰

Search strategy

Studies were identified with a search strategy across 2 English language databases (Medline and Embase) between 1966 and October 2009 accommodating different MeSH terms or subcategories available on each database (Table S1, supplemental material). Bibliographies of selected articles were screened for additional relevant articles.

Inclusion and Exclusion criteria

Included were published TCD studies of human cerebral autoregulation after ischemic stroke. Eligibility was assessed by reading abstracts and, if necessary, whole articles. The effects of impaired cerebral autoregulation on neurological outcome were assessed. Excluded were case reports, non-English language articles, posterior territory stroke studies and studies with ultrasound contrast agent injection. Carotid stenosis or known intracranial artery stenosis confounds the effect of stroke on cerebral autoregulation and were an additional reason for exclusion of studies.

Data extraction

The following data were extracted: (1) stroke population; (2) stroke severity; (3) number of patients and controls; (4) acute (<96 hours after index stroke) vs chronic phase assessment (>96 hours after index stroke); (5) cerebral autoregulation challenges (input); (6) method of data analysis; (7) autoregulation evaluation method (steady-state versus dynamic autoregulation); (8) neurological outcome (Barthel score, NIHSS change or necessity of craniectomy); (9) main conclusions of the authors; (10) presence, timing and conclusion of follow-up studies; and (11) status of cerebral autoregulation in both hemispheres. Furthermore, important technical aspects of TCD observational studies such as bilateral probe recordings, reporting of CO₂ values, and use of continuous BP recording during the measurements were extracted.

Study quality was assessed using a checklist proposed previously for authors, editors and reviewers of meta-analyses of observational studies.²⁰ This checklist was adapted to include 13 items relevant to TCD autoregulation observational studies (Table S2, supplemental material).^{6-8,13,18,19}

RESULTS

Literature

Two-hundred thirty-eight publications met the search criteria and were evaluated. Inclusion criteria were met by 14 controlled studies and 13 observational studies. Three studies were excluded because of unclear timing of measurements after stroke onset,²¹⁻²³ and 1 was excluded because TIA and minor stroke patients were grouped together.²⁴ Hence, 23 publications were eligible for review. Study details are summarized in Tables 1 and 2. Patient number ranged from 6 to 100. Sixteen studies included patients in the acute (range 20-96 hours) and 7 in the chronic (range 7-458 days) phase of stroke. Six studies had follow-up measurements between 3 days and 3 months after stroke. In 9 studies, the initial stroke severity was not reported,²⁵⁻³³ and eight studies failed to provide information about other clinical conditions (such as arrhythmias, diabetes mellitus and carotid pathology) associated with impaired cerebral autoregulation.^{25,30,32-37} All studies allowed hypertensive patients to be included. In 2 studies, only information about the nonaffected hemisphere was presented because of permanent occlusion of contralateral middle cerebral artery.^{32,38} One study only provided information about the residual CBFV in the affected hemisphere.³⁴ Eleven studies reported the end-tidal CO₂ levels during the measurements.^{25, 31,36,38-45} Six studies did not use continuous BP monitoring.^{25,27,29,34,37,45} One study included patients who received tissue plasminogen activator treatment.⁴¹ Information about clinical course and outcome after acute stroke in relation to autoregulation was provided in 5 studies.^{32,35,41,45,46} One study reported about the correlation between cerebral autoregulation and outcome after stroke.³⁷ The Figure summarizes the different methods used to provoke cerebral hemodynamics and assess autoregulation in the selected stroke studies. The median score on the proposed quality checklist for observational TCD autoregulation studies was 7 of 13 (range 11), reflecting incomplete reporting of key methodological criteria in most studies.

Table 1 Overview of Transcranial Doppler studies with measurements after >96 hours after index stroke

Study	Stroke type	Stroke Severity	Age, y (SD)	Input Method	Analysis Method	N of patients	Timing (mean)	Follow-Up (mo)	Hemisphere affected?	Main results and conclusions (N of patients)
Molina 1999	LAS	Unknown	57 (13)	ACZ	CVR	46	3 mo	NP	Unclear (mean of both used)	Chemical vasomotor CA is impaired in lacunar stroke; there is an association between infarct load and decreased CVR
De Leeuw 2003	LAS	Unknown	52 (12)	CO ₂	CVR	12	Day 7	NP	Both	Chemical vasomotor CA is impaired in both hemispheres
Novak 2003	ATS	Minor	52 (2)	CO ₂ pTTT	CVR	20	2 mo	NP	One (affected)	Chemical vasomotor CA is impaired during orthostatic stress; significant CBFV asymmetry during pTTT (80°) differentiated stroke patients from control (20) en hypertensive (30) group
Kwan 2004	ATS	Unknown	73 (11)	HGM	TFA (without coherence)	6	< 7 d	At 15 and 3 months	Both	Dynamic pressure CA (phase) improves globally up to 3 mo after stroke
Novak 2004	ATS	Minor	53 (2)	VM	Nonlinear frequency analysis	15	18 mo	NP	Both	Dynamic pressure CA is altered globally in hypertension (20) and stroke patients as compared to healthy controls (15); differentiation was not possible by using ARI method and rate of autoregulation regression model
Treger 2006	ATS	Unknown	58 (12)	pTTT	CBFV	13	Day 16	NP	Both	Orthostatic hypotension with pTTT (static pressure CA) is associated with low CBFV in both hemispheres
Gommer 2009	LAS	Unknown	67	SBPF ACZ	TFA CVR	24	3 mo	NP	None	Dynamic pressure and chemical vasomotor CA is not impaired in both hemispheres; poor correlations between CVR values and dynamic CA phase angles

ATS indicates Anterior Territory Stroke; PTS, Posterior Territory Stroke; LAS, Lacunar Stroke; CBFV, Cerebral blood flow velocity; pTTT, Passive Tilt Table Test; HGM, Handgrip method; NP, Not Performed; ACZ, Acetazolamide; VM, Valsalva maneuver; CVR, Cerebrovascular reactivity; TFA, Transfer function analysis; ARI, Autoregulatory index; SBPF, Spontaneous blood pressure fluctuations; CA, Cerebral autoregulation.

Acute stroke and steady-state autoregulation

Three studies used different tests to calculate cerebrovascular reactivity in the acute phase of stroke. Cupini et al used the breath holding index in different infarct types, to show, particularly in 14 patients who already had multiple subcortical infarcts, impaired cerebrovascular reactivity in both hemispheres during the acute phase of a new stroke.³¹ Gur et al, using slow infusion of acetazolamide in patients with moderate stroke, found impaired autoregulation in cortical strokes only. Bilateral nonsignificant impairment was detected in the subgroup of 24 patients with subcortical stroke, although no corrections were made for asymptomatic lacunar infarct status. Additionally, they failed to find a correlation between baseline severity, disability scores and cerebrovascular reactivity.³⁷ Cerebrovascular reactivity measurement using 5% CO₂ inhalation in 100 minor stroke patients showed that impaired reserve capacity in the affected hemisphere was independently associated with early neurological deterioration within 72 hours.⁴⁵

Acute stroke and dynamic autoregulation

All studies are unanimous in their conclusion that dynamic pressure cerebral autoregulation is impaired in acute stroke,^{30,41-44,47,48} particularly when stroke is moderate to severe,⁴¹⁻⁴⁴ or after follow-up.^{36,41} In 5 studies impaired autoregulation could also be demonstrated in the nonaffected hemisphere,⁴¹⁻⁴⁴ which was particularly the case for first ever lacunar stroke.⁴⁷ Eames et al showed that these bilateral changes are unrelated to previous antihypertensive treatment, baseline BP levels or BP changes after stroke, age, and stroke subtype or stroke severity.⁴² In 3 studies dynamic cerebral autoregulation was recorded from spontaneous fluctuations of BP using the approaches of frequency domain (transfer function analysis (TFA)) and time domain analysis.^{36,41,47} In sum, TFA is a complex linear analysis to estimate the magnitude and the phase relationship between spontaneous or induced changes in BP and CBFV.^{5,49} In the time domain analysis, either the delay of CBFV counter-regulation during changes in BP or the degree of correlation between averaged CBFV and BP over time is used.^{18,47} Five studies calculated the autoregulatory index (ARI).^{30,42-44,48} In sum, this is a linear curve-fitting procedure, which compares the CBFV response (measured directly or predicted) after a rapid step-like decrease in BP with a family of 10 theoretical flow-velocity curves to calculate dynamic cerebral autoregulation.^{6,10,13} Two studies used rapid thigh-cuff method deflation as input challenges.^{43,44} Three studies used spontaneous BP changes to reconstruct (by inverse fast-Fourier transform using TFA functions)^{5,49} the (predicted) CBFV step response.^{30,42,48} Comparable low-frequency ranges (0.06-0.12 Hz) were used for TFA analyses.

Autoregulation seemed increasingly impaired in the first few days after a large stroke (mainly affected side) with unsuccessful thrombolysis,⁴¹ and did not improve in moderate stroke over two weeks time.⁴³ In minor stroke patients, (after adjustment for covariates) cerebral autoregulation was similar to healthy controls after 2 weeks.^{30,48}

Table 2 Overview of TCD studies with measurements <96 hours after index stroke

Study	Stroke type	Stroke Severity	Age, y (SD)	Input Method	Analytical Method	No of pts	Timing (mean)	Follow-Up (d)	Hemispheres affected?	Main results and conclusions (N of patients)
Dawson 2000	ATS PTS	Moderate	69 (12)	TCM HGM	ARI CBFV	54	<96 hr	NP	Both	Dynamic pressure but not static pressure CA appears to be globally impaired in comparison to healthy controls (61)
Cupini 2001	ATS PTS	Unknown	60 (10)	BHI CO ₂	CVR	41	Between 1 and 3 mo	NP	Both	Static pressure and chemical vasomotor CA appears to be globally impaired in (multiple) subcortical infarctions in comparison with healthy controls (15)
Georgiadis 2001	ATS PTS	Severe	49 (12)	PEEP	CBFV	14	< 96 hr	NP	None (only healthy side tested)	No significant difference in CBFV and ICP on the various PEEP levels with increasing mean BP, yet in 3 hemicraniectomy patients a decrease in mean BP resulted in CBFV decrease (static pressure CA)
Schwarz 2002	ATS	Severe	59 (2)	Norepinephrine infusion	CBFV	19	58 hr	NP	Both	Induced hypertension enhances CPP (30%) and augments the CBFV (static pressure CA). This was more pronounced on the affected side, and in patients that underwent decompressive craniectomy (8)
Georgiadis 2002	ATS	Severe	58 (11)	Norepinephrine infusion	CBFV	16	<96 hr	NP	None (only healthy side tested)	Induced hypertension (22% increase) under moderate hypothermia does not affect static pressure CA
Eames 2002	ATS PTS	Moderate	70 (9)	SBPF	ARI	56	<72 hr	NP	Both	Dynamic pressure CA is globally impaired in comparison to healthy controls (56)
Schwarz 2002	ATS	Severe	61 (2)	HOBT	CBFV	18	<96 hr	NP	Both	Moving from horizontal to 30° HOB position decreased CBFV by 25% in affected hemisphere (static pressure CA), and more in patients that underwent decompressive craniectomy (7)
Dawson 2003	ATS PTS	Moderate	69 (11)	TCM	ARI CBFV	30	<96 hr	14 d	Both	Dynamic, but not static, pressure CA is globally impaired and remains abnormal for at least 2 weeks in comparison to healthy controls (51)
Alvarez 2004	ATS	Minor	70 (10)	CO ₂	CVR	100	<24 hr	NP	Both	Chemical vasomotor CA impairment is associated with higher risk of early neurologic deterioration
Wojner 2004	ATS	Large	60 (15)	HOBT	CBFV	22	<24 hr	NP	One (only affected side tested)	Moving from horizontal to 30° HOB position residual CBFV decreased by 17%, indicating impaired static pressure CA. Neurologic improvement in 3 patients was noticed
Immink 2005	ATS LAS	Severe/moderate	60 (4)	SBPF	TFA	20	<72 hr	NP	Both (LAS)	Compared to healthy controls (10) dynamic pressure CA is impaired in affected hemisphere in large AIS stroke, and bilaterally in moderately severe LAS

Reinhard 2005	ATS	Minor	61 (12)	SBPF	Mx TFA	33	<22 hr	6 d	Both	Dynamic pressure CA not seem to be relevantly disturbed, at the sub acute stage, slight global autoregulatory disturbance may be present
Cur 2007	ATS	Moderate/ severe	76 (13)	ACZ	CVR	47	<24 hr	NP	Both	Chemical vasomotor CA disturbance in cortical > subcortical stroke CA impairment not associated with baseline stroke severity and disability
Reinhard 2008	ATS	Severe	67 (12)	SBPF	Mx TFA	16	<20 hr	3-5 d	One (affected)	Dynamic pressure CA is increasingly impaired, mainly on the affected side, over the first 5 days of stroke after unsuccessful tissue plasminogen activator thrombolysis
Brodie 2009	ATS	Minor	69	SPBF	ARI	39	<42 hr	14 d	One (affected)	Dynamic pressure CA was reduced in the affected hemisphere, but after 14 days it was no longer significantly different from healthy controls (22)
Atkins 2010	ATS	Minor	67 (11)	SPBF	ARI	19	<36 hr	4 d	Both	As compared with TIA (17) and healthy controls (22) dynamic CA is only impaired in the affected hemisphere at baseline (even after correction for ipsilateral significant carotid stenosis)

ATS indicates Anterior Territory Stroke; PTS, Posterior Territory Stroke; LAS, Lacunar Stroke; CBFV, Cerebral blood flow velocity; HGM, Handgrip method; TCM, Thigh Cuff Method; ACZ, Acetazolamide; SBPF, spontaneous blood pressure fluctuations; HOBt, Head of Bed Test; CVR, cerebrovascular resistance; NP, Not Performed; PEEP, Positive End Expiratory Pressure; ARI, Autoregulatory index; CA, Cerebral autoregulation; BHI, Breath Holding Index; TFA, Transfer function analysis; Mx, Correlation index; ICP, Intracranial pressure; CPP, Cerebral Perfusion Pressure.

Chronic phase of stroke and steady-state and dynamic autoregulation

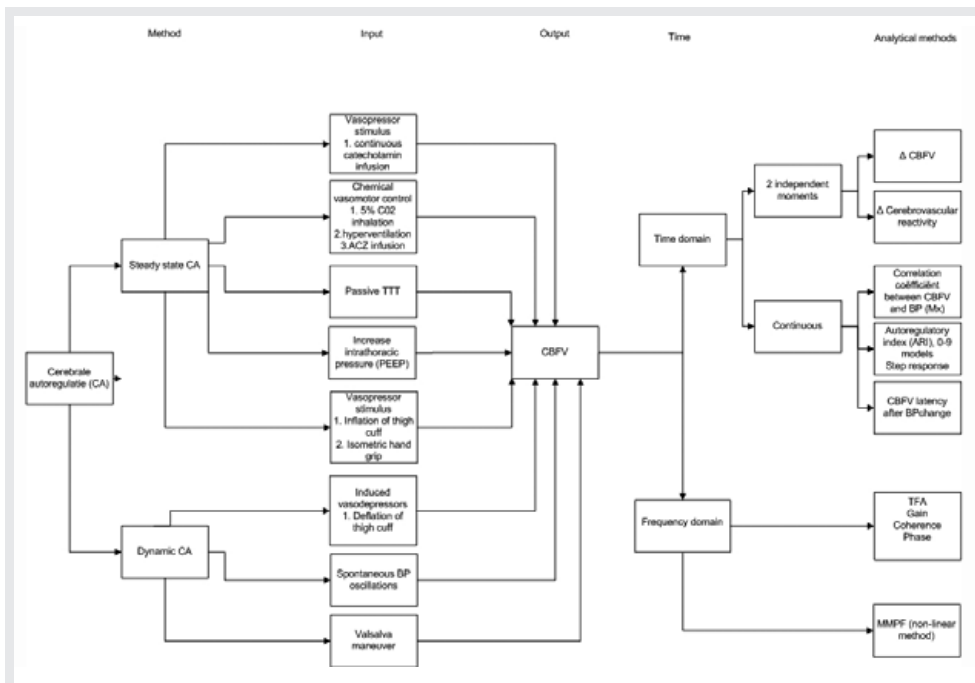
Five of 7 studies found bilaterally impaired autoregulation between week 1 and 18 months after minor and moderate stroke.^{25, 27-29, 40} Novak et al only detected changes in the affected hemisphere of minor stroke patients,³⁹ although the same group detected impaired dynamic autoregulation in both hemispheres during the Valsalva maneuver in 15 minor stroke patients using a nonlinear frequency shift method.⁴⁰ Gommer et al, studying first ever lacunar infarct, found TFA values and cerebrovascular reserve capacities in the normal range when examining their patients after 3 months or longer.²⁶ Information about stroke severity was not documented in this study. One research group repeated their initial measurements in the chronic phase and found some improvement after 3 months.²⁸ Three studies included both steady-state and dynamic cerebral autoregulation measurements in the same patients and found disturbed dynamic autoregulation only.^{26, 43, 44}

DISCUSSION

There seems to be general agreement that stroke is associated with impaired cerebral autoregulation, even in minor stroke. Cerebral autoregulation may become impaired in both hemispheres, although in some large stroke studies only measurements in the nonoccluded middle cerebral artery vessel (nonaffected hemisphere) were possible. Interestingly, this bilateral effect seems to be more pronounced in lacunar stroke. Two studies showed (some degree of) progressive impairment of cerebral autoregulation in the first days after stroke, which may affect the penumbral salvage.^{36, 41} Cerebral autoregulation has been shown to recover over the next 3 months. Impaired cerebral autoregulation in stroke is related to acute neurological deterioration, necessity of decompressive surgery, and poor outcome. How the process of cerebral autoregulation progresses from impairment to improvement and which factors determine this process, is unclear. Three studies investigated both dynamic and steady state autoregulation and found dynamic impairment only.^{26, 43, 44} This may be explained by differences in underlying mechanisms studied by dynamic vs steady-state investigation techniques or simply a greater sensitivity of dynamic investigation techniques for detection of stroke related autoregulation changes. The clinical relevance of such changes is unclear. In only 1 study with healthy subjects, dynamic measurement of cerebral autoregulation (with rapid cuff deflation) yielded results similar to classical static testing (phenylephrine infusion) under conditions of intact autoregulation and following pharmacologically induced impairment.¹⁰ However, these evaluation of the 'classical' lower limits of the cerebral pressure autoregulatory plateau requires considerable manipulations of BP, making the method invasive and potentially harmful for stroke patients.¹² Therefore, attention has been increasingly directed toward dynamic autoregulation.^{6-8, 13} However, Zhang et al found that dynamic autoregulation may interact with changes in steady-state cerebrovascular resistance or vascular compliance or both leading to changes in dynamic

autoregulation by TFA function. In this regard, a more comprehensive model to include both the autoregulatory mechanisms and steady-state vascular parameters should be explored to improve the precision of the model prediction.^{15, 50}

The interpretation of the TCD autoregulation studies is hampered by several methodological issues. First, studies using TCD rely on the assumption that changes in CBFV are directly proportional to changes in CBF. For that to be true, the cross-sectional area of the insonated artery needs to remain constant.^{51,52} For this reason, the results of any TCD study of cerebral autoregulation should always be interpreted with caution, keeping in mind the possibility that a change in MCA diameter might have occurred.⁷ Disadvantages of TCD compared to other techniques are the limited spatial resolution of the ultrasound images (not allowing a spatial allocation of impaired autoregulation to specific cortical areas). Although cerebral autoregulation initially has been studied and defined at the small vessel level in experimental animal models, it can only be defined in living humans in terms of measuring regional large vessel or whole brain blood flow.^{53, 54} More specifically, the characterization of blood flow or velocity in a single vessel provides an approximation of the regional cerebral autoregulatory capacity.^{14,51,55} It is also conceivable that the perfused territory of the insonated vessel might change under pathologic conditions, such as focal ischemia or nonpathological conditions such as hypercapnia or hypocapnia and extreme hypoxia.⁷ Furthermore, in approximately 5% to 15% of the (stroke) patients an insufficient acoustic bone window is present. Second, in general there is a lack of a clear definition of cerebral autoregulation, a gold standard technique for steady-state and dynamic cerebral autoregulation assessment, and a reference value for clinically relevant 'impaired' cerebral autoregulation.¹⁸ Together with great heterogeneity in study methods, (Figure) analytical methods and patient categories selected this complicates comparing studies to a quality standard. Third, direct comparisons with other diagnostic techniques such as positron emission tomography and MRI are lacking because of major differences in temporal resolution. Also, there are several well-known confounders of TCD assessment of cerebral autoregulation regulation,^{13,18,56} some of which are difficult to control outside the intensive care unit setting. For example, with protocols involving changes in posture and observations set to as much as minutes apart, there is always the possibility of the pressure-velocity relationship being strongly affected by changes in physiological parameters like sympathetic activation, cerebral venous pressure, breathing frequency and CO₂ levels.¹³ Only 11 studies reported CO₂ levels during their measurements. Since CO₂ has a marked influence on CBFV and also on autoregulation itself, the interpretation of measurements can be severely confounded in situations where significant changes in CO₂ go undetected. As already mentioned, changes in steady-state cerebrovascular resistance or vascular compliance or both, for example, during steady-state cerebral autoregulation may influence beat-to-beat changes in CBF independent of dynamic autoregulation.^{15, 50} In addition, 6 studies (all steady-state) did not measure BP continuously. To determine autoregulation BP should ideally be measured continuously.⁶ Also, relatively small numbers of patients were studied, with even smaller numbers of control subjects



Overview of linear models and analytical methods used in autoregulation studies in ischemic stroke. More in-depth information is available in the reviews of Panerai et al 2008 and Beek van et al 2008.^{6,8} CA indicates Cerebral autoregulation; ACZ, Acetazolamide; TTT, Tilt Table Testing; BP, Blood Pressure; CBFV, Cerebral blood flow velocity; MPMF, Multi Model Pressure Flow; TFA, Transfer function analysis.

recruited.⁵⁷ All this emphasizes the importance of more complex models with a multivariate approach to take into account the contribution of other variables that can influence CBF regulation.^{7, 8, 13} Finally, severe extra cranial or intracranial artery stenosis and clinical conditions (e.g. chronic hypertension, diabetes mellitus and silent infarcts) may confound the assessment of cerebral autoregulation.^{2, 17, 21, 58, 17, 23} The effects of presence of collateral or cross-flow needs to established in future studies. As an illustration, the finding of generally impaired autoregulation in lacunar stroke may be related to generalized small vessel disease attributable to chronic hypertension or diabetes. Longitudinal studies are required for lacunar stroke to show whether impaired cerebral autoregulation is a consequence of acute lacunar stroke or a correlate of widespread small vessel disease.

Additional knowledge is needed about the physiological and pathological determinants of cerebral autoregulation in stroke, so that determinants of autoregulation can be better controlled for in future studies, or taken into account with the help of multivariate (time and frequency domain) models. Until proven otherwise, it is possible that some clinical conditions disrupt myogenic mechanisms while others impair autoregulation by blocking

metabolic or neurogenic pathways.⁷ Dohmen et al demonstrated impaired autoregulation in the peri-infarct tissue of large middle cerebral artery infarct patients who had malignant brain edema by studying the relation between perfusion pressure and local oxygen pressure (invasive monitoring), together with metabolic makers of brain damage (microdialysis). They stress the important issue of combining continuous monitoring of surrogate markers of CBF (like CBFV) with local brain information.⁵⁹ In that view, the use of (multichannel) near-infrared spectroscopy in stroke seems promising.^{18,60} Near-infrared spectroscopy is a noninvasive technique that allows continuous monitoring of cerebral hemoglobin oxygen desaturation, with significant positive relationship between CBFV en NIRS changes during clamping with carotid artery surgery.⁶¹ Also, MRI with blood oxygen level dependent signal is used to monitor dynamic autoregulation changes, with the benefit of allowing good spatial resolution.⁶²

CONCLUSION

In summary, TCD appears to offer a practical bedside method with a high temporal resolution for cerebral autoregulation evaluation in stroke patients. TCD studies have shown impairment of cerebral autoregulation in various subtypes of ischemic stroke. In some patients, this impaired autoregulation is probably temporary and caused by the stroke, in others it is pre-existent and might have contributed to the stroke (e.g., in chronic hypertension). In view of intervention studies in the stroke unit such as the ongoing BP-lowering trials in acute stroke, correct identification of patients with impaired or adapted autoregulation may lead to the establishment of important subgroups in such trials.⁶³ Although some general conclusions can be drawn on the course of autoregulation over time, this topic requires further study. Variances in TCD study techniques, parameters and interpretations limits further conclusions (Figure). To improve the synthesis of data from various research groups (including stroke), there is great need for a uniform assessment of cerebral autoregulation in the whole field of autoregulation studies.

Future study goals are: (1) the determinants of cerebral autoregulation after stroke; (2) the development of multivariate models; (3) the status of both steady-state and dynamic autoregulation; (4) the course of cerebral autoregulation over time, and (5) the impact of cerebral autoregulation impairment on outcome with clinically relevant cut-off points.

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SUPPLEMENTAL MATERIAL

Table S1 Search Strategy used in Medline

A similar strategy using the closest available terms was used in Embase. The following key terms were used: (stroke (MESH) OR stroke (all fields)) AND (dynamic cerebral autoregulation (all fields) OR cerebrovascular autoregulation (all fields) OR cerebral autoregulation (all fields) OR cerebral vasomotor reactivity (all fields) OR cerebral perfusion (all fields) OR cerebral vasoregulation (all fields) OR cerebrovascular reactivity (all fields) OR chemical vasomotor autoregulation (all fields)) AND ((Doppler ultrasonography, transcranial (MESH) OR Doppler ultrasonography, transcranial (all fields) OR Doppler ultrasonography (all fields)).

Table S2 A proposed checklist of observational TCD autoregulation studies²⁰

Hypothesis statement in introduction or method section	1
Threshold values of study outcome parameters described in introduction and/or methods	1
Sample size calculation before start of experiment	1
Publication in peer reviewed journal	1
Medical ethics review with informed consent	1
Conflict of interest authors described	1
Patient spectrum/population described sufficiently	1
Confounding factors sufficiently mentioned in introduction, methods or limitations	1
Analysis described sufficiently (mathematical and statistics)	1
Proven reproducibility of data	1
Consecutive patient recruitment	1
Type of intervention/exposure described sufficiently (or with literature reference)	1
Considerations of alternative explanation for observed results in discussion	1
Total points	13



CHAPTER 4

REPRODUCIBILITY AND VARIABILITY OF DYNAMIC CEREBRAL AUTOREGULATION DURING PASSIVE CYCLIC LEG RAISING

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Submitted

ABSTRACT

Introduction

Dynamic cerebral autoregulation (dCA) estimates require blood pressure (BP) fluctuations of sufficient amplitude. Current methods to induce fluctuations are not easily implemented or require patient cooperation. In search of an alternative method, we evaluated if BP fluctuations could be increased by cyclic passive leg raising (PCLR). We tested if reproducibility and variability of dCA parameters could be improved with this maneuver in 16 healthy subjects.

Methods

Middle cerebral artery cerebral blood flow velocity (MCA CBFV), BP and end tidal CO₂ (etCO₂) were obtained at rest and during PCLR at 0.1 Hz. The BP-CBFV phase difference and gain were determined at 0.1 Hz and in the low frequency (LF) range (0.06 – 0.14 Hz). In addition the autoregulation index (ARI) was calculated.

Results

The PCLR maneuver increased the power of BP fluctuations at 0.1 Hz and across the LF range. Only the reproducibility of gain increased significantly with the maneuver. Variability was not reduced by PCLR for any of the dCA parameters. During the maneuver patients were breathing faster and more irregularly, accompanied by increased etCO₂ fluctuations and increased coherence between etCO₂ and MCA CBFV. Multiple regression analysis showed that these concomitant changes were negatively correlated with the BP-MCA CBFV phase difference at 0.1 Hz.

Conclusions

The clinical utility of the PCLR maneuver is limited because of the concomitant changes in etCO₂. This limits reproducibility of the most important dCA parameters. Future research on reproducibility and variability of dCA parameters should incorporate etCO₂ variability or find methods to keep etCO₂ levels constant.

INTRODUCTION

Dynamic cerebral autoregulation (dCA) describes the process of how cerebral blood flow (CBF) is regulated after blood pressure (BP) alterations of relatively short duration.¹ This is different from the concept of static autoregulation, where the steady-state response of CBF is assessed after a prolonged large alteration in BP, classically induced by vasoactive drugs.² Several methods exist to estimate the dynamic response directly from the time domain, like with inflation and deflation of thigh cuffs.³ However, these methods are used infrequently due to fact that sudden decreases in BP poses a risk of brain ischemia and sympathetic nerve system activation due to painful inflation of cuffs.^{4,5}

In search for alternative methods, research has focused on using spontaneous BP fluctuations to challenge dCA.⁶ The dCA is often quantified by transfer function analysis (TFA), which results in a phase and gain spectrum.⁷ Another parameter is the autoregulation index (ARI) which describes the system response to a step-like disturbance.^{6,8} An inherent problem with these strategies is that spontaneous BP fluctuations have to be of sufficient amplitude to obtain reliable estimates of the dCA parameters. Although healthy subjects usually demonstrate sufficient spontaneous BP fluctuations, in 15% to 30% of patients this requirement is not fulfilled.^{9,10} Several maneuvers have been developed to increase BP fluctuations. These include deep breathing,¹¹⁻¹³ oscillatory lower body negative pressure,¹⁴ repeated squat-stand maneuvers,^{15,16} the hand grip test,¹⁷ repeated head-up tilt,^{18,19} the cold stress test and the Valsalva maneuver.²⁰ Some authors have shown improvement of reproducibility and/or variability of dCA parameters with these methods,^{13,16,21} others reported no difference in reproducibility.^{22,23}

If methods to increase BP fluctuations are to be used in the clinical setting, they have to be practical, applicable at the bedside and require minimal patient cooperation. The latter requirement applies especially to certain neurological disorders, like in patients with decreased consciousness or aphasia. In search for alternative methods to induce BP fluctuations in the clinical setting, we tested the effect of passive cyclic leg raising (PCLR) on dCA calculation. During this maneuver venous blood shifts from the legs into the intra-thoracic compartment, increasing both ventricular preloads, and subsequently cardiac output and BP. In its static form, leg raising is used to predict fluid responsiveness in patients with circulatory failure.²⁴ By alternating raising and returning the legs to the horizontal plane, BP fluctuations are likely to occur. The objective of this study was to evaluate whether PCLR is able to increase the low frequency (LF) BP power with improvement of reproducibility and variability of dCA parameters.

MATERIAL AND METHODS

Subjects

We tested 16 healthy subjects (8 males, mean age 32.5 ± 9.5 years). Approval for this study was obtained from the local ethics committee. Informed consent was obtained from all subjects. None had a history of cardiovascular or neurological illness, hypertension or smoking.

Measurement protocol

Subjects were positioned in an adjustable medical chair, which was brought in a supine position for the measurement. If necessary, the chair was adjusted slightly to increase comfort. To prevent movement artifact, a semicircular inflatable pillow was positioned around the neck to overcome contact of the Transcranial Doppler (TCD) fixation system with the surface of the chair during PCLR. Non invasive BP estimates were obtained from a plethysmography system (Finometer-Pro, Finapres Medical Systems, Amsterdam, Netherlands), with a cuff placed around the index finger. Bilateral middle cerebral artery cerebral blood flow velocity (MCA CBFV) was measured with TCD (Nicolet Pioneer TC8080, Carefusion Corporation, San Diego, USA) using 2 MHz probes that were fixated using an adjustable headframe. End tidal CO_2 (etCO_2) was measured with a capnograph (Capnomac Ultima, GE Healthcare, Chalfont St Giles UK). All data were measured continuously at a sample frequency of 250 Hz. An analogue-digital converter in combination with Labview 9.0 software (National Instruments, Austin, USA) was used to capture the data for storage.

All participants had four measurement periods of 5 minutes each: two periods at rest, and two periods of leg raising. To minimize any time effects, an alternating measurement protocol was used, i.e. period 1: rest (R1), period 2: PCLR (PCLR1), period 3: rest (R2), period 4: PCLR (PCLR2). After each period of leg raising a short pause (between 2-3 minutes) during which no measurements were taken was inserted, to allow hemodynamic stabilization. Subjects were instructed to lie completely still, not to oppose the leg raising. No breathing instructions were given. The PCLR maneuver was executed as follows: both legs were lifted at the ankles and brought to about a 60° angle from the horizontal plane in about 1 second. After holding this position for 4 seconds, the legs were brought back to the horizontal plane in about 1 second, after which this position was kept for 4 seconds. This maneuver was then repeated which resulted in a period of 10 seconds (0.1 Hz). First, a few cycles were executed to verify that no movement artifact occurred. If necessary the neck pillow or head frame were adjusted. PCLR at 0.1 Hz was maintained throughout the 5 minute leg raising period.

Data analysis

The recorded signals were visually inspected for artifacts. Occasional artifacts of short duration which were visible as narrow spikes in the TCD or BP signal were removed by linear interpolation. Beat to beat data were obtained from the BP signal by triggering on the ascending slope during systole. The data were resampled at 10 Hz by spline interpolation

to create a uniform time base. EtCO₂ was determined from the capnography trace as the maximum over each cycle, and was subjected to separate interpolation at 10 Hz. Respiratory frequency was calculated from the etCO₂ cycle length. Detrending was performed using a high pass 8th order zero phase Butterworth filter, with a cut-off frequency set at 0.04 Hz. This was followed by mean normalization and subtraction of 1 to create zero mean signals. A Hanning window was applied to the data, and the Welch method of spectral estimation based on Fast Fourier Transformation (FFT) was used with 50% overlap on data segments of 51.2 seconds. This resulted in spectral estimates averaged over 10 segments. The transfer function analysis (TFA) was calculated without attempts to unwrap the phase spectra, but the phase estimates were visually inspected for phase wrap around. TFA graphs were produced at each iteration during averaging. If any sudden change in phase in the LF range occurred (visual inspection), the data were excluded. Coherence was considered significant if it exceeded the 95% confidence interval (CI) level of 'no linear association': $1-(0.05)^{1/L-1}$,²⁵ where L is the number of data segments used in the averaging. This resulted in a significant coherence level of 0.28. Gain and phase parameters were calculated at the 0.1 Hz frequency (in case of significant coherence). All frequencies were rounded off to two decimal places. Mean values of gain and circular mean values of phase were also calculated in the LF range (0.06 - 0.14 Hz) by averaging the values from these bins, i.e. the mean of 5 bins.

Power Spectral Density (PSD: i.e., power normalized by frequency bin width) of BP, etCO₂, and respiratory frequency signals were determined at 0.1 Hz. The total power in the LF frequency range was calculated by integration. For etCO₂ analysis, bins that were above the Nyquist frequency (i.e. respiratory frequency/2) as a consequence of the interpolation procedure were excluded. The Nyquist frequency was usually between 0.1 and 0.15 Hz. Because it is unlikely that significant fluctuations in alveolar etCO₂ above these frequencies occur frequently, we assumed any effects of aliasing of little importance. ARI was calculated by transforming the real and imaginary parts of the TFA back to the time domain with inverse FFT. The impulse response function thus created was integrated to yield the step response function. The first 10 seconds of the step response function were compared with the original Tiecks curves and the best fitting curve was determined by implementing a least squares fitting procedure, resulting in a ARI ranging from 0-9.²⁶

Statistics

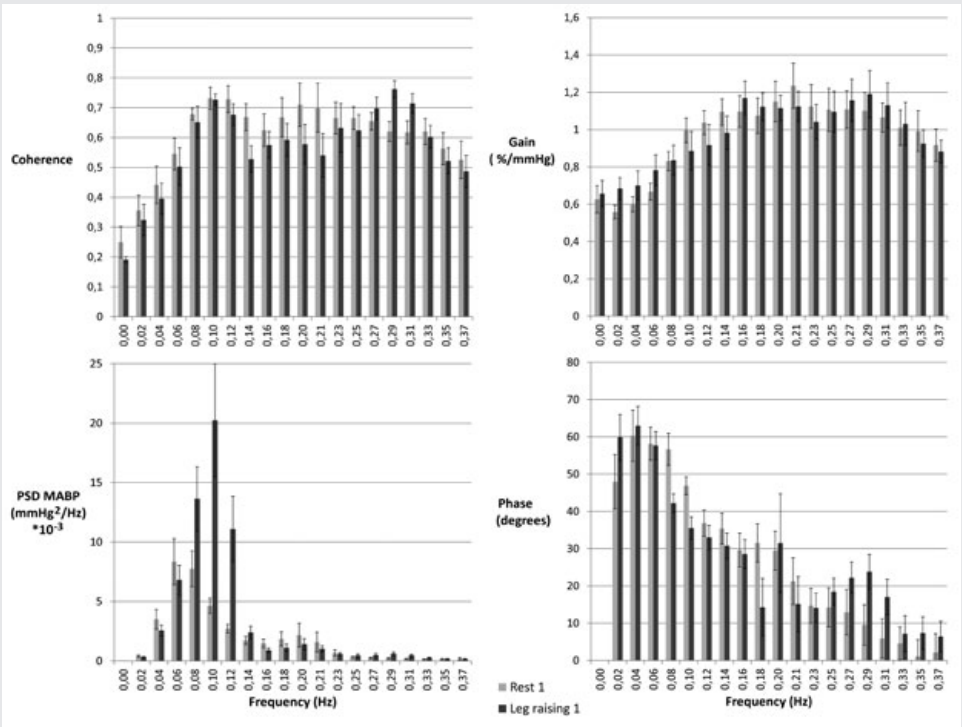
SPSS 16.0 and SAS 9.2 software were used. Repeated measures analysis of variance (ANOVA) tests with post-hoc correction (Bonferroni and Dunnett T₃ tests) were used. The following post-hoc comparisons were done: R1 vs R2, PCLR1 vs PCLR2, R1 vs PCLR1 and R2 vs PCLR2. After logarithmic transformation, all transformed variables were normally distributed in this study. To assess any differences in variability the Levene statistics was used. Intraclass correlation coefficient (ICC) analysis was used to assess reproducibility. Differences in ICCs were assessed with a difference test based on the CI for two dependent ICCs.²⁷ No formal power calculation was done. The relation between dCA estimates and independent variables

(BP, etCO_2 and derivatives) was evaluated with multiple regression analysis using a stepwise forward strategy. We accepted a variance inflation factor of < 10 as evidence that the input variables were indeed independent (co-linearity diagnostics).

RESULTS

The PCLR maneuver was well tolerated by all 16 subjects with good quality measurements. Mean data and spectral data of all relevant variables during the experiment can be found in Table 1 and in Figure 1.

Figure 1



Coherence, PSD MAPB, gain and phase spectra for all measured frequency bins are depicted. Data of the first rest period (gray bars) and the first PCLR period (black bars) are shown (mean \pm standard error of the mean). Left and right hemispheres were averaged. Note that coherence does not increase despite a clear increase in BP power in the frequency bins around 0.1 Hz. There is significant leakage into the 0.08 Hz bin, and to a lesser extent into the 0.12 Hz bin. Gain remains similar for all frequency bins, while for phase, a focal decrease is present at the 0.1 and 0.08 Hz frequency bins, but not elsewhere in the low frequency (LF) or very low frequency band. Statistics were performed on the LF band data only (Table 2).

Abbreviations: BP indicates blood pressure; PCLR, passive cyclic leg raising; PSD MAPB, power spectral density mean arterial blood pressure.

Table 1 Physiological and spectral characteristics during different test periods

	Rest (1)	PCLR (1)	Rest (2)	PCLR (2)	p value ANOVA
Blood pressure (BP) (mmHg)	78.1 ± 13.1	81.6 ± 14.5 *	81.7 ± 13.7 #	84.1 ± 14.4 *	<0.001
Mean CBFV (cm/s)	Left MCA 57.1 ± 12.1 Right MCA 64.6 ± 14.1	57.4 ± 12.3 66.6 ± 15.5	57.0 ± 12.4 65.3 ± 14.1	55.9 ± 12.0 64.9 ± 15.2	0.444 0.099
etCO ₂ (kPa)	4.56 ± 0.50	4.41 ± 0.50 *	4.46 ± 0.51 #	4.28 ± 0.53 *#	<0.001
Heart rate (beats/min)	63.5 ± 7.1	64.2 ± 8.2	62.2 ± 7.4	64.2 ± 8.7	0.226
Respiratory frequency (RF) (cycles/min)	13.8 ± 3.4	15.2 ± 3.1 *	13.9 ± 3.3	15.4 ± 2.7 *	0.003
PSD total BP (mmHg ² * 10 ⁻³)/Hz	18.2 ± 12.3	35.5 ± 49.4 *	18.5 ± 12.5	29.6 ± 31.3 *	<0.001
PSD 0.1 Hz BP (mmHg ² * 10 ⁻³)/Hz	4.4 ± 2.5	11.2 ± 21.1 *	4.3 ± 3.1	11.5 ± 14.0 *	<0.001
PSD BP peak frequency (Hz)	0.07 ± 0.02	0.10 ± 0.00 *	0.08 ± 0.02 #	0.10 ± 0.00 *	<0.001
PSD total CBFV (mmHg ² * 10 ⁻³)/Hz	Left MCA 21.6 ± 8.9 Right MCA 22.5 ± 8.7	37.6 ± 45.9 * 27.0 ± 35.6 *	18.2 ± 16.1 20.1 ± 15.0	36.3 ± 30.5 * 34.8 ± 37.8 *	0.019 0.040
PSD 0.1 Hz CBFV (mmHg ² * 10 ⁻³)/Hz	Left MCA 5.5 ± 4.0 Right MCA 5.9 ± 3.2	13.0 ± 17.3 * 11.3 ± 12.1 *	4.8 ± 4.8 5.1 ± 5.4	14.0 ± 11.7 * 13.1 ± 17.2 *	0.003 0.005
PSD total etCO ₂ (kPa ² * 10 ⁻³)/Hz	3.7 ± 5.8	14.7 ± 44.1 *	5.6 ± 5.2	14.2 ± 32.7 *	<0.001
PSD 0.1 Hz etCO ₂ (kPa ² * 10 ⁻³)/Hz	0.49 ± 1.4	2.6 ± 10.5 *	0.81 ± 0.97	3.0 ± 6.0 *	<0.001
PSD total RF (cycles/min ² * 10 ⁻²)/Hz	11.8 ± 15.4	44.1 ± 54.6 *	12.0 ± 13.5	25.5 ± 26.0 *#	<0.001
PSD 0.1 Hz RF (cycles/min ² * 10 ⁻²)/Hz	1.9 ± 2.0	11.1 ± 16.8 *	1.9 ± 3.9	5.6 ± 9.2 *	<0.001

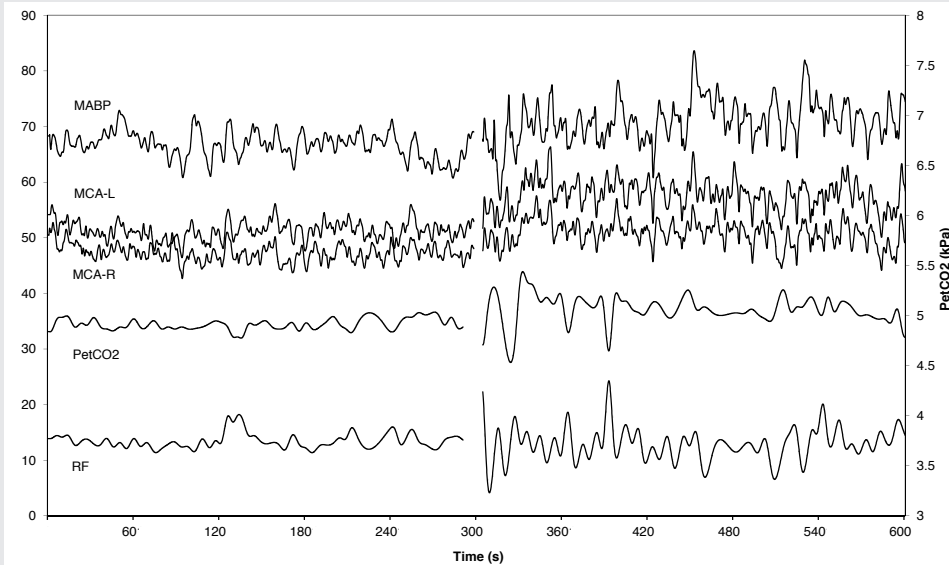
Physiological data are shown as mean ± standard deviation; Spectral data are expressed as median ± Inter Quartile Range (IQR) because of non-normal distributions.

Abbreviations: PSD indicates power spectral density; CBFV, cerebral blood flow velocity; MCA, middle cerebral artery.

indicates $p < 0.05$ vs previous similar condition; * indicates $p < 0.05$ vs previous different condition (after correction for multiple comparisons). 'Total' refers to 'total PSD in the 0.06 - 0.14 Hz range (low frequency)'.

Changes induced by PCLR

Leg raising significantly increased the power of BP in the LF band. This was accompanied by a shift in the peak of BP power from around 0.07 to 0.08 Hz during rest to 0.1 Hz during PCLR. Absolute levels of BP changed slightly, albeit significantly. At 0.1 Hz, BP power markedly increased (median ± interquartile range (IQR); R1: 4.4 ± 2.5, PCLR1: 11.2 ± 21.1, R2: 4.3 ± 3.1, PCLR2: 11.5 ± 14.0, (mmHg² * 10⁻³)/Hz, $p < 0.001$). Mean CBFV remained unchanged during the experiment, but total LF and 0.1 Hz power increased significantly during PCLR. Absolute etCO₂ levels decreased significantly during leg raising, although only by a small amount. A much larger increase was observed in the total LF and 0.1 Hz power of etCO₂ fluctuations (Table 1). An increase in absolute respiratory frequency occurred during PCLR. The total LF and 0.1 Hz power of the respiratory frequency curve also increased. The HR remained unchanged during the experiment. Data of a representative subject can be found in Figure 2.

Figure 2

Left panel represents rest period 1 and the right panel leg passive leg raising period (PCLR) 1. Only etCO_2 is plotted on the secondary Y-axis, all other variables are plotted on the primary Y-axis. Note the increase in amplitude of BP and MCA CBFV fluctuations in both middle cerebral arteries. Also an increase in etCO_2 and respiratory frequency oscillations during the PCLR maneuver can be seen. Abbreviations: MABP indicates mean arterial blood pressure; MCA-L/R, middle cerebral artery (flow velocity) left/right; RF, respiratory frequency.

Table 2 Transfer function and Autoregulation Index (ARI) results

		Rest 1	Leg raising 1	Rest 2	Leg raising 2	P value ANOVA
Mean LF phase (°)	L	42.4 ± 12.7	36.9 ± 9.6	40.1 ± 14.5	40.6 ± 13.2	0.500
	R	44.8 ± 11.9	38.4 ± 11.2	40.9 ± 14.4	43.5 ± 13.9	0.190
Phase 0.1 Hz (°)	L	47.6 ± 11.2	33.8 ± 10.7*	44.1 ± 12.7	37.1 ± 14.5	0.017
	R	46.1 ± 10.9	35.9 ± 14.4	44.5 ± 15.1	46.6 ± 16.1	0.130
Mean LF gain (%/mmHg)	L	1.02 ± 0.25	1.02 ± 0.37	1.11 ± 0.28	1.14 ± 0.29	0.404
	R	0.97 ± 0.26	0.93 ± 0.31	1.07 ± 0.19	1.06 ± 0.23	0.080
Gain 0.1 Hz (%/mmHg)	L	0.99 ± 0.29	0.93 ± 0.52	0.91 ± 0.26	1.05 ± 0.49	0.613
	R	0.99 ± 0.25	0.83 ± 0.34	1.01 ± 0.19	0.94 ± 0.40	0.594
ARI	L	6.2 ± 2.2	6.1 ± 1.9	6.1 ± 2.1	5.7 ± 2.2	0.935
	R	6.9 ± 1.9	6.9 ± 1.4	6.4 ± 1.9	6.4 ± 2.1	0.385
Mean LF Coh. BP-CBFV	L	0.67 ± 0.14	0.61 ± 0.12	0.62 ± 0.15	0.61 ± 0.15	0.060
	R	0.67 ± 0.13	0.62 ± 0.11	0.62 ± 0.15	0.61 ± 0.15	0.315
Coh. BP-CBFV 0.1 Hz	L	0.72 ± 0.17	0.71 ± 0.21	0.65 ± 0.24	0.74 ± 0.18	0.843
	R	0.75 ± 0.16	0.74 ± 0.13	0.69 ± 0.25	0.73 ± 0.21	0.450
Mean LF Coh. etCO_2 -CBFV	L	0.10 ± 0.04	0.14 ± 0.07	0.11 ± 0.05	0.15 ± 0.08	0.288
	R	0.09 ± 0.04	0.15 ± 0.09	0.13 ± 0.06	0.14 ± 0.07	0.133
Coh. etCO_2 -CBFV 0.1 Hz	L	0.10 ± 0.07	0.24 ± 0.17*	0.15 ± 0.11	0.25 ± 0.15	0.013
	R	0.10 ± 0.08	0.23 ± 0.17	0.15 ± 0.13	0.23 ± 0.16	0.009

Data are presented as means ± standard deviation.

Abbreviations: Coh. indicates coherence; BP, blood pressure; CBFV, cerebral blood flow velocity.

* Indicates $p < 0.05$ vs previous different condition (after correction for multiple comparisons).

Dynamic cerebral autoregulation parameters (Table 2)

Circular mean LF phase was not different between the four periods. The phase difference between BP and MCA CBFV at 0.1 Hz was different for the left hemisphere recording, with a significant difference between the first rest and first PCLR period (R1: $47.6^\circ \pm 11.2$, PCLR1: $33.8^\circ \pm 10.7$, R2: $44.1^\circ \pm 12.7$, PCLR2: $37.1^\circ \pm 14.5$, $p = 0.017$, R1 vs PCLR1, $p < 0.05$), but not between other periods. Mean LF gain, gain at 0.1 Hz and ARI were not different between the four periods. Mean LF coherence and coherence at 0.1 Hz between BP and MCA CBFV were similar across all periods. However, coherence between etCO_2 and MCA CBFV at 0.1 Hz was different with significant post hoc differences between R1 and PCLR1 (both hemispheres, $p < 0.05$, Table 2). No significant differences were found for mean LF coherence between etCO_2 and CBFV.

Table 3 Intraclass correlation analyses

		Rest 1 vs Rest 2	95% CI	PCLR 1 vs PCLR 2	95% CI
Mean LF phase	L	0.51	0.05 - 0.79	0.59	0.16 - 0.83
	R	0.76	0.43 - 0.91	0.31	-0.19 - 0.68
Phase 0.1 Hz	L	0.57	0.11 - 0.84	0.47	-0.04 - 0.79
	R	0.36	-0.17 - 0.74	0.38	-0.13 - 0.74
Mean LF gain	L	0.46	-0.01 - 0.77	0.67	0.29 - 0.87
	R	0.26	-0.25 - 0.67	0.62	0.21 - 0.85
Gain 0.1 Hz	L	0.43*	-0.09 - 0.77	0.84*	0.60 - 0.94
	R	0.25*	-0.29 - 0.67	0.70*	0.49 - 0.94
ARI	L	0.57	0.13 - 0.82	0.65	0.24 - 0.87
	R	0.82	0.56 - 0.93	0.60	-0.84

*denotes a significant difference ($p < 0.05$) in intraclass correlations between the passive cyclic leg raising maneuver and rest conditions.

Abbreviations: 95%-CI indicates 95% confidence interval; PCLR, cyclic passive leg raising

Reproducibility and variability (Table 3)

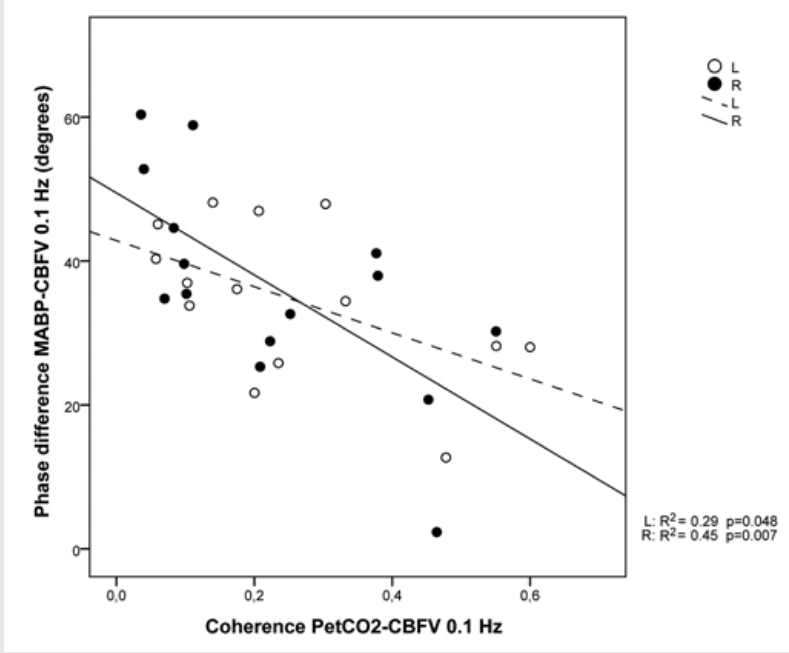
The ICC values for the rest period comparison were generally low for mean LF phase and 0.1 Hz phase and did not improve during PCLR. The ICC values for mean LF and 0.1 Hz gain were low in the rest period comparison, but improved significantly during PCLR, especially for the 0.1 Hz gain (left hemisphere: ICC for R1 vs R2: 0.43 and ICC for PCLR1 vs PCLR2: 0.84, $p = 0.02$); right hemisphere: ICC for R1 vs R2: 0.25 and ICC for PCLR1 vs PCLR2: 0.70, $p = 0.05$). The ICC values for ARI did not improve during PCLR. The variability was not different between the four periods (both hemispheres) for all dCA estimates (data not shown).

Relationship between variables

Additional analyses were performed to explore the significant lower 0.1 Hz BP-MCA CBFV phase difference during PCLR1, while no such difference occurred for the 0.1 Hz gain. Absolute levels of BP and etCO_2 as well as (the log-transformed) 0.1 Hz BP and etCO_2 power, as well as the 0.1 Hz coherence levels of BP-MCA CBFV and etCO_2 -MCA CBFV were entered as independent variables in the multiple regression model. Only the 0.1 Hz etCO_2 -MCA CBFV

coherence was significantly related to the 0.1 Hz phase difference (left hemisphere: $p = 0.048$; right hemisphere: $p = 0.007$). Figure 3 shows the linear relationship between the 0.1 Hz etCO_2 -MCA CBFV coherence and the 0.1 Hz phase. For the 0.1 Hz gain, only the 0.1 Hz BP power was significant correlated during both PCLR periods (data not shown). Figure 4 shows the relation between the 0.1 Hz gain and the 0.1 Hz BP power.

Figure 3



Correlation plot of the 0.1 Hz etCO_2 -CBFV coherence and the 0.1 Hz BP-CBFV phase for both hemispheres during the first PCLR period.
Abbreviations: CBFV indicates cerebral blood flow velocity; (MA)BP, (mean arterial) blood pressure; PCLR, passive cyclic leg raising.

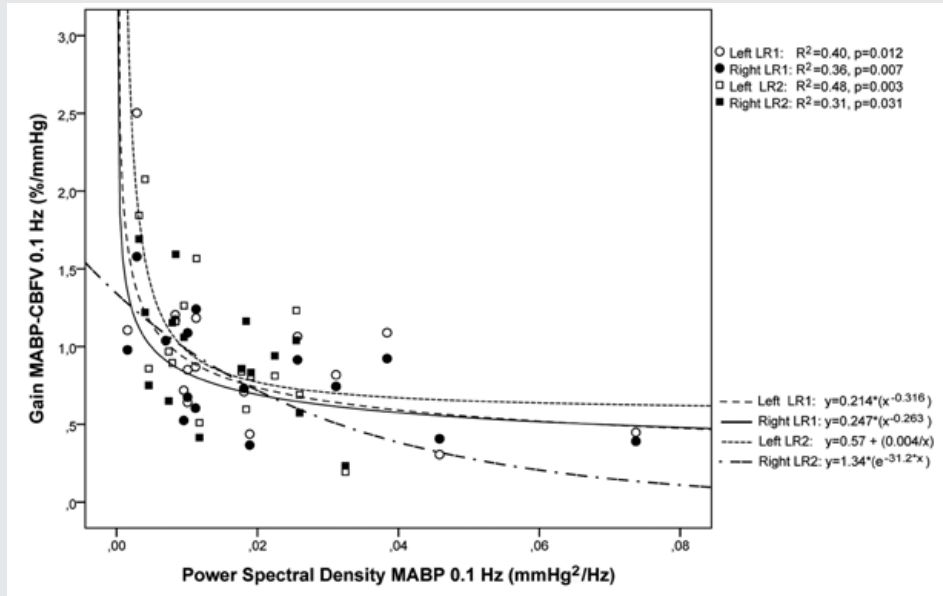
DISCUSSION

CHANGES DURING THE PCLR MANEUVER

Coherence

The results of this study show that the well tolerated PCLR maneuver increased the power of BP and MCA CBFV at 0.1 Hz significantly in healthy subjects. However, the BP-MCA CBFV coherence did not increase. This may be partly attributed to the fact that in the resting condition, the LF coherence was already quite high in our (relatively young) study population. Furthermore, during 0.1 Hz PCLR subjects started to breathe faster and more irregular with significantly increasing etCO_2 fluctuations and 0.1 Hz etCO_2 -CBFV coherence.

Figure 4



This figure shows the relationship between 0.1 Hz BP-MCA CBFV gain and the PSD of BP fluctuations. Data of the first and second passive cyclic leg raising (PCLR1 and PCLR2) periods were used. A significant inverse relation existed, which was best described by non linear inverse functions. After logarithmic transformation of the PSD of BP fluctuations a linear inverse relation was the best fitting function, and these transformed data were used in the multiple regression analysis. Abbreviations: CBFV indicates cerebral blood flow velocity; (MA)BP, (mean arterial) blood pressure; PSD, power spectrum density.

Phase

The 0.1 Hz BP-MCA CBFV phase tended to decrease during the PCLR maneuver, which would indicate impaired autoregulation. The 0.1 Hz etCO_2 -MCA CBFV coherence was negatively correlated with the phase estimate (Figure 3). We hypothesize that the decrease in phase was caused by the disruptive effect of increased etCO_2 fluctuations during PCLR. During the second PCLR period, these effects were less pronounced, despite a similar increase in etCO_2 power. An increase in etCO_2 fluctuations after BP fluctuation inducing maneuvers has also been described after repeated LF squat-stand maneuvers.¹⁶ In that study also a decrease in phase (with unaffected gain) was found. This was not interpreted as a CO_2 effect, but rather as an alteration in cerebrovascular tone due to increase in shear stress caused by the large squat-stand BP fluctuations. However, the coherence between etCO_2 and MCA CBFV was not assessed in the squat-stand study. Our findings might indicate that induced CO_2 fluctuations disturb the phase estimate in the LF range significantly.

Gain and ARI

Gain and ARI estimates remained unchanged during PCLR. In our experiment the major determinant for gain was the BP power, with less influence of etCO_2 . Therefore, different factors seem to influence frequently used estimates to describe dCA. The relation between BP power and gain was present during PCLR, but not during rest. The decrease in gain with increasing BP power is best described by a 'non linear inverse function' (Figure 4). This may indicate two things. Firstly, a threshold phenomenon, with cerebral autoregulation becoming active above a certain BP threshold. Secondly, at higher BP fluctuation levels the variability of gain decreases. However, reduction in inter-individual variability could not be demonstrated with formal statistics, although intra-individual variability was lower (see section on reproducibility and variability).

Sensitivity of ARI to both static and dynamic etCO_2 changes have been described before, using autoregressive moving average models with time varying estimates of ARI.^{28,29} We did not use a time varying estimate of ARI and this difference in analyzing technique might be a possible explanation for these different results.

Reproducibility and Variability

Only the reproducibility of the 0.1 Hz gain estimate increased significantly with PCLR. Gain seems less sensitive to etCO_2 fluctuations with reproducibility improving with increasing BP power. The fact that the inter-individual variability remained unchanged despite increased reproducibility indicates that a large proportion of the total variability of dCA estimates is due to inter-individual variability. Reductions in dCA estimate variability with increasing BP fluctuations have been reported by others.²¹ The limited number of subjects in our study, and the fact that not every subject showed a large increase in BP power with PCLR can be another explanation for this discrepancy.

Limitations

Several limitations deserve mentioning. Firstly, the physiological mechanism for the increase in BP power after PCLR is not entirely clear. Besides an increase in venous return, the altered breathing pattern may also have contributed to the increase in BP fluctuations. Breathing depth was not measured, so we were not able to analyze this option extensively. Secondly, in contrast to the LF band, limited coherence is more often problematic in the very low frequency (VLF) band (< 0.05 Hz).¹⁶ However, in this experiment we chose to focus on the LF band, because in this band BP (power) is considered to be the most important determinant for coherence.⁷ In the VLF band spontaneous oscillations in etCO_2 and non linear system interactions have been shown to exert a significant influence on the BP-MCA CBFV coherence calculation.^{30,31,32} Thirdly, although we hypothesize that concomitant etCO_2 fluctuations significantly influenced reproducibility of phase and ARI during PCLR, we cannot exclude the possibility that limitations in methodology have contributed. Our methodology only provides a single estimate of dCA parameters for the entire recording period. Other

techniques such as autoregressive moving average modeling, phase synchronization, multimodal pressure-flow analysis or wavelet analysis provide multiple estimates over time and are less sensitive to non stationarities.³³ Multivariate models may be able to correct for etCO_2 changes. Alternatively, methods filtering out short lasting changes in dCA parameters caused by etCO_2 changes may be developed. However, recent experiments have failed to show improvements in reproducibility with these methods and techniques.²²

Implications for clinical use and future directions

We aimed to obtain a practical bedside test that would increase BP power with minimal patient cooperation. Although the PCLR was well tolerated and significantly increased BP power, the first variability and reproducibility results of our selected dCA estimates were disappointing. Only the reproducibility for the gain estimate improved, most probably because it is less affected by (unexpected) concomitant etCO_2 changes. Therefore, at present the clinical utility of PCLR to improve diagnostic properties for testing dCA status is limited. In cooperative patients the use of breathing instructions at a fixed pace could be considered and in mechanically ventilated patients there might be less risk of concomitant breathing and etCO_2 changes. Alternatively, one could employ methods to ensure that etCO_2 remains constant, such as sequential gas delivery breathing circuit devices that can accurately target and control etCO_2 .³⁴ The fact that etCO_2 fluctuations have an important influence on dCA estimates further illustrates the need to incorporate or at least report etCO_2 variability in future dCA analysis.^{30,31,35}

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CHAPTER 5

VARIATIONS OF BLOOD PRESSURE IN STROKE UNIT PATIENTS MAY RESULT FROM ALTERNATING BODY POSITIONS

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ABSTRACT

Background

Blood pressure is one of the major vital parameters monitored in the stroke unit. The accuracy of indirect blood pressure measurement is strongly influenced by the position of both patient and arm during the measurement. Acute stroke patients are often nursed in lateral decubitus positions.

Objective

The effect of these alternating body positions in relation to affected body side on the outcome and reliability of blood pressure readings in acute stroke patients is unknown.

Methods

An automatic oscillometric blood pressure device was used. Blood pressure was measured in both arms in the (back) supine and both lateral decubitus positions.

Results

In total, 54 consecutive acute stroke patients were included. Thirty-five patients had right-sided deficits and 19 left-sided deficits. Supine blood pressure readings were similar in right and left arms regardless of side of deficit. Measurements of blood pressure in the lateral decubitus positions resulted in significantly lower blood pressure readings in the uppermost arm (around 12 mmHg in both arms) and significantly higher readings in the right lowermost arm (around 6 mmHg) compared to the supine position. This effect seemed less pronounced when the left lowermost arm was measured. There was no relation between change of blood pressure readings in various lateral positions and side of stroke.

Conclusions

Alternating lateral decubitus positions according to nursing standards in acute stroke patients lead to a mean 18 mm Hg blood pressure fluctuation. This may largely be explained by hydrostatic pressure effects, partly by anatomical factors in the left lowermost arm, but not by the side of stroke.

INTRODUCTION

There is increasing evidence that disturbance of vital parameters after stroke is associated with poor outcome.¹ This has led to a strong focus on monitoring of vital parameters in stroke units and development of strategies to maintain physiological homeostasis.² Changing body positions has been shown to prevent decubitus and pneumonia, and has led patients to be nursed in alternating supine and lateral decubitus positions.^{3,4} However, the changes of body position may also affect physiological homeostasis as illustrated by changes in oxygenation, changes in blood pressure (BP), in cerebral blood flow and in intracranial pressure.^{5,6} The effect of lateral decubitus positions on vital parameters in acute stroke patients has not yet been investigated.

Not only can different body positions affect vital parameters, they can also affect the measurement itself. BP is one of the vital parameters most prominently monitored in the stroke unit setting and many stroke treatment guidelines take into account indirect BP levels. The accuracy of BP measurement strongly depends on both the number of measurements and the way the procedure is performed. One of the important confounders is the position of both patient and arm during the measurement, and the resulting hydrostatic gradients.⁷⁻⁹ At present, guidelines about BP monitoring recommend measuring with the arm at heart level, but how to determine heart level in the lateral decubitus position is not specified.^{10,11} Before the effect of body position on vital parameters in stroke patients can be assessed, information about the effects of different body positions on the methodological accuracy of BP measurements is needed.

The aims of this study in admitted consecutive stroke patients in the first 24 hours were therefore to evaluate (1) the effects of lateral decubitus body positions on vital parameters accounting for affected body side, (2) the effects of lateral body position on BP readings.

METHODS

Study participants

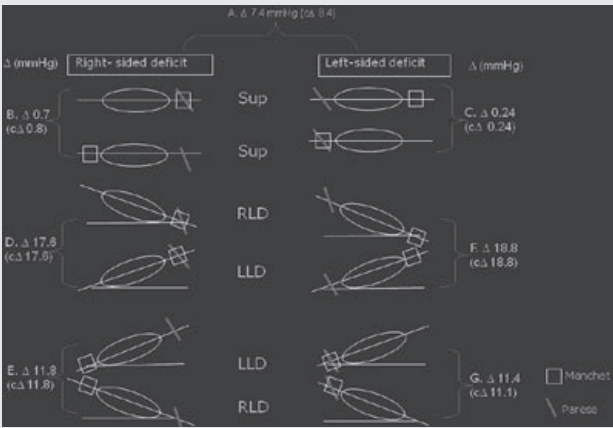
This observational study was conducted in the University Medical Center Groningen, during the period January-August 2009. Consecutive patients with an ischemic stroke within 24 hours of stroke unit admission without cardiac arrhythmias or hemodynamic instability were included. The measurements were done with the patient being installed on the stroke unit. Initial stroke severity was assessed with the National Institute of Health Stroke Scale (NIHSS). Stroke subtype was defined according to the Oxfordshire Community Stroke project.¹² Demographics, vascular risk factors, and medication were recorded. A noncontrast brain CT scan and routine hematologic and chemical analyses were carried out prior to treatment and admission in all patients. Patients received tissue plasminogen activator (tPA) treatment

according to protocols.¹³ The study was approved by the local medical ethics committee and all subjects gave informed consent.

Study Methods

All measurements were carried out by one investigator (M.A.). A Philips Intellivue MP30 (Philips Medical Systems, Best, The Netherlands) automatic oscillometric instrument was used. This oscillometric BP device measures oscillations from the blood vessel wall during cuff deflation. The pressure at which the oscillations are maximal is defined as mean arterial pressure (MAP). The device then calculates the systolic blood pressure (SBP) and diastolic blood pressure (DBP) with an algorithm. Continuous peripheral oxygen saturation monitoring was performed with the Intellivue MP30 device with the Fourier Artifact Suppression Technology (FAST) algorithm. The instruments are regularly calibrated. The cuff size was adapted to arm circumference. Heart rate (HR) was recorded from a diagnostic 6-lead electrocardiogram with multi-lead arrhythmia alarm. BP was measured in both arms in the supine and both lateral recumbent positions (Figure 1). The patients rested for 3 minutes after a change in position before a new measurement took place. The order of lateral turning was determined by coin toss. In the lateral position the back was supported by a firm pillow with the head resting on one pillow. The uppermost arms rested on the patients' flank, and the lowermost arm rested on the mattress. The term supine is used with the patient on the back with both arms positioned at the phlebostatic level.

Figure 1



Overview of main Mean Arterial Pressure (MAP) differences in patients with right-sides (n = 35) and left-sides (n = 19)-sided deficits in the three body positions (supine (Sup), left lateral decubitus (LLD), and right lateral decubitus (RLD)) with changing of blood pressure (BP) cuff (left or right arm). Values between brackets represent corrected MAP differences (cΔ) after adding covariates to the model.

Statistical analysis

The outcomes in this study were MAP, SBP, DBP, HR (beats per minute (bpm)) and peripheral oxygen saturation (%) in each position. Values are presented as means ± standard error (SE) unless presented otherwise. In a two-level model the body positions (supine, left lateral decubitus or right lateral decubitus) and cuff side (left arm or right arm) were evaluated. A multilevel model was chosen because measurements were nested in patients. The effects of the covariates age, sex, NIHSS, Oxford stroke classification, history of hypertension, cardiac disease, and atrial fibrillation were evaluated. The covariate age was centred at 37 years. A value of $p < 0.05$ was considered to indicate a significant effect. SPSS (16.0; SPSS Inc, Chicago, IL) was used for statistical analysis. Bonferroni adjustments for multiple comparisons were used in all the presented results.

We performed a literature search using PubMed. A combination of the key words ‘blood pressure’ or ‘vital parameters’ and ‘lateral body position’ or ‘body position’ or ‘recumbent body positions’ or ‘lateral decubitus position’ was used.

RESULTS

Fifty-four patients were included. Thirty-five patients had right-sided deficits and 19 had left-sided deficits. All patients had 18 measurements. Data on 31 measurements were incomplete or missing. Baseline characteristics are summarized in Table 1 and were comparable for both sides of deficit. Twenty-six patients (48%) were taking antihypertensive medication on admission, most of them because of a history of hypertension (39%). Table 2 shows the hemodynamic readings at different body and cuff positions in relation to side of deficit. The 35 patients with right-sided deficits had lower MAP recordings than the 19 with left-sided deficit (difference, 7.4 mmHg (4.0); $p = 0.07$; Figure 1, A). Both HR (2.1 bpm (3.6); $p = 0.58$) and oxygen saturation (0.47% (0.5); $p = 0.30$) were similar.

In both those with left- and those with right-sided deficit, the MAP – with HR and oxygen saturation – was not different in both arms in the supine position ($p = 0.1$; Figure 1, B and C). The supine MAP recordings were lower in the patients with right-sided deficits compared to the patients with left-sided deficits (estimate 5.2 mmHg (4.1); $p > 0.99$). The supine HR and oxygen saturation were not different (0.88 bpm (3.6); $p > 0.99$ and 0.65% (0.47); $p > 0.99$) between the two groups of patients.

Studying both lateral decubitus positions, the MAP in patients with a right-sided deficit was 17.6 (1.0) mmHg higher in the right lateral decubitus position with the cuff on the right arm (right lowermost arm) than in the left lateral decubitus position with the cuff on the right arm (right uppermost arm; $p < 0.001$; Figure 1, D) and 11.8 mmHg (1.0) higher in the left lateral decubitus position with cuff on the left arm (left lowermost arm) than in the right lateral decubitus position with the cuff on the left arm (left uppermost arm; $p < 0.001$; Figure 1, E). For the group with a left-sided deficit these numbers amounted to 18.8

Table 1 Patient characteristics

Variable	Total (n = 54)	Right side affected (n = 35)	Left side affected (n = 19)	P value
Mean age (SD), y	69 (15)	71 (14)	67 (17)	0.35
Male	33 (61)	24 (69)	9 (47)	0.15
Baseline median NIHSS score [IQR]	8 [4-12]	8 [5-12]	7 [4-12]	0.39
History of hypertension	21 (39)	16 (46)	5 (26)	0.25
Cardiac disease	11 (20)	7 (20)	(21)	>0.99
Atrial fibrillation	5 (9)	4 (11)	1 (5)	0.64
Oxford LACI PACI TACI POCI	13 (24) 25 (46) 8 (15) 8 (15)	5 (14) 18 (51) 6 (17) 6 (17)	8 (42) 7 (36) 2 (11) 2 (11)	0.16
Diabetes Mellitus	11 (20)	6 (17)	5 (26)	0.49
Antihypertensive medication	26 (48)	18 (51)	8 (42)	0.58
Mean systolic blood pressure (SE) on stroke unit, mmHg	139 (4)	132 (4)	147 (5)	0.04
Mean diastolic blood pressure on stroke unit (SE), mmHg	66 (2)	63 (2)	68 (3)	0.21

Values are numbers (%), unless otherwise indicated. *P* values are not adjusted for multiple comparisons.

Abbreviations: SD indicates standard deviation; SE, standard error; IQR, interquartile range; NIHSS, national institutes of health stroke scale; TACI/PACI/LACI/POCI total/partial anterior circulation/lacunar infarction/posterior circulation infarction.

mmHg (1.2; $p < 0.001$) and 11.4 mmHg (1.3; $p < 0.001$), respectively (Figure 1 F and G). The MAP in the left lateral decubitus position with the cuff on the right arm and right lateral decubitus position with the cuff on the left arm (both uppermost arms) were not different for both sides of deficit (0.3 mmHg (1.0), $p > 0.99$; and 1.7 mmHg (1.2), $p > 0.99$), yet the MAP in the left lateral decubitus position with the cuff on the left arm (left lowermost arm) was significantly lower than in the right lateral decubitus position with the cuff on the right arm (right lowermost arm; 6.1 mmHg (1.0), $p < 0.001$; and 6.0 mmHg (1.3), $p < 0.001$). Comparable results were found using SBP and DBP recordings (Table 2).

Significantly lower HR were found in the left lateral decubitus position compared to the right lateral decubitus position (both groups, 1.3 bpm (0.4); $p = 0.03$) and compared to the supine position only for the patients with right sided deficits (1.9 bpm (0.3); $p < 0.001$). Only for patients with left-sided deficits, oxygen saturation was significant lower in the left lateral decubitus position compared to the right lateral decubitus position (0.7% (0.2); $p < 0.001$). Adding covariates to the model did not change the results for all variables (for MAP, Figure 1).

Table 2 Absolute levels of Mean Arterial Pressure, Systolic and Diastolic Blood Pressure, Heart Rate and Saturation level in various body positions separated for affected side

Body position and cuff side	Right side affected (n = 35)					Left side affected (n = 19)				
	MAP (SE)	Systolic BP (SE)	Diastolic BP (SE)	HR (SE)	Sat (SE)	MAP (SE)	Systolic BP (SE)	Diastolic BP (SE)	HR (SE)	Sat (SE)
Supine with cuff on the left arm	82.9 (2.5)	132.5 (7.4)	68.4 (4.6)	75.2 (2.2)	97.3 (0.3)	88.4 (3.3)	148.2 (8.1)	71.4 (5.1)	75.5 (2.9)	96.8 (0.4)
Supine with the cuff on the right arm	83.7 (2.5)	136.7 (7.4)	68.2 (4.6)	74.8 (2.2)	97.3 (0.3)	88.6 (3.2)	147.2 (8.1)	72.3 (5.1)	76.3 (2.9)	96.5 (0.4)
Left lateral decubitus with the cuff on the left arm	82.2 (2.5)	131.1 (7.4)	67.7 (4.6)	72.5 (2.2)	96.8 (0.3)	90.8 (3.3)	149.7 (8.1)	74.0 (5.1)	76.2 (2.9)	96.2 (0.4)
Left lateral decubitus with the cuff on the right arm	70.7 (2.5)	122.3 (7.4)	55.8 (4.6)	73.7 (2.2)	96.7 (0.3)	78.0 (3.3)	137.5 (8.1)	59.9 (5.1)	75.1 (2.9)	96.2 (0.4)
Right lateral decubitus with the cuff on the right arm	88.3 (2.5)	139.7 (7.4)	72.5 (4.6)	74.3 (2.2)	97.2 (0.3)	96.8 (3.3)	157.7 (8.1)	79.0 (5.1)	77.3 (2.9)	96.8 (0.4)
Right lateral decubitus with the cuff on the left arm	70.4 (2.5)	119.2 (7.4)	55.4 (4.6)	74.3 (2.2)	97.0 (0.3)	79.7 (3.3)	138.0 (8.1)	63.9 (5.1)	77.0 (2.9)	97.0 (0.4)

Abbreviations: BP indicates blood pressure; HR, heart rate; MAP, mean arterial pressure; Sat, saturation; SE, standard error.

DISCUSSION

In the stroke unit, patients are often monitored in alternating lateral decubitus positions either spontaneously or as part of commonly used nursing protocols. These alternating lateral decubitus positions lead to major fluctuations in BP readings. Moreover, this effect seems to be muted when patients are measured in the left lateral decubitus position with the cuff on the left arm (left lowermost arm). Change of BP reading in lateral decubitus positions does not seem to be affected by side of deficit. HR and oxygen saturation were slightly lower in left lateral position.

We were able to compare our results with 19 published studies (Table 3). All these studies were in nonstroke patients. Some of them lack data on the comparison of the two lateral decubitus positions or they lack measurements in both arms. Only 11 studies provide information about the angle of inclination. For all intraarterial BP studies, transducer height adaptations for the lateral positions are not clear. In the article of Bein et al, critically ill patients with intraarterial BP lines in the left or right brachial arteries were compared in the lateral decubitus positions with the difference possibly explained by a selection bias.¹⁴ Eventually, we were able to compare our results with five studies concerning cardiac, hypertensive or healthy subjects.¹⁵⁻¹⁹ In accordance with these studies, the BP difference

Table 3 Effect of lateral decubitus position on Blood Pressure measurements

Study	No of patients	Category of patients	Type of measurement	Both arms measured (in one patient)	
Foley, 1971 ¹⁵	60	Unanaesthetised and anaesthetized healthy subjects	Brachial cuff (auscultation method) or Intraarterial (with hydrostatic correction)	Yes	
Newton, 1981 ¹⁶	13	PTCA patients	Brachial cuff (ultrasound method) or Intraarterial (both with hydrostatic correction)	Yes	
Kirchhoff et al, 1983 ²³	29	Cardiac patients	Intraarterial (with hydrostatic correction)	Unknown	
Emerson et al, 1994 ¹⁷	120	CABG patients	Brachial cuff (oscillometric method)	Yes	
Hallak et al, 1997 ²⁴	30	Pregnant women	Brachial cuff (mercury method)	Yes	
Bein et al, 1996 ¹⁴	12	Critically ill patients	Intraarterial (with hydrostatic correction)	Yes	
Fujise et al, 1998 ²⁵	15	Urologic surgical patients (during operation)	Intraarterial (with hydrostatic correction)	No	
Cavelaars et al, 2000 ²⁶	16	Hypertensive healthy patients	Brachial cuff (oscillometric method)	No	
Van der Steen et al, 2000 ¹⁸	40	Hypertensive/ healthy patients	Brachial cuff (oscillometric method)	Yes	
Schou et al, 2001 ²⁷	12	Healthy subjects	Brachial cuff (aneroid method) and Finapres recording (with hydrostatic correction)	No	
Pump et al, 2002 ²⁸	8	Healthy subjects	Brachial cuff (oscillometric method, with hydrostatic correction)	No	
Kinsella et al, 2006 ²⁹	32	Pregnant women	Brachial cuff (mercury and oscillometric method)	Yes	
De Laat et al, 2007 ³⁰	55	CABG patients	Intraarterial (with hydrostatic correction)	Unknown	
Jones et al, 2004 ³¹	32	Healthy subjects	Brachial cuff (oscillometric method)	Yes	
Clochesy, 1986 ¹⁹	10	Healthy subjects	Brachial cuff (oscillometric method)	Yes	
Stein, 1952 ³²	100	Cardiovascular disease	Unknown	Unknown	
Thomas et al, 2007 ³³	34	Critically Ill patients	Intraarterial (hydrostatic correction not clear)	No	
Gordon et al, 2009 ³⁴	26	Healthy elderly	Brachial cuff (aneroid method)	No	
Almeida et al, 2009 ³⁵	11	Pregnant women	Brachial cuff (mercury method)	No	

Abbreviations: CABG indicates coronary artery bypass graft; MAP, mean arterial pressure; PTCA, percutaneous trans coronary angiography; BP blood pressure (systolic and diastolic).

* Uppermost arm: The arm opposite to the patients' lateral decubitus position.

Lowermost arm: The arm on the same side of the patients' lateral decubitus position.

	Cuff on uppermost (U)* or Lowermost (L) arm #	Main conclusion (BP or MAP U/L compared to supine, unless indicated otherwise)
	U and L	In the lateral positions, BP decreased in all patients in both U arms (> 10 mmHg). On average, BP increased slightly in L arms in the lateral position, but varied considerably among patients
	U and L	Hydrostatic effects were the most likely cause of the drop in both U arms BP (14 mmHg; inclination 90°). Both L arms BP were lower than expected
	Unknown	In stable cardiac patients, the MAP for the supine and lateral position were comparable
	U and L	BP was significant lower in both U arms (4 mmHg) and higher in both L-arms (3 mmHg; inclination 45°)
	U and L	BP in the L arms was comparable to U arms, indicating that hydrostatic pressure does not account for these changes in pregnancy
	L	The MAP was lower in the right lateral (> 13 mmHg) compared to supine and left lateral position. (inclination 63°)
	Unknown	The MAP of 8 patients in the right lateral position (inclination 70° to 80°) was higher than the MAP of 7 patients in the left lateral position during urological surgery. No measurements in the supine position
	U and L	The MAP in the U arms was significant lower (> 10 mmHg) than measured in the supine or L arm position
	U and L	In both groups, the MAP in both U arms was significant lower (16 mmHg) and higher (4 mmHg) in both L arms in the lateral position (inclination 90°)
	Unknown	The MAP in the left lateral position was not different compared to the supine recordings taken after 30 minutes
	U	The MAP in the U arm decreased significantly in the left lateral position (5 mmHg) compared to supine position
	U and L	The MAP in the U arm was lower (10 mmHg), and higher (6 mm Hg) in the L arm compared to supine. Only measurements in right lateral position (inclination 90°)
	Unknown	The MAP does not significant change (< 5 mmHg) much in the lateral position (inclination 30°)
	U	BP in U arms decreased significantly (> 10 mmHg) in both lateral position (inclination 90°), more evident in the left lateral position
	U and L	BP in the both U-arm is significantly lower in both lateral positions (inclination 35° to 45°). The BP in the L arm is only slightly lower (2 mmHg) in the left lateral position
	Unknown	The MAP was found to be around 20 mmHg lower in the left lateral than in the sitting, supine and right lateral position, respectively
	Not clear	The MAP remained stable in the 90° lateral positions
	U	The MAP of U arms was significant lower in both lateral 90° positions. No difference between right and left lateral recordings
	U	Systolic and diastolic BP is significant lower in the left lateral position

between both lateral decubitus positions while leaving the right cuff in position in our study is explained by the change in hydrostatic pressure.

Measurements of BP in the lateral decubitus position results in a lower BP reading at the arm in top position (left lateral decubitus position with cuff on the right arm) and a higher BP reading in the lower arm (right lateral decubitus position with the cuff on the right arm). Several studies have shown that BP differences caused by a change of the arm relative to that of the right atrium correlate with differences in hydrostatic pressure.⁷⁻⁹ The five studies we retrieved from the literature, however, do not report significant differences between BP readings between both arms in the lateral decubitus position. We are the first to report significantly lower BP recordings in the left lateral decubitus position with the cuff on the left arm (left lowermost arm) in a group of stroke patients, regardless of side of deficit. Although the study was conducted in a small heterogeneous population admitted on the stroke unit and full standardisation of posturing was difficult, measurements had only small statistical errors and seemed consistent across the range. Comparing our cohort with stroke unit effectiveness trial cohorts revealed a slightly lower prevalence of history of hypertension in our patients.²⁰ We found similar BP recordings in both uppermost arms (left lateral decubitus position with cuff on right arm compared to right lateral decubitus position with cuff on the left arm) and no major changes in HR and saturation. Heart displacement (with change of hydrostatic level) or compression, and different autonomic postural states are therefore unlikely explanations.²¹ A study concerning sleep position dimensions across age groups revealed a clear preference for the right side in elderly patients.²² Discomfort or altered cardiovascular functions were suggested. Postural compression of vascular structures in the left arm or shoulder region attenuated by a stroke may be hypothesized but, to our knowledge, are not supported by any literature. Further investigations will be required. In order to improve correct indirect BP measurements in stroke patients, it is important to recognise substantial hydrostatic pressure effects in lateral decubitus positions.⁸ Treatment decisions regarding optimal perfusion pressure should take these sources of BP variation into account. Practical advices for correct BP monitoring, including alternating lateral decubitus positions, should be added to BP monitoring guidelines. Moreover, every study reporting BP values should ideally mention body, arm and cuff (or intraarterial line, with or without height correction) position.

In conclusion, we recommend performing indirect BP measurement in stroke patients in the back supine position. In case of frequent turning, we suggest measurements on the right arm while taking into account the hydrostatic effects for optimal lateral decubitus BP readings.

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CHAPTER 6

INTRAARTERIAL BLOOD PRESSURE READING IN INTENSIVE CARE UNIT PATIENTS IN THE LATERAL POSITION

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ABSTRACT

Background

Routine lateral turning of patients has become an accepted standard of care to prevent complications of immobility. The hemodynamic and oxygenation effects for patients in both lateral positions (45°) are still a matter of debate. We aimed to study the effect of these positions on blood pressure, heart rate and oxygenation in a general intensive care population.

Design

Observational study.

Method

Twenty stable intensive care unit patients with intraarterial blood pressure recordings in the supine and lateral positions with correction of hydrostatic height compared to a fixed reference point (phlebostatic level). A multilevel model was used to analyse the data.

Results

Mean arterial pressure readings in the lateral positions were, on average, 5 mmHg higher than in the supine position ($p < 0.001$). There were no significant differences between MAP recordings in the left and right lateral position ($p = 1.0$). No important differences in peripheral oxygenation saturation and heart rate were observed. After correction for covariates, the effects persisted.

Conclusions

Our study demonstrated an increase, albeit small, of blood pressure in the lateral positions. No major differences between the left and right lateral position were found. No important differences in oxygenation and heart rate were observed.

Relevance to clinical practice

Turning hemodynamically stable patients in the intensive care has no important effects on blood pressure measurements when continuous hydrostatic height correction is applied.

INTRODUCTION

Critically ill patients in the intensive care unit (ICU) are at high risk for complications of immobility such as pneumonia and pressure ulcers.^{1,2} Routine lateral turning of patients has become the standard of care to prevent these complications. Whenever blood pressure (BP) is measured in varying body positions, the location on a vertical axis of BP measurement compared to the right atrium (RA) needs to be accounted for. This need for hydrostatic height correction in ICU invasive BP measurements is generally recognised.³ However, whether lateral turning has hemodynamic and oxygenation effects beside these hydrostatic effects is still partly unclear. Several studies found contradictory effects of turning in different patient groups. In 1951, Stein introduced the term 'left lateral hypotension' syndrome,⁴ and in 1996 Bein et al. advised to avoid the hypotensive right lateral position in critically ill patients.⁵ Different hemodynamic or physiological explanations including hydrostatic, mechanical, hormonal or body side-specific sympathetic nervous modulations were suggested.⁵⁻⁷

Our objective was to quantify the hemodynamic (intraarterial (IA) BP, heart rate (HR)) and peripheral oxygenation saturation effects of 45° lateral turning in a general stable ICU population.

METHODS

Study participants

This observational prospective study was conducted in the 47-bed mixed ICU with 2900 admissions per year in a 1300-bed tertiary referral hospital with transplant, trauma, neurosurgical and thoracic programs. Twenty patients were included in the period June till August 2009. Demographic data, vascular risk factors, sedation, side of IA line, ventilation conditions and medication (analgesics, vasopressors and antihypertensives) were recorded. Exclusion criteria were a diagnosis of (severe) traumatic brain injury or subarachnoid haemorrhage, hemodynamic instability (systolic BP < 90 mmHg and/or mean arterial pressure (MAP) < 60 mmHg), cardiac dysrhythmias, difficult ventilation (plateau pressures above 25-cm H₂O and inspired oxygen fraction > 0.5), inability to lie in the lateral body position, restlessness or delirium, and a left-right arm difference of MAP > 8 mmHg (mean value of three brachial cuff measurements) in the supine back position. The study was approved by the local medical ethical committee.

Invasive BP recordings with transducer reference

The BP values were obtained from a bedside IA BP monitor (model Philips Intellivue MP70; Philips Medical Systems, Best, The Netherlands). This monitor displays electrocardiogram (ECG), arterial waveforms, systolic and diastolic pressures, MAP and HR measurements. The MAP was determined by time averaged mean calculation. The monitors are routinely

calibrated. In all patients, a 20-gauge catheter was placed in the radial artery and connected to a pressure tubing with a physiological transducer that was electrically connected to the monitor. The transducer was fixed to the bed. The RA was considered as the reference point for the transducer (continuous hydrostatic height correction). In the supine position, the RA level was consistently measured at the phlebostatic level, the junction between the transverse plane of the body along the fourth intercostal space and the midline between the anterior and posterior chest (coronal plane). No alterations of the transducer level were made in the lateral positions. The monitor was zeroed at atmospheric pressure and electronically calibrated at bedside before every measurement. The arterial waveform was observed for artefact or dampening. A finger pulse oximeter (Massimo SET, Intellivue model; Philips Medical Systems) was used to obtain continuous arterial oxygenation levels. All measurements were carried out by first and second author of this manuscript.

Body positions

The patients were studied in the supine and lateral body positions. In one patient, supine recordings were not possible because of painful sacral decubitus. The patients rested for 3 minutes after a change in position before the measurements. In the lateral position (45°) the back was supported by a wedge shaped firm pillow with the head resting on one soft pillow. The uppermost arm rested on the patient's flank, and the lowermost (dependent) arm rested on the mattress. When supine, both arms rested on the mattress. The order of lateral turning was determined by coin toss. The next ten values were recorded for systolic and diastolic BP, MAP, HR and peripheral oxygen saturation. If patients were mechanically ventilated, the recordings were all done at the end-expiratory stage.

Statistical analysis

The outcomes in this study were BP, expressed as MAP, systolic and diastolic BP (mmHg), HR (beats/minute) and oxygenation (%) in each position. The primary outcome was MAP. Values are presented as means \pm standard error (SE). Because of nested measurements in patients, a multilevel model was employed evaluating the effects of different body positions (supine, right lateral and left lateral) with and without accounting for side of IA line. Age, sex, history of hypertension and cardiac disease, positive end expiratory pressure (PEEP), morphine and BP medication were incorporated as covariates. The covariate age was centered at 37 years. A value of $p < 0.05$ was considered to indicate a significant effect. SPSS 16.0 was used for statistical analysis. Bonferroni adjustments were used for all multiple comparisons. Taking into account inaccuracy of BP measurements and possible effects of different arm (body) positions with fixed transducer level, we considered a MAP difference of less than 10 mmHg due to position change as clinically unimportant.^{8,9}

Results

Twenty patients were included. The clinical characteristics are given in Table 1. Nine patients had a right-sided IA line. These patients had more noradrenalin support and administration of morphine, and higher HRs compared to patients with left IA line. Ten patients were ventilated during the measurements. Table 2 shows the mean hemodynamic absolute values in the three body positions. MAP readings in the lateral positions were, on average, 4.5 mmHg higher than in the supine position ($p < 0.001$). There were no significant differences between MAP recordings in the left and right lateral position ($p = 1.0$). The systolic BP increased more than 5 mmHg in the lateral positions ($p = 0.001$), with no significant difference between both lateral positions ($p = 1.0$). The effects were less pronounced for the diastolic BP. The HR

Table 1 Patient characteristics

	Total N = 20	IA line right n = 9	IA line left n = 11	P value
Male (%)	13 (65)	7 (78)	6 (55)	0.28
Age (y), mean (SD)	59 (12)	61 (11)	58 (13)	0.63
Ventilation (%)	10 (50)	4 (44)	6 (54)	0.65
Inspiration pressure, mean (SD) *	15 (3)	9 (9)	9 (8)	0.98
PEEP, mean (SD) *	7 (1)	4 (4)	4 (4)	0.78
Oxygen support, mean (SD) *	43 (13)	41 (18)	37 (18)	0.68
Noradrenalin support (%)	6 (30)	5 (56)	1 (9)	0.02
Morphine (%)	11 (55)	8 (89)	3 (27)	0.01
Propofol (%)	4 (20)	1 (11)	3 (27)	0.37
Midazolam (%)	4 (20)	2 (22)	2 (18)	0.82
Epidural anaesthesia (%)	3 (15)	1 (11)	2 (18)	0.66
BP medication (%)	10 (50)	4 (45)	6 (55)	0.65
History of hypertension (%)	7 (35)	5 (56)	2 (18)	0.08
History of cardiac disease (%)	6 (30)	4 (44)	2 (18)	0.20

Data represent numbers (percentages) or mean (standard deviation).

* n = 10 (ventilated patients).

Abbreviations: SD indicates standard deviation; IA, intraarterial; BP, blood pressure; PEEP, positive end expiratory pressure.

Table 2 Mean absolute values (SE) during different body positions

Parameter	Supine	Right Lateral	Left Lateral
MAP (mmHg)	80.8 (3.1)	85.3 (2.9)	85.2 (3.1)
Systolic BP (mmHg)	124.1 (4.9)	129.3 (4.8)	130.8 (5.2)
Diastolic BP (mmHg)	60.2 (2.5)	64.7 (2.4)	63.5 (2.4)
Heart rate (beats/minute)	96.1 (3.9)	97.2 (3.7)	94.2 (3.8)
Oxygenation (%)	97.1 (0.4)	97.1 (0.3)	97.2 (0.5)

Abbreviations: SE indicates standard error; MAP, mean arterial pressure; BP, blood pressure.

decreased two bpm in the left lateral position compared to supine ($p = 0.37$), and three beats/minute compared to right lateral position ($p = 0.06$). No significant changes in oxygenation levels between the three positions were seen (all $p = 1.0$). Because the covariate analysis had similar results, only the univariate analysis is shown. Table 3 shows the mean hemodynamic absolute values in the three body positions for patients with the IA line on the right or left side. For right IA line patients the effects of turning on BP values diminished but increased for left IA line patients with significantly higher values in both lateral positions. Comparable responses for HR and saturation were observed in both patient groups.

DISCUSSION

Our study shows that intraarterial BP recordings in the (45°) lateral positions are higher by around 5 mmHg in a stable ICU population, with no differences between measurements on the left or right lateral side. No clinically important changes for HR and oxygenation were observed in the different positions. Our results are in line with two small cardiac studies and one with hemodynamically unstable patients.^{10, 11}

In these studies, no clinically important hemodynamic changes in the lateral position were observed, yet it was unclear, unfortunately, whether both lateral positions or both arms were measured (Table 4).^{10, 11} Likewise, Bein et al. found a 13 mmHg lower mean MAP in the right lateral position (inclination 63°) but it remains unclear whether only the dependent (lowermost) arm was used for comparison.⁵ The reported differences may be fully explained by different patient characteristics instead of posture or body side specific effects. Fujise et al. compared the hemodynamic changes during laparoscopic urological surgery between eight patients in the right and seven in the left lateral position. Different baseline measurements

Table 3 Mean hemodynamic absolute values (SE) during different body positions concerning side of IA line

Position	Right IA line (n = 9)	Left IA line (n = 11)
MAP		
Supine	80.3 (4.9)	81.3 (3.7)
Left lateral	82.2 (5.0)	88.3 (3.7)
Right lateral	83.2 (4.5)	87.3 (3.6)
Systolic BP		
Supine	121.2 (7.2)	127.0 (7.0)
Left lateral	124.9 (7.9)	136.8 (6.8)
Right lateral	124.7 (6.5)	133.9 (7.1)
Diastolic BP		
Supine	62 (4.4)	58.5 (2.5)
Left lateral	63.5 (4.3)	63.4 (2.2)
Right lateral	64.4 (4.0)	65.0 (2.6)
Heart rate		
Supine	104.4 (5.5)	87.9 (5.5)
Left lateral	102.0 (4.9)	86.4 (5.9)
Right lateral	105.1 (5.0)	89.4 (5.4)
Saturation		
Supine	96.9 (0.6)	97.4 (0.5)
Left lateral	97.3 (0.6)	97.1 (0.7)
Right lateral	97.4 (0.4)	96.8 (0.5)

Abbreviations: SE indicates standard error; IA, intraarterial; BP, blood pressure; MAP, mean arterial pressure.

and different responses to induced pneumoperitoneum were observed. Insufficient patient characteristics were presented to determine whether these observations were related to patient characteristics or body position.¹² Stein found that the average systolic BP was 22 mmHg lower in the left lateral than the sitting, supine or right lateral positions of 100 patients. However, an unequal distribution of side of IA lines without height correction could fully explain these clinically important differences.⁴

Some limitations of this study deserve mentioning. Firstly, the study had a small sample size. While this generally limits sensitivity and generalisability of the study results, the small standard errors render it unlikely that clinically important effects were missed. Secondly, an angle of inclination was chosen that was different from previous studies (Table 4). While that makes comparison to previous studies difficult, the angles of inclination chosen represent the effects of turning as carried out in daily practice.

Blood pressure measurement is one of the most frequently performed clinical procedures

Table 4 Effect of lateral position on IA blood pressure measurements

Study	No of patients	Category of patients	Type of measurement	Both arms measured (in one patient)	Uppermost (U) or lowermost (L) arm	Main conclusion (blood pressure or mean arterial pressure U/L compared to supine, unless indicated otherwise)
Kirchhoff et al. 1983 ¹⁰	29	Cardiac patients	Intraarterial (with hydrostatic correction*)	Unknown	Unknown	In stable cardiac patients, the MAP for the supine and lateral position were comparable
Bein et al. 1996 ⁵	12	Critically ill patients	Intraarterial (with hydrostatic correction*)	Yes	L	The MAP was lower in the right lateral (> 13 mmHg) compared to supine and left lateral position (inclination 63°)
Fujise et al. 1998 ¹²	15	Urologic surgical patients (during operation)	Intraarterial (with hydrostatic correction*)	No	L	The MAP of 8 patients in the right lateral position (inclination 70° to 80°) was higher than the MAP of 7 patients in the left lateral position during urological surgery. No measurements in the supine position
Laat de et al. 2007 ¹³	55	CABG patients	Intraarterial (with hydrostatic correction*)	Unknown	Unknown	The MAP does not significant change (< 5 mmHg) much in the lateral position (inclination 30°)
Stein P 1952 ⁴	100	Cardio-vascular disease	Intraarterial (hydrostatic correction not clear)	Unknown	Unknown	The MAP was found to be around 20 mmHg lower in the left lateral than in the sitting, supine and right lateral position, respectively
Thomas et al. 2007 ¹¹	34	Critically ill patients	Intraarterial (hydrostatic correction not clear)	No	Not clear	The MAP remained stable in the 90° lateral positions

Abbreviations: CABG indicates coronary artery bypass graft; MAP, mean arterial pressure; BP, blood pressure (systolic and diastolic); IA, intraarterial.

* Hydrostatic correction: as blood flows vertically from the heart, there will be a reduction in arterial pressure that is related to the weight of a column of blood. Hydrostatic (height) correction is to compensate for the BP IA line position (arm) with respect to the heart (right atrium) level.

on the ICU to guide optimal perfusion therapy. With the transducer for hydrostatic correction continuously fixed at around the right atrial level the BP in our study shows acceptable changes. These absolute changes are comparable with IA recordings in a small group of supine healthy volunteers in whom the position of the arm above and below the fixed transducer were varied.⁹

CONCLUSION

For daily practice with routine turning of hemodynamically stable ICU patients, no clinically important changes of BP in the lateral positions are encountered. Our results show no major differences between the left and right lateral position. Also, no important differences in oxygenation and HR were observed. Comparison with previous literature suggests that hemodynamic effects may vary with hemodynamic status of patient groups which may explain observations in the past.

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CHAPTER 7

EXAGGERATED POSTURAL BLOOD PRESSURE RISE IS RELATED TO FAVORABLE OUTCOME IN PATIENTS WITH ACUTE ISCHEMIC STROKE

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ABSTRACT

Background and purpose

The effects of early upright positioning in the acute phase of ischemic stroke on both blood pressure and functional outcome have not been previously examined.

Methods

Prospective investigation of mean arterial pressure, heart rate and peripheral oxygen saturation in the supine, sitting and (if achievable) active standing position 1, 2 and 3 days after an acute stroke was performed. Also investigated was the presence of significant postural BP rise and fall using orthostatic definitions and the relation to functional outcome after 3 months.

Results

One hundred sixty-seven patients were included (mean age, 68.5 ± 15.2 years; median National Institutes of Health Stroke Scale, 7). About 60% of the patients were able to stand. On average the mean arterial pressure increased when patients moved from the supine to sitting (Day 1: $\Delta 3.9$ mmHg; $p < 0.001$) and from sitting to an active standing position (Day 1: $\Delta 4.6$ mmHg; $p < 0.001$). Changes were most pronounced within the first 24 hours after stroke. Blood pressure decreased significantly (fall) upon standing in 13% of patients and increased significantly (rise) in 20% of the patients. The latter was independently associated with favorable outcome ($p = 0.003$). Moving to the standing position was accompanied by an increase of heart rate. No difference in peripheral oxygen saturation was observed in the various positions over the period of investigation.

Conclusions

We found that a significant blood pressure rise during early upright positioning in acute stroke patients was independently associated with favorable outcome. No contraindication to early mobilization was found in this study.

INTRODUCTION

Early mobilization and rehabilitation (in and out of bed) is increasingly applied in the setting of acute stroke, although largely based on low levels of evidence.¹² Such early mobilization may prevent venous thrombosis, cardiopulmonary deconditioning, and may improve early plasticity of the brain.³⁻⁵ However, it may also increase metabolic demands of the damaged brain and decrease penumbral perfusion. Especially, the upright positioning in the setting of early mobilization after stroke may be detrimental to perfusion.⁶ In healthy subjects, upright positioning leads to a transient period of decreased blood pressure (BP; < 30 seconds), but intact cerebral autoregulation maintains a constant cerebral perfusion through increased cardiac output and cerebral vasodilatation.⁷ In acute stroke patients however, the responses to upright positioning may be disturbed due to (1) diminished or overactive cerebral autoregulation;⁸ (2) ischemic lesions that disturb autonomic nervous function;⁹ and (3) a potential correlation between stroke and orthostatic hypotension through shared risk factors such as old age, diabetes, and the use of antihypertensive medication.

There is increasing evidence that disturbed cerebral autoregulation affects the outcome of stroke, especially in the setting of cervical artery disease.¹⁰ Also, various strategies in the stroke unit are geared towards monitoring and optimizing physiological parameters, partly in an attempt to salvage penumbra.^{11,12} However, there is only 1 study that reports BP responses to upright positioning in acute stroke patients.¹³ That study reports a 10% rate of postural hypotension in acute stroke patients, yet BP increases upon upright positioning in most patients. The relation to outcome is not addressed. It is unclear how postural changes in hemodynamic parameters affect the average patient in the acute stroke unit, when mobilized to the upright position within 24 hours of symptom onset. The aim of our study was to address how changes in physiological parameters upon upright positioning affect outcome after 3 months of an acute stroke.

METHODS

Patients

This study was conducted in the stroke unit of a large teaching hospital from August 2008 to June 2010. Inclusion criteria were the diagnosis of an acute stroke, age > 18 years, and admission to the stroke unit within 24 hours. Exclusion criteria were decrease of consciousness, decreased cooperation, hemodynamic instability, and fever. Baseline stroke work-up with baseline brain Computed Tomography (CT) scanning, electrocardiogram, duplex carotid ultrasound and laboratory investigation were performed. Use of any medication, especially anti-arrhythmic and antihypertensive medication, were registered. Discontinuation of preadmission antihypertensive medication was registered. Initial and follow-up stroke severity was assessed with the National Institute of Health Stroke Scale (NIHSS). The stroke

subtype was classified using the Oxfordshire Community Stroke Project classification.¹⁴ Functional outcome at 3 months was assessed with the modified Rankin Scale by a trained person blinded to BP data.¹⁵ A favorable outcome was defined as a modified Rankin Scale score ≤ 1 . The study was approved by the local medical ethics committee.

Measurements

Measurements of vital parameters in the different body positions were performed in a standardized fashion by a single physician. The first postural measurements were taken a few hours after admission in the stroke unit (Day 1, < 24 hours after ictus). BP and heart rate (HR) readings were taken with an automatic oscillometric device (Philips Intellivue MP30 monitor, Philips Medical Systems, Best, The Netherlands). This BP device measures oscillations from the blood vessel wall during bladder deflation. The pressure at which the oscillations are at a maximum is defined as mean arterial pressure (MAP). The device then calculates systolic blood pressure (SBP) and diastolic blood pressure (DBP) with an unknown patented algorithm. Continuous peripheral oxygen saturation (SpO₂) monitoring was performed with the Intellivue MP30 device with the Fourier Artifact Suppression Technology (FAST) algorithm. The aim was to repeat the measurements at Days 2 and 3 at the same time of the day. Potential confounders for correct BP recordings were avoided,¹⁶ the instruments were regularly calibrated, and the size of the bladder within the cuff was adapted to arm circumference.

Body positions

To mimic the stroke unit mobilisation process patients were always brought in the sitting position first before carefully moving to the active standing position. Stroke patients who were unable to stand independently or with minimal help (e.g., because of their neurological deficits) were not investigated in the standing posture. The ability to stand was evaluated daily. Hypotensive symptoms during the sitting or standing phases were noted. In both sitting and standing positions the cuff was positioned close to the armpit approaching the level of the right atrium. In the supine position, the arm used for BP measurement was routinely supported by a pillow to keep it halfway the distance between the sternum and the bed. In the sitting position the patient was upright in bed (approximately 70°) with the legs in the horizontal position. Both arms were depending besides the thorax with the forearms in the lap. In the standing position, the arms were depending next to the body.

Measurements

After 3 minutes of supine rest the supine BP was measured twice bilaterally to screen for important (> 8 mmHg) differences between both arms, in which case patients were excluded. The 4 supine BP readings were averaged. The cuff was left on the arm with the mean highest supine value. Three separate measurements were then averaged after 3 minutes of rest in the sitting position. This procedure was then repeated with the subjects in the standing

position. The incidence of significant postural fall as defined by ≥ 20 mmHg systolic or ≥ 10 mmHg diastolic drop was determined by calculating the difference between standing after 3 minutes and supine values. Similarly significant postural rise was defined as a systolic increase of ≥ 20 mmHg.¹⁷ HR and SpO₂ were also measured in the 3 positions.

Statistical analysis

It was calculated (paired means) that around 150 subjects were needed to detect a within group BP change of > 5 mmHg with a power of 80% at the 5% significance level, given that the standard deviation (SD) of the supine to standing systolic BP difference in elderly hospitalized stroke patients is ≥ 20 mmHg.¹³ The outcomes in this study were MAP, SBP, DBP (all mmHg), HR (beats/minute), and SpO₂ (%) in each position. Values are presented as means \pm standard error (SE) unless otherwise indicated. In a 2-level model, the body positions (supine, sitting, and standing) and days after stroke (Day 1, 2, and 3) were evaluated. A multilevel model was chosen because measurements were nested in patients. The effects of the covariates age, sex, NIHSS, history of hypertension, history of diabetes mellitus, discontinuation of antihypertensive medication and supine SBP (Day 1) were evaluated. The covariate age was centered at 37 years. To investigate whether significant BP rise or fall was independently associated with favorable outcome, the same covariates as in the multilevel model were entered in a logistic regression model where all covariates were treated simultaneously and on equal footing. These covariates have previously been associated with outcome of stroke or orthostatic hypotension. $P < 0.05$ was considered statistically significant. Statistical Package for the Social Sciences (version 16.0; SPSS Inc, Chicago, IL) was used for statistical analysis. Bonferroni adjustments for multiple comparisons were used in all presented results.

RESULTS

Patient characteristics

In total 167 patients were included of which 156 patients were measured on Day 1, 132 on Day 2 and 101 on Day 3. Demographic and clinical characteristics are shown in Table 1. Median NIHSS was 7 with more than half (52%) being mildly affected (NIHSS < 7) and 23% being severely affected (NIHSS > 12). Mean supine SBP and DBP on Day 1 were 140 ± 24 mmHg and 69 ± 14 mmHg, respectively. Mean HR was 77 ± 15 beats/minute and SpO₂ $97 \pm 1.6\%$. On Day one 52% was able to stand, increasing to 66 and 68% on Days 2 and 3, respectively. Forty-three percent of the patients had a favorable outcome.

Hemodynamic parameters in various positions in the first three days after stroke

Mean SBP, DBP, MAP, HR and SpO₂ values over the first 3 days in the supine, sitting and standing position are presented in Table 2. SpO₂ remained stable during mobilisation in almost all patients. BP increased going from the supine to the standing position. This was

Table 1 Patient Characteristics (n = 167)

Variable	
Age, mean (SD), y	68.5 (15.2)
Male (%)	91 (54.5)
Median NIHSS [IQR]	7.0 [4-12]
Stroke-subtype (%)	
Total Anterior Circulation Infarct	22 (13.2)
Partial Anterior Circulation Infarct	81 (48.5)
Lacunar Circulation Infarct	43 (25.7)
Posterior Circulation Infarct	21 (12.6)
Stroke etiology (%)	
Atherosclerosis	34 (20.4)
Small-vessel disease	38 (22.8)
Cardioembolism	42 (25.1)
Unknown	51 (30.5)
Dissection	2 (1.2)
Left-sided impairment (%)	64 (38.3)
Mean SBP (SD), mmHg #	140 (24.0)
Mean DBP (SD), mmHg #	69 (13.6)
Median glucose (SD), mmol/l*	6.7 (3.1)
Mean total cholesterol (SD), mmol/l^w	5.1 (1.2)
Prior medical history (%)	
Hypertension	87 (52.1)
Diabetes Mellitus	29 (17.4)
Hyperlipidemia	37 (22.2)
Myocardial infarction	27 (16.2)
Atrial fibrillation	26 (15.6)
Previous stroke	32 (19.2)
Prior use of antihypertensives	90 (53.9)

Data are numbers with either standard deviation (SD) or percentages (%) in parentheses.

* Five missing values.

^w Six missing values.

All baseline blood pressure measurements were carried out in the stroke unit.

Abbreviations: NIHSS indicates national institutes of health stroke scale; IQR, interquartile range; SBP, systolic blood pressure; DBP, diastolic blood pressure; SD standard deviation.

most pronounced on Day 1 after stroke (e.g., mean MAP change 8.5 mmHg; $p < 0.001$, and mean HR change 12 beats/minute; $p < 0.001$ on Day 1). The Figure also shows this increase of BP on attaining an upright position. It also shows that the MAP is highest on day one and tends to decrease over the next days. In comparison to BP, the HR response is relatively stable over the 3 days (Table 2). Adding covariates to the model did not influence the results. Only 1 stroke patient developed dizziness on standing and had a systolic fall of > 25 mmHg. In total 107 patients had supine and standing measurements on at least one day. The overall frequency of a significant BP fall in this group was 13.1% ($n = 14$). Ten individuals (9.3%) showed a postural SBP fall of 20 mmHg. In addition, 6 individuals (5.6%) had a postural DBP fall of 10 mmHg. Two patients fulfilled both criteria. The percentage of patients with a

Table 2 Blood pressure, heart rate and oxygenation in different body positions in the first 3 Days after stroke

Position change (No.)	SBP, mmHg	DBP, mmHg	MAP, mmHg	HR, Beats/minute	SpO ₂ (%)
Day 1 Supine	140 (24)	69 (15)	85 (14)	77 (15)	97 (2)
Supine-Sitting (156)	-4.0 (0.8)#	-4.4 (0.5)#	-3.9 (0.5)#	-1.3 (0.5)	-0.1 (0.1)
Supine-Standing (82)	-6.7 (1.0)#	-9.1 (0.7)#	-8.5 (0.7)#	-12.0 (0.6)#	-0.3 (0.1)
Sitting-Standing (82)	-2.7 (1.1)	-4.8 (0.7)#	-4.6 (0.7)#	-10.7 (0.7)#	-0.2 (0.1)
Day 2 Supine	135 (22)	67 (14)	84 (15)	74 (14)	97 (2)
Supine-Sitting (132)	-2.6 (0.9)	-5.0 (0.6)#	-4.5 (0.6)#	-1.8 (0.6)	-0.1 (0.1)
Supine-Standing (86)	-4.1 (1.0)*	-7.9 (0.7)#	-7.4 (0.7)#	-11.7 (0.7)#	-0.1 (0.1)
Sitting-Standing (88)	-1.5 (1.0)	-2.9 (0.7)#	-2.9 (0.7)*	-9.9 (0.7)#	-0.0 (0.1)
Day 3 Supine	135 (21)	69 (13)	85 (14)	73 (15)	97 (2)
Supine-Sitting (101)	-1.5 (1.0)	-3.3 (0.7)#	-3.4 (0.7)#	-2.8 (0.7)#	-0.3 (0.1)
Supine-Standing (67)	1.3 (1.2)	-5.6 (0.8)#	-3.8 (0.8)#	-10.8 (0.8)#	-0.5 (0.1)*
Sitting-Standing (69)	2.7 (1.2)	-2.3 (0.8)	-0.4 (0.8)	-8.0 (0.8)#	-0.3 (0.1)

Rows in gray show supine values for SBP, DBP, MAP, HR and SpO₂. SD is mentioned in parentheses. Other rows show changes of these values in response to various position changes. SE is mentioned in parentheses. A negative value indicates an increase upon the position change. All data are adjusted for multiple comparisons (Bonferroni).

Abbreviations: SBP indicates systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate; SpO₂, oxygen saturation.

$p < 0.001$.

* $p < 0.05$.

significant postural SBP fall was 1.2%, 3.5% and 10.4% on Days 1, 2 and 3, respectively. The 14 patients with this significant BP fall more often had a history of hypertension (78.6% versus 49.5%; $p = 0.04$) and their antihypertensive medication was more frequently discontinued at admission (50% versus 20.4%; $p = 0.04$). HR responses did not differ between the group with significant BP drops compared to the rest ($p = 0.42$). A SBP rise > 20 mmHg occurred in 19.6% of patients. On Day 1, 10 patients had a significant BP rise (12.2%) and during the following days these percentages decreased to 10.5% and 6.0%, respectively. Patient characteristics were similar for those with and without this BP rise of > 20 mmHg. HR responses did not differ significantly either ($p = 0.28$).

Change in hemodynamic parameters and outcome

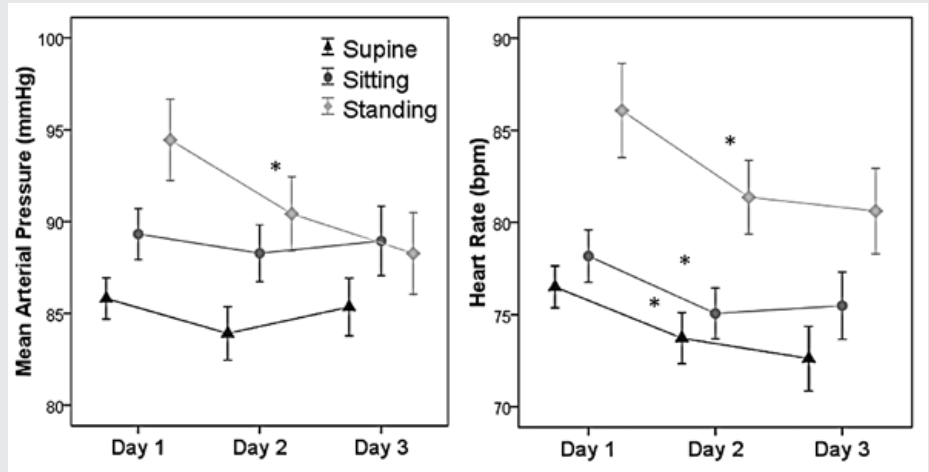
Patients with a significant SBP rise had a significantly better outcome with 81% favorable outcome rates versus 51% in the group without this response ($p = 0.01$). In the multivariate analysis significant BP rise was an independent predictor of favorable outcome (odds ratio (OR) 7.95; 95%-confidence interval (CI) 2.02-31.28; $p = 0.003$; Table 3). There was no significant relationship between significant BP fall and outcome.

Table 3 Prediction of favorable outcome (Defined as mRS 0-1; n = 107)

Variable	OR	95% CI	P value
Sex (male)	0.77	0.31-1.91	0.57
Age, y	0.98	0.95-1.02	0.35
NIHSS per point increase	0.82	0.72-0.93	0.002
History of DM	0.44	0.13-1.53	0.20
History of HT	0.51	0.17-1.53	0.23
Significant postural BP rise	7.95	2.02-31.28	0.003
Mean supine SBP (Day 1)	1.01	0.99-1.03	0.30
Discontinuation of AHT	1.32	0.43-3.99	0.63

Abbreviations: OR indicates odds ratio; CI, confidence interval; NIHSS, national institutes of health stroke scale; DM, diabetes mellitus; (S)BP, (systolic) blood pressure; HT, hypertension; AHT, antihypertensive medication; mRS, modified Rankin score.

Figure 1



Blood pressure and heart rate on Days 1, 2 and 3 in supine, sitting, and standing position. Bars represent standard errors of the mean (SEM). Temporal trends were calculated and the asterisk (*) represents significance ($p < 0.001$) over the following 3 days.

DISCUSSION

In this prospective study, we evaluated the influence of the supine, sitting and active standing body positions on indirect BP, HR and SpO₂ over the first 3 days of acute ischemic stroke patients. The results demonstrated increases of mean SBP, DBP and MAP upon sitting and standing, especially on Day 1. Moving to the standing position was accompanied by an increase of HR, which was only slightly more pronounced on admission. SpO₂ was not different in the various positions over the days. The incidence of significant postural BP fall and rise were approximately 13% and 20%. Interestingly, a significant BP rise was independently associated with a favorable outcome 3 months after stroke.

This is the first study to demonstrate a relationship between hemodynamic responses to various body positions and outcome in stroke patients. Our findings are in agreement with a previous study of 40 elderly stroke patients with DBP and MAP increasing significantly upon sitting and active standing on admission and 1 week after stroke. The incidence of significant postural BP fall in that group was approximately 10%.¹³ Later the same group reported that the use of antihypertensive medication in the acute phase does not contribute to significant postural BP fall.¹⁸ Although the results are comparable to ours, patients in both studies were asked to move directly from the supine to the active standing position, bypassing the sitting position. Their approach allows a formal assessment of the presence of orthostatic hypotension according to published criteria.¹⁹ Our more gradual approach does not allow such a formal assessment, but is a better simulation of the actual physiological challenges to the patient when mobilized at the stroke unit. Two other stroke studies used passive tilt table investigation in the acute and chronic phase of stroke. Again, the physiological response on tilting is different from our active standing protocol making comparison difficult.^{9,20}

The incidence of significant postural BP fall was very low in our cohort on Day 1 (1.2%) and increases to approximately 10% which is comparable to the known incidence of orthostatic hypotension in the normotensive and hypertensive elderly.^{13,21,22} The incidence of significant postural BP rise was around 12% on admission and decreased slowly over the next days. Interestingly, this acute hypertensive postural response was an independent predictor for favorable outcome. To our best knowledge this direct relationship with outcome has not been reported in acute stroke patients previously. Chronic orthostatic hypertension in Japanese patients with essential hypertension has been associated with silent cerebrovascular ischemia and infarction,²³ but this is most probably a different phenomenon than the one we observed in the acute phase of stroke.

An acute hypertensive response defined as an elevation of BP above normal within the first 24 hours of symptom onset is reported in > 60% of stroke cases.²⁴ Spontaneous reduction in the initial BP over the next few days in most patients supports the role of a transient and stroke-specific mechanism. Spontaneous reduction of BP after vessel recanalisation also implies stroke-specific mechanisms.²⁵ Several underlying mechanisms like damage to cardiovascular and autonomic brain centers,²⁶ an excessive reaction to venous pooling in the

legs,²⁷ an increased sympathetic nervous system and/or reduced parasympathetic activity, an impaired cardiac baroreceptor sensitivity and raised levels of circulating catecholamines may all contribute to this hypertensive response.^{28,29} Our results relate favorable outcome to an exaggerated postural BP increase without important contributions of HR. The effect persisted after correction for known confounders (such as medical history, NIHSS, age or BP medication).³⁰ It is known that BP changes on tilting reflect sympathetic nervous system function.³¹ All together this suggests a positive role of an intact or enhanced sympathetic autonomic function in recovery after stroke by allowing adequate responses to physiological challenges such as early mobilisation.^{29,32}

Because not all patients were included consecutively, we assessed external validity by comparing baseline characteristics to those of the stroke registry of our centre (Table S1) and data published.³³ The only important difference was a higher NIHSS in our study population. Patients with early complete or nearly complete recovery may have been less likely included. Patients dropped out on Days 2 and 3 due to transfers to other hospital or discharge, which may have influenced changes seen from Days 1 to 3. The impact of this is likely limited as patient characteristics for drop-outs were comparable to those who finished the study and main results were similar excluding patients who failed all repeat measures (Table S2 and Figure S1). Furthermore, in our study, upper extremities were depending instead of horizontal when BP was measured in the sitting and standing position because of paresis or fatigue of extremity. However, attention should be paid to the position of the BP cuff to the right atrial level to obtain correct measurements.³⁴ BP measurement will result in higher values if the cuff is below the right atrium. Favorable outcome was defined as modified Rankin Scale score of 0 to 1. This seems appropriate for the active standing stroke group with mild to moderate disability (median NIHSS of 5 [4-8], n = 107).

CONCLUSION

The present study shows that upright positioning as part of early mobilization in mildly to moderately affected acute stroke patients does not lead to important decreases in BP, HR or SpO₂. This constitutes an additional argument for the safety of early mobilization after stroke.³⁵ Exaggerated postural BP rises seem to be related to favorable outcome in the acute phase of ischemic stroke. It is an underappreciated, yet easily diagnosed, clinical phenomenon. Further studies to confirm and explain these findings in the setting of acute stroke are required. Greater attention for postural BP changes seems warranted when designing and interpreting acute stroke hypertension treatment and mobilization trials.^{36,37}

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SUPPLEMENTAL MATERIAL

Table S1 Patient Characteristics of study cohort and Stroke database registry Groningen (period 2010-2011)

	Study (n = 167)	Stroke database registry (2010-2011) (n = 288)	
Age, mean (SD), y	68.5 (15.2)	69.3 (14.7)	
Male (%)	91 (54.5)	148 (51)	
Median NIHSS [IQR]	7.0 [4-12]	4.0 [2-10]	N=229
Stroke-subtype (%)			
Total Anterior Circulation Infarct	22 (13.2)	34 (23)	
Partial Anterior Circulation Infarct	81 (48.5)	40 (27)	
Lacunar Circulation Infarct	43 (25.7)	58 (39)	
Posterior Circulation Infarct	21 (12.6)	18 (12)	N=150
Stroke etiology (%)			
Atherosclerosis	34 (20.4)	27 (19)	
Small vessel disease	38 (22.8)	52 (35)	
Cardio-embolism	42 (25.1)	30 (21)	
Unknown	51 (30.5)	31 (22)	
Dissection	2 (1.2)	4 (3)	N=144
Left-sided handicap (%)	64 (38.3)	65 (40)	N=161
Mean SBP (SD), mmHg	140 (24.0)#	152 (26)\$	N=242
Mean DBP (SD), mmHg	69 (13.6)#	81 (17)\$	N=242
Median glucose (SD), mmol/l	6.7 (3.1)*	6.4 (2.8)	N=229
Mean total cholesterol (SD), mmol/l	5.1 (1.2) ^w	5.3 (1.4)	N=229
Prior medical history (%)			
Hypertension	87 (52.1)	147 (60)	
Diabetes Mellitus	29 (17.4)	60 (24)	
Hyperlipidemia	37 (22.2)	84 (35)	
Myocardial infarction	27 (16.2)	36 (15)	
Atrial fibrillation	26 (15.6)	43 (17)	
Previous stroke	32 (19.2)	51 (22)	
Prior use of antihypertensives	90 (53.9)	146 (60)	N=242

Data are numbers with either SD or percentages (%) in parentheses.

Abbreviations: NIHSS indicates national institutes of health stroke scale; IQR, interquartile range; SBP, systolic blood pressure; DBP, diastolic blood pressure; SD, standard deviation.

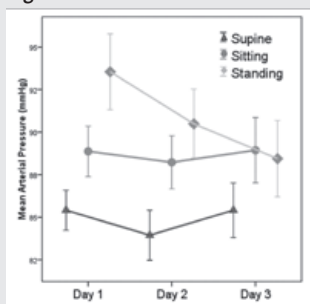
* 5 missing values.

^w 6 missing values.

All baseline blood pressure measurements were carried out in the stroke unit.

\$ All baseline blood pressure measurements were carried out in the emergency ward.

Figure S1



Blood pressure on Days 1, 2 and 3 in supine, sitting, and standing position without the patients who failed all repeat measures (n = 142). Bars represent standard errors of the mean (SEM).

Table S2 Prediction of favorable outcome (Defined as mRS 0-1; n = 93) without the patients who failed all repeat measures

Variable	OR	95% CI	P value
Sex (male)	0.67	0.25 - 1.70	0.42
Age, y	0.98	0.95 - 1.02	0.34
NIHSS per point increase	0.84	0.73 - 0.96	0.01
History of DM	0.38	0.10 - 1.50	0.17
History of HT	0.48	0.14 - 1.60	0.24
Significant postural BP rise	9.70	2.07 - 45.3	0.004
Mean supine SBP (Day 1)	1.01	0.99 - 1.04	0.27
Discontinuation of AHT	1.01	0.32 - 3.20	0.30

Abbreviations: OR indicates odds ratio; CI, confidence interval; NIHSS, national institutes of health stroke scale; DM, diabetes mellitus; SBP, systolic blood pressure; HT, hypertension; AHT, antihypertensive medication; mRS, modified Rankin score.



CHAPTER 8

THE IMPACT OF UPRIGHT POSITIONING IN BED ON CEREBRAL BLOOD FLOW VELOCITY AFTER ACUTE STROKE. IMPLICATIONS FOR SAFETY OF EARLY MOBILIZATION AFTER STROKE

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Submitted

ABSTRACT

Background

International guidelines recommend mobilisation of acute stroke patients in and out of bed as soon as their clinical condition permits. Little is known about the influence of different body positions on real time cerebral flow variables in the acute ischemic stroke phase. We aimed to assess whether cerebral blood flow velocity (CBFV) changes significantly after upright positioning in bed and related this to changes in neurological status, functional outcome and dynamic autoregulatory status.

Methods

We investigated postural changes in neurological status and simultaneously recorded bilateral Transcranial Doppler (TCD), near-infrared spectroscopy, end-tidal CO₂ and non-invasive continuous blood pressure (BP) data in patients with first ever acute middle cerebral artery ischemic stroke. Postures included supine, half sitting (45°), sitting (70°) and Trendelenburg (-15°) position. Dynamic autoregulation was evaluated by estimating phase, gain and autoregulation index (ARI) of TCD flow velocity correlations with spontaneous BP fluctuations in the supine position. Using multilevel analyses, we compared postural changes between hemispheres, follow-up measurements, and outcome groups and between stroke patients and 20 controls.

Results

The final analysis included 52 patients, 47 and 33 within 24 h and 72 h after symptom onset, respectively. Mean age was 62.0 ± 15 years and median National Institutes of Health Stroke Scale score (NIHSS) on admission was 7 (IQR 5-14). During the upright positioning, no neurological worsening or improvement (using motor NIHSS) was observed in any of the patients. Mean CBFV decrease upon sitting (70°) was comparable between controls and stroke patients, with a mean difference of 4% on Day 1 for the affected hemisphere (95% CI: -11% to 3%, $p=1.0$) and 1% (95% CI: -8% to 6%, $p=1.0$) on Day 3. No significant differences were found between affected and unaffected stroke hemispheres and between patients with unfavorable and favorable outcome. Dynamic cerebral autoregulation was impaired in stroke patients which showed a bilateral decrease in phase and ARI estimates. No correlation between bilateral impaired autoregulation status and positional mean CBFV changes was found.

Conclusions

Upright positioning in bed of mildly to moderately affected stroke patients appears to be safe during the first 3 days on the stroke unit, despite a bilaterally impaired dynamic cerebral autoregulation. Supine or Trendelenburg positioning did not seem to augment real time flow variables or improve neurological status.

INTRODUCTION

Brain ischemia is a potentially reversible process that is dependent on restoration of cerebral blood flow (CBF) within a time window of cellular viability that varies according to the severity and duration of the flow cessation.¹ Any activity that alters CBF during the acute phase of ischemic stroke may directly contribute to extension of the ischemic core and compromise clinical outcome. International guidelines recommend mobilisation in and out of bed as early as possible (depending on clinical condition) after stroke.²⁻⁵ Such early upright positioning prevents venous thrombosis, cardiopulmonary deconditioning and may improve early plasticity of the brain.^{5,6} However, there is insufficient evidence in support of early activity in and out of bed after acute stroke.⁷ Also, there is fear of gravity-induced diminished CBF to ischemic brain tissue by upright positioning in the setting of a (potentially) disturbed cerebral autoregulation.^{8,9} As a result, stroke physicians do not universally accept early mobilisation.

Little is known in acute stroke patients about the influence of different body positions on systemic blood pressure (BP), or, more importantly, on real time CBF variables.⁹ Transcranial Doppler (TCD) of the middle cerebral artery (MCA) may be used to assess cerebral blood flow velocity (CBFV) at the bedside in the stroke unit. Wojner et al. reported that different recumbent head of bed (HOB) positions (30° to 0°) augmented MCA CBFV by 20% on the affected side in 20 patients with severe acute stroke with improvement of deficits in a proportion. They advised to nurse stroke patients 'heads down'.¹⁰ If such relatively minor changes in HOB position have such impact on CBFV and neurological status, the question arises what the consequences of early in bed upright HOB positioning in acute stroke patients would be in terms of cerebral perfusion. In this study we sought to assess whether MCA CBFV changes significantly after upright HOB positioning, in affected as well as unaffected stroke hemispheres. Any changes were compared between positions, hemispheres, follow-up measurements and between patients and controls. Any effect of in bed upright positioning on neurological status, and outcome was determined.

While this bedside evaluation addresses the hemodynamic and clinical effects of upright positioning, it cannot serve as a formal evaluation of cerebral (pressure) autoregulation. For evaluation of static cerebral autoregulation (CA), larger fluctuations of BP would need to be induced than would normally occur during upright positioning in the stroke unit.¹¹ However, challenges such as tilt table testing and pharmacological manipulation of BP are not feasible in the setting of acute stroke. An alternative method to formally evaluate autoregulation and which is feasible at the bedside of the patient is the assessment of dynamic CA (in response to spontaneous BP fluctuations). Dynamic CA was evaluated to assess how hemodynamic and clinical effects of postural changes in stroke are related to disturbances in autoregulation.

METHODS

Study design and patients

This study was conducted in the stroke unit of a large teaching hospital between August 2008 and May 2011. Patients aged over 18 years with a first ever ischemic stroke in the MCA territory, admitted to the stroke unit within 24 h after stroke onset were considered eligible. Patients had to be conscious, cooperative, and hemodynamically stable without fever. These factors were incorporated into the final clinical and nursing judgment whether patients were deemed too severely affected by the stroke or too severely ill to position upright and be included in this study. Brain CT, electrocardiography, bilateral duplex carotid ultrasound, and laboratory investigations were performed. Thrombolytic therapy was administered according to (inter)national guidelines. Use of any medication, especially antiarrhythmics and antihypertensive medication, was registered. The National Institute of Health Stroke Scale score (NIHSS) was used to determine initial (on admission) and Day 3 neurological deficit. Neurological deterioration or improvement after 72 h was defined as any change on the NIHSS score. The stroke subtype was classified using the Oxfordshire Community Stroke Project (OXFORD) classification,¹² and stroke cause according to Trial of Org 10172 in Acute Stroke Treatment definitions.¹³ The modified Rankin Scale (mRS) score at 3 months was determined by a certified assessor by telephone interview, who was blinded to the physiological data.¹⁴ The study was reviewed by the local medical ethics committee that allowed execution. All participants or next of kin gave informed consent. Twenty age and sex matched controls were recruited and their medical history was reviewed.

Sample size calculation

In the literature, the standard deviation (SD) of the intraindividual supine to sitting MCA CBFV difference is estimated to be around $\pm 5\%$ for elderly hospitalized patients,¹⁵ and $\pm 20\%$ for severe stroke patients going from 30° to 0° .¹⁰ To detect a difference in CBFV of more than 6 cm/s (10% to 20%) between supine and sitting upright in bed with a probability (power) of 90% when testing at a two-sided significance level of 5%, a sample size of 45 subjects was required.

Procedures

BP was measured with a finger servo-controlled plethysmograph (Finometer-Pro, Finapres Medical Systems, Amsterdam, The Netherlands). The cuff was applied to the middle finger of the non-dominant or paretic hand placed at the heart level with the arm across the chest and supported by a sling. Mean arterial pressure at the MCA level (MAP_{mca} , mmHg) was automatically calculated from the MAP measured at heart level and the vertical finger-to-TCD probe distance. TCD was performed by the same neurosonographer (MA) over the temporal bone window on both sides. Subjects were evaluated for an adequate temporal window for insonation of the MCA. MCA wave forms were identified at a depth range of 40

to 60 mm and a stable forward waveform with good intensity was selected for monitoring. Using the time-averaged mean velocities of the maximum velocity outlines of the Doppler spectrum, the mean flow velocity (MCA CBFV_{mean}, cm/s) was calculated (Nicolet Pioneer TC8080, Carefusion Corporation, San Diego, USA). Patients with permanent MCA occlusion on TCD were excluded. TCD probes (2.0 MHz) were mounted by a head frame to ensure a constant angle of insonation throughout the positioning procedure. End-tidal CO₂ (etCO₂, kPa) was measured by a mask using an infrared CO₂ analyzer (Capnomac Ultima, GE Healthcare, Chalfont St Giles, UK) as an approximation of partial arterial CO₂ pressure. The beginning and ending time-points of the postural transitions were marked. These data periods (\pm 30 sec) were not used for analysis.

From 2010 onwards, the data collection protocol was changed. Firstly, bifrontal near-infrared spectroscopy (NIRS) recording was added. Secondly, all signals (including the positional marks) were captured synchronously at 250 Hz using a A/D converter. This allowed calculation of dynamic CA estimates in the baseline supine position (see later) with Labview software (Labview 9.0, National Instruments, Austin, USA). The INVOS 5100C NIRS device (Somanetics Corp, Detroit, MI) has a sampling frequency of 0.2 Hz for regional cerebral oxygenation (rSO₂, %) calculation. Adhesive optodes were placed on each side of the forehead, high enough to avoid muscle artifact and sufficiently lateral to avoid the superior sagittal sinus.

Data analysis

The recorded signals were visually inspected for artifacts and ectopy. Occasional artifacts of short duration, visible as narrow spikes in the TCD, BP or rSO₂ signal, were removed by linear interpolation. Using the high frequency data, beat to beat data were obtained by triggering on the ascending slope during BP systole. The data were resampled at 10 Hz by spline interpolation to create a uniform time base. This was followed by mean normalization and subtraction of 1 to create zero mean signals. A Hanning window was applied to the data, and the Welch method of spectral estimation was used with 50% overlap on data segments of 51.2 seconds. This resulted in spectral estimates averaged over 10 segments in the baseline supine position.¹⁶

The coherence and transfer function analysis (TFA) estimates were calculated at the low frequency (LF) range (0.06 to 0.14 Hz) without attempts to unwrap the phase spectra. The LF was taken because in this range coherence is high in healthy volunteers using spontaneous BP fluctuations.¹⁷ The coherence between BP and CBFV was considered significant if it exceeds the 95% confidence interval (95% CI) level of 'no linear' association: $1-(0.05)^{1/L-1}$,¹⁸ where L is the number of data segments used in the averaging, resulting in a significance level of 0.28. Transfer functions were calculated for each subject over the frequency range meeting the significance coherence criterion and averaged to obtain mean values. The phase shift (°) is a measure of the extent of which each frequency component of the respective time series leads the BP time series, and it represents continuous, early counter regulation of CBFV

against rise and fall of BP. By dividing the CBFV by the BP spectra the amplitude frequency response or gain (cm/s mmHg^{-1}) can be calculated quantifying the damping effect of the system on the magnitude of spontaneous BP fluctuations. This means that higher phase shift and lower gain in the LF range indicates better dynamic CA.¹⁹

The autoregulation index (ARI) was calculated by transforming the real and imaginary parts of the transfer function back to the time domain with inverse Fast Fourier transformation. The impulse response function thus created was integrated to yield the step response function. The first 10 seconds of the step response function were compared with the original Tiecks curves and the best fitting curve was determined by implementing a least squares fitting procedure. This resulted in a score ranging from 0 to 9, with 0 representing total absence of dynamic CA and 9 the most effective CA.¹¹

Positioning protocol

After admission to the stroke unit, patients were instrumented. Subjects were requested to abstain from moving and talking in order to minimize artifacts and activity related CBFV changes. Great care was taken to keep the head in the neutral midline position (without shifting of the headband) and the BP cuff at heart level during positioning. A test run was performed. After 10 min of supine rest (baseline supine) the subjects were passively tilted by changing HOB angles to 45° (half sitting), 70° (sitting) and -15° (Trendelenburg) position for 3 to 5 minutes each. Patients were brought in the sitting position twice. Periods of tilts were interspaced with 3 to 5 min of supine rest to re-establish control values (supine position). The first measurement was performed within 24 h after symptom onset and the second (if possible) 48 h later. Before and after establishing each position the motor NIHSS (affected arm and leg) was evaluated. Control subjects were recorded in a quiet, temperature controlled research room using the same positioning protocol.

Statistical analysis

We calculated a mean hemodynamic value for every position period. To compare responses in each position, percentage changes in the variables ($\text{MCA CBFV}_{\text{mean}}$, rSO_2 , MAP_{mca} , heart rate (HR), etCO_2) were calculated as the differences between the positions after normalization to the mean baseline supine value. We averaged these percentage changes to obtain a mean percentage change for each of the four different positions: supine, half sitting, sitting and Trendelenburg. For control subjects, the mean of both $\text{MCA CBFV}_{\text{mean}}$ and rSO_2 signals was taken. To account for, and to take advantage of the correlation between repeated measures in the same individual, a multilevel model was used to estimate the effects of positioning, affected hemisphere and day of recording on changes in the main variables ($\text{MCA CBFV}_{\text{mean}}$ and rSO_2).²⁰ The relation between $\text{MCA CBFV}_{\text{mean}}$ and outcome (dichotomized as mRS 0-2 for favorable outcome) was analysed in a similar way. Significant carotid stenosis, stroke subtype, NIHSS, age and sex were used as potential confounding covariates in stroke group comparisons. Age, sex and history of hypertension, cardiac disease and diabetes were used

as covariates for healthy control and stroke group comparisons. Bonferroni adjustments for multiple comparisons were used for all results presented. Dynamic CA data were explored using analysis of variance. Simple correlation analysis was used to compare $\text{CBFV}_{\text{mean}}$ response upon sitting and dynamic CA estimates (in baseline supine period). Statistical analysis was done with SAS (version 9.2).

RESULTS

In total we enrolled 52 acute stroke patients in the study. We measured 47 patients within 24 h (Day 1 measurement) and 33 patients within 72 h (Day 3 measurement) after symptom onset. Twenty-eight patients had measurements on both days (Day 1 and 3 measurements). Five patients were measured on Day 3 only. Table 1 shows the demographic characteristics of the study sample. Mean patient age was 62.0 ± 15 years and median baseline NIHSS was 7 points [IQR 5-14 points]. NIRS recordings and calculation of dynamic CA parameters were done in 34 patients (65%) and 17 controls (85%).

Figure 1 shows that systemic and cerebral hemodynamic changes were most pronounced when moving from supine to sitting position (70°) for both patients and controls. The results presented, including Table 2 and 3, therefore focus on changes from supine to sitting position, with information on other positions, unaffected hemisphere and additional comparisons available as supplemental material (SM; Table S1-S11). In the sitting position on Day 1 for both affected and unaffected hemisphere MCA $\text{CBFV}_{\text{mean}}$ decreased in 28 patients (60%) and rSO_2 decreased in 18 patients (55%). On Day 3 these percentages were 64% and 57%, respectively. None of the univariate results presented below were different after adjustment for predefined covariates, except for the outcome analysis.

Positional changes, neurological status and outcome for all positions

We observed no neurological worsening or improvement during the postural changes in any of the patients. Eighteen patients (64%) had improved neurologically on Day 3. In total 3 patients had deteriorated (11%) with a NIHSS decline of 1 point (due to recurrent embolic stroke), 3 points (due to progression from carotid stenosis to occlusion) and 2 points (due to edema) on Day 3. There was no significantly greater MCA $\text{CBFV}_{\text{mean}}$ decrease upon positioning in patients with unfavorable compared to favorable outcome after correction for confounding covariates (mean difference upon sitting, for the affected hemisphere on Day 1: -5%, 95% CI -14% to 5%, $p = 1.0$). There were no significant differences between large and small vessel strokes (using OXFORD classification) on both days and hemispheres concerning MCA $\text{CBFV}_{\text{mean}}$ changes upon sitting (all $p = 1.0$).

Figure 1

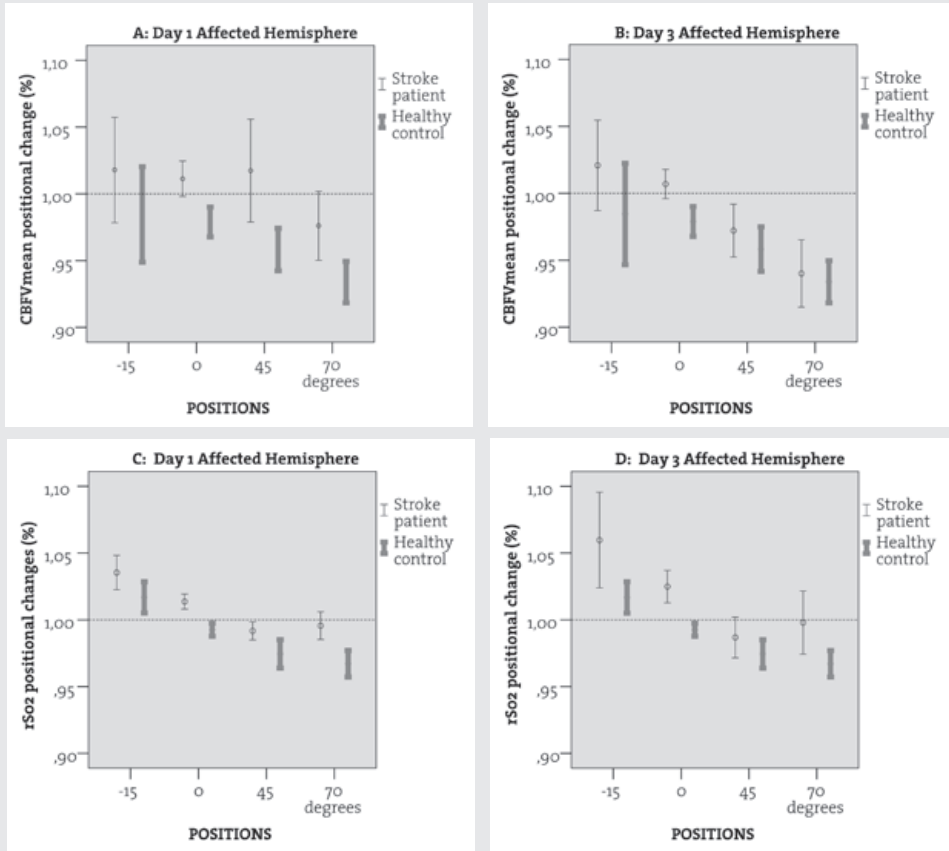


Image showing the changes of MCA CBFV_{mean} in the different bed positions on Day 1 (Figure A) and Day 3 (Figure B) following acute ischemic stroke, for both patients (affected hemisphere) and healthy controls. Changes in rSO₂ in the different bed positions on Day 1 (Figure C) and Day 3 (Figure D) following acute ischemic stroke for both patients and controls are also shown. Data were normalized with regard to the baseline supine position. Error bars represent standard error of the mean (SEM).

Positional CBFV changes upon sitting in stroke patients and controls

MCA CBFV_{mean} dropped slightly more (but not significantly) in controls compared to stroke patients on Day 1 (for affected hemisphere: -4%, 95% CI -11% to 3%, $p = 1.0$) and Day 3 (for affected hemisphere: -1%, 95% CI -8% to 6%, $p = 1.0$) (SM: Table 7 and 8).

Positional CBFV changes upon sitting in affected and unaffected hemisphere

MCA CBFV_{mean} was not different between the affected and the unaffected hemisphere in the sitting position (on both days: -2%, 95% CI -5% to 2%, $p = 1.0$) (SM: Table 5 and 6).

Table 1 Patient characteristics

Measure	Patients Day 1 (n = 47)	Patients Day 3 (n = 33)	Control subjects (n = 20)
Age, mean (SD), y	62 (15)	60 (15)	52 (20)
Male (%)	32 (70)	21 (66)	11 (55)
Affected right hemisphere (%)	24 (52)	16 (50)	-
Median NIHSS score on admission [IQR]	7 [5-14]	6 [3-11]	-
History of hypertension (%)	21 (46)	15 (47)	7 (35)
History of cardiac disease (%)	17 (37)	10 (31)	0 (0)
Significant carotid stenosis (%)	8 (17)	6 (19)	Unknown
Stroke etiology (%)			
Atherosclerosis	15 (33)	8 (25)	
Cardioembolism	10 (22)	8 (25)	
Small-vessel disease	14 (30)	10 (31)	
Dissection	2 (4)	2 (6)	
Unknown	5 (11)	4 (13)	
Stroke subtype (%)			
Total Anterior Circulation Infarct	9 (20)	5 (16)	
Partial Anterior Circulation Infarct	19 (41)	14 (44)	
Lacunar Circulation Infarct	18 (40)	13 (41)	
Posterior Circulation Infarct	0 (0)	0 (0)	
History of Diabetes Mellitus (%)	8 (17)	3 (9)	0 (0)
Antihypertensive medication on admission (%)	25 (54)	16 (50)	6 (30)
IV Thrombolysis treatment received (%)	20 (44)	14 (44)	-
Mean Arterial Pressure (SD), mmHg	84 (21)	81 (19)	78 (13)
Mean Heart rate (SD), beats/minute	77 (18)	71 (13)	64 (7)

Data are absolute numbers with either SD or percentages (%) in parentheses.

Abbreviations: SD indicates standard deviation; IQR, interquartile range; NIHSS, national institutes of health stroke scale.

Table 2 Changes of MCA CBFV_{mean} and rSO₂ in supine (0°) and sitting (70°) position on Days 1 and 3

	MCA CBFV _{mean} Supine (0°)	Δ MCA CBFV _{mean}	P value [#]	rSO ₂ Supine (0°)	Δ rSO ₂	P value [#]
Affected Hemisphere (Day 1) n = 47*	1.00 (0.99 to 1.04)	-0.04 (-0.06 to -0.03)	0.005	1.01 (1.0 to 1.01)	-0.02 (-0.03 to -0.01)	0.006
Unaffected Hemisphere (Day 1) n = 47	1.00 (0.98 to 1.01)	-0.02 (-0.05 to 0)	1.0	1.01 (1.0 to 1.01)	-0.02 (-0.03 to -0.01)	0.009
Control subjects n = 20	0.98 (0.95 to 1.01)	-0.04 (-0.08 to -0.01)	0.04	0.99 (0.98 to 1.01)	-0.03 (-0.05 to -0.01)	0.002
Affected Hemisphere (Day 3) n = 33*	1.01 (0.99 to 1.03)	-0.07 (-0.10 to -0.03)	<0.001	1.03 (1.01 to 1.04)	-0.03 (-0.05 to -0.01)	0.004
Unaffected Hemisphere (Day 3) n = 33	1.01 (1.0 to 1.03)	-0.05 (-0.08 to -0.02)	<0.001	1.02 (1.01 to 1.03)	-0.02 (-0.04 to -0.01)	0.02

Data are normalized values with 95% CI in parentheses.

Abbreviations: MCA CBFV_{mean} indicates middle cerebral artery cerebral blood flow velocity; rSO₂, regional cerebral oxygen saturation.

*Thirty-two and twenty-two patients had appropriate near-infrared spectroscopy recordings on Days 1 and 3, respectively.

[#]p values with (Bonferroni) correction for multiple comparisons.

Table 3 Changes of MAP_{mca}, HR and etCO₂ in supine (0°) and sitting (70°) position (normalized values) on Days 1 and 3

	MAP _{mca} Supine (0°)	Δ MAP _{mca}	p value#	HR Supine (0°)	Δ HR	p value#	etCO ₂ Supine (0°)	Δ etCO ₂	p value#
Stroke patients (Day 1) n = 47*	1.05 (1.02 to 1.07)	-0.15 (-0.19 to -0.10)	<0.001	1.0 (0.99 to 1.02)	0.04 (0.01 to 0.06)	<0.001	1.0 (0.98 to 1.01)	-0.03 (-0.05 to -0.01)	<0.001
Control subjects n = 20	1.02 (0.99 to 1.06)	-0.17 (-0.24 to -0.11)	<0.001	0.98 (0.96 to 1.0)	0.06 (0.02 to 0.09)	<0.001	0.98 (0.96 to 1.0)	-0.03 (-0.06 to 0)	0.15
Stroke patients (Day 3) n = 33*	1.05 (1.02 to 1.08)	-0.17 (-0.22 to -0.12)	<0.001	1.01 (0.99 to 1.02)	0.05 (0.02 to 0.08)	<0.001	0.98 (0.97 to 0.99)	-0.04 (-0.07 to -0.02)	<0.001

Table legend (3)

Data are normalized values with 95% CI in parentheses.

Abbreviations: MAP_{mca} indicates mean arterial pressure at circle of Willis level; HR, heart rate; etCO₂, end-tidal CO₂.

*Thirty-two and twenty-two patients had appropriate near-infrared spectroscopy recordings on Days 1 and 3, respectively.

p values with (Bonferroni) correction for multiple comparisons.

Positional CBFV changes upon sitting on Days 1 and 3

MCA CBFV_{mean} decreased significantly with moving to the sitting position on Day 1 (-4%, 95% CI -6% to -3%, $p = 0.005$) and Day 3 (-7%, 95% CI -10% to -3%, $p < 0.001$) for the affected hemisphere (Table 2). MCA CBFV_{mean} in the sitting position was not different between Day 1 and Day 3 (for affected hemisphere -3%, 95% CI: -7% to 1%, $p = 0.29$) (SM: Table 4).

Positional changes of rSO₂, MAP and etCO₂ upon sitting

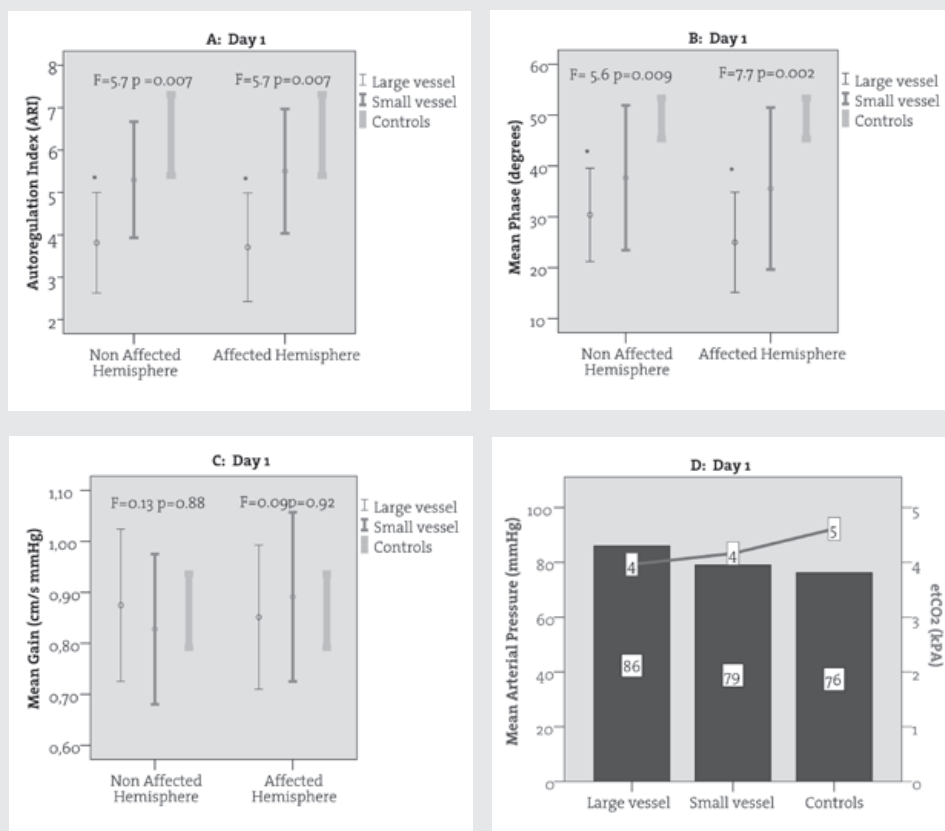
rSO₂ decreased significantly with moving to the sitting position on Day 1 (-2%, 95% CI -3% to -1%, $p = 0.006$) and Day 3 (-3%, 95% CI: -5% to -1%, $p = 0.004$) for the affected hemisphere (Table 2). In agreement with MCA CBFV_{mean}, the small rSO₂ positional responses were not significantly different between both hemispheres, between measurements on the two Days and between patients and controls (SM: table 4-8). MCA CBFV_{mean} and rSO₂ were positively correlated for the affected hemisphere on Day 1 ($r = 0.33$, $p = 0.01$).

In stroke patients MAP_{mca} decreased on average by 15% on Day 1 (95% CI -19% to -10%, $p < 0.001$) and 17% (95% CI -22% to -12%, $p < 0.001$) on Day 3, similar to controls (-17%, 95% CI -24% to -11%, $p < 0.001$). MAP_{mca} increased during the course of the experiment, for both patients and controls, looking at MAP_{mca} values during the supine rest periods (Table 3). The postural responses were accompanied by only minor HR changes. EtCO₂ decreased with moving to the sitting position on Day 1 (-3%, 95% CI -5% to -1%, $p < 0.001$) and Day 3 (-4%, 95% CI -7% to -2%, $p < 0.001$) for the patients (Table 3).

Dynamic autoregulation estimates

Because of absence of significant coherence, dynamic CA estimates were not available in 5 patients on Day 1 (16%). Results of the averaged different estimates are shown in Table 4 with

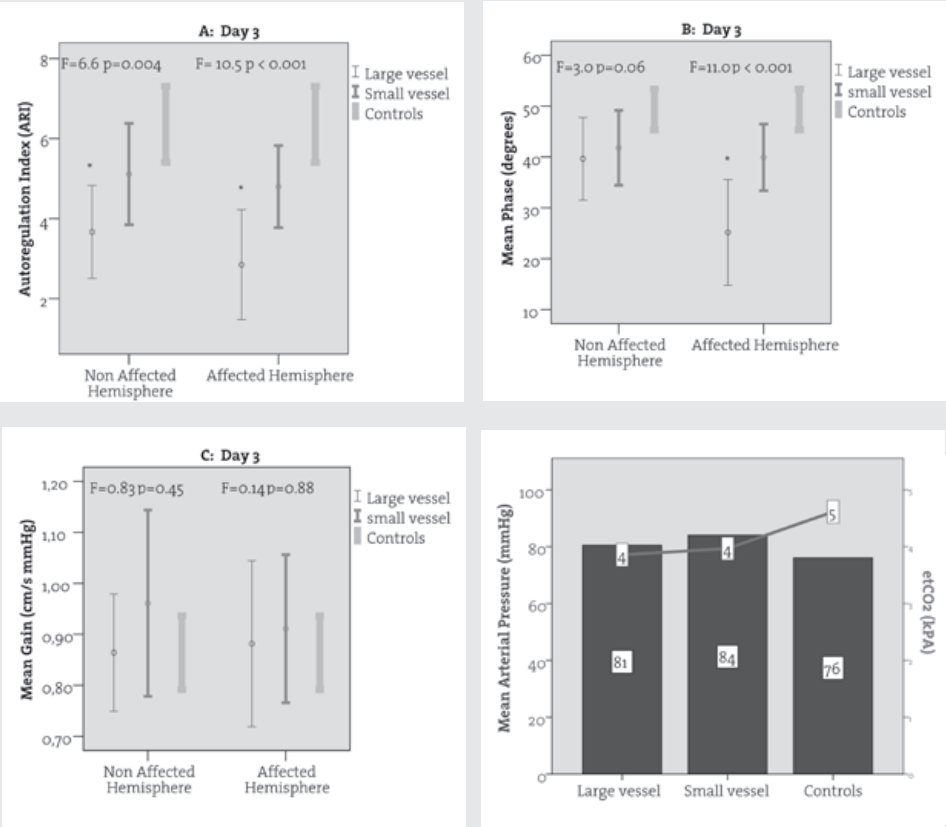
Figure 2



Dynamic autoregulation estimates (ARI, gain and phase) on Day 1. Data are divided into non affected and affected hemisphere, stroke subtype (large vessel (PACI together with TACI, $n = 17$) versus small vessel (LACI, $n = 10$) strokes) and compared to controls (average value of both hemispheres, $n = 17$). Analysis of variance shows that significant lower ARI and phase estimates are present for large vessel strokes for both hemispheres compared to controls (* $p < 0.05$ in posthoc testing) (Figure 2 A and B). Error bars represent standard error of the mean (SEM). In Figure 2 D the averaged supine mean arterial pressure (MAP) and etCO₂ (secondary y-axis) levels are depicted.

evidence of bilaterally significant lower ARI and phase on both days in stroke patients (Table 4). In the baseline supine position etCO₂ levels were significantly lower for stroke patients in comparison to controls on both days (for Day 1; 4.0 versus 4.6 kPa, $p = 0.002$). Parameters of dynamic CA were more impaired in large vessel strokes with some improvement on Day 3 for the unaffected hemisphere (Figure 2 and 3). This phenomenon persisted after exclusion of the 4 patients with symptomatic carotid stenosis. Interestingly, there is no correlation between MCA CBFV_{mean} response upon sitting and any of dynamic CA estimates (for example on Day 1 for the affected hemisphere: ARI $r = 0.16$, $p = 0.43$; phase $r = -0.31$, $p = 0.14$; gain $r = -0.14$, $p = 0.44$).

Figure 3



Dynamic autoregulation estimates (ARI, gain and phase) on Day 3. Data are divided into non affected and affected hemisphere, stroke subtype (large vessel (PACI together with TACI, $n = 13$) versus small vessel (LACI, $n = 10$) strokes) and compared to controls (average value of both hemispheres, $n = 17$). Analysis of variance shows that significant lower ARI and phase estimates are still present for large vessel strokes compared to controls ($* p < 0.05$ in posthoc testing), with suggestions for some improvement of dynamic autoregulation in the non affected hemisphere (Figure 3 A and B). Error bars represent standard error of the mean (SEM). In Figure 3 D the averaged supine mean arterial pressure (MAP) and etCO₂ levels (secondary y-axis) are depicted.

DISCUSSION

Our study showed that following acute ischemic stroke in MCA territory early upright positioning in bed resulted in minor average changes in the CBFV_{mean} only. The postural responses were not significantly different between the affected and unaffected hemispheres, between follow-up measurements, and between patients and controls. Passive upright positioning was not accompanied by worsening of the (motor) stroke

Table 4 Dynamic autoregulation estimates in low frequency range on Days 1 and 3

	ARI	Phase (°)	Gain (cm/s mmHg-1)	Coherence
Affected hemisphere Day 1 (n = 27)	4.4 (2.6)*	33 (21)*	0.86 (0.28)	0.55 (0.24)
Unaffected hemisphere Day 1 (n = 26)§	4.4 (2.4)*	34 (18)*	0.86 (0.27)	0.51 (0.23)
Control subjects (n = 17)	6.4 (2.0)	49 (8)	0.86 (0.14)	0.55 (0.15)
Affected hemisphere Day 3 (n = 23)	3.7 (2.3)*	32 (17)*	0.89 (0.26)	0.61 (0.15)
Unaffected hemisphere Day 3 (n = 21)§	4.3 (2.1)*	41 (12)*	0.91 (0.23)	0.53 (0.14)

Data are mean ± standard deviation.

Abbreviation: ARI indicates autoregulation index.

*There was a significant ($p < 0.05$, ANOVA) difference between patient hemisphere and controls (both sides averaged).

Sixteen patients had measurements on both days.

§ On Day 1 one and on Day 3 two patients had artefacts and low coherence for the non affected hemisphere measurements.

severity score. No improvement was noticed in the flat supine and Trendelenburg positions. The relative postural hemodynamic and etCO_2 changes were largely comparable between patients and controls, although etCO_2 was lower in the patients in the supine position. This study suggests that upright positioning compromises neither flow nor neurological function in the affected MCA territory in mild to moderately affected acute stroke patients. No correlations between flow changes (upon sitting), outcome and dynamic autoregulatory status were found. The effects of upright positioning were even less pronounced on Day 1, suggesting effective local or systemic hemodynamic adjustments to overcome gravitational force during postural changes in the acute phase of mild to moderate stroke. The potential of the Trendelenburg position to augment flow seems to be limited and may not outweigh concurrent cardiopulmonary complications.²¹

Measurements

Although CBFV measurements cannot be used to calculate CBF volume, the observed relative CBFV changes can be considered proportionate to CBF changes as long as the angle of insonation and the MCA diameter remain constant during the brief test interval. The MCA diameter is thought to remain constant over a ± 30 mmHg range of BP and ± 2 kPa of CO_2 .²² This requirement was fulfilled in our study. TCD is prone to several errors because the measurements are operator- and patient-dependent. Even small probe position changes may alter the CBFV readings. However, frontal cerebral oxygenation (rSO_2) followed MCA $\text{CBFV}_{\text{mean}}$ changes in size and direction in the affected hemisphere, which further strengthens our findings. Assuming a constant arterial O_2 content and cerebral metabolic rate during

the measurement, rSO_2 is predominantly a function of local CBF.^{23,24} Furthermore, TCD monitoring is the only noninvasive method to monitor CBF changes continuously in stroke. It is generally accepted that CBF changes are closely reflected by TCD readings.²⁵

Stroke population

Patients in our study predominantly had mild to moderate strokes. Patients with MCA occlusion were excluded. It was left to clinical and nursing judgment whether patients were deemed too severely affected by the stroke or too severely ill to be positioned upright for this study.⁵ Although NIHSS was not found to be a confounder for postural CBFV changes, too few patients with severe stroke (NIHSS > 16) were included to be able to generalize our findings to patients with severe strokes. Furthermore, fully ambulatory patients at Day 1 may have been less likely to be included. The practical implication of the latter drawback in generalization is probably limited. When mild to moderate strokes are unlikely to be affected by upright positioning, very mild strokes are even less likely affected. Patients dropped out on Day 3 due to transfers to other hospital or discharge, which may have influenced changes seen from Days 1 to 3. The impact of this appears limited as patient characteristics were comparable on Day 1 and 3 (Table 1).

Postural effects on CBFV in acute stroke

Three studies have investigated the postural effects on MCA CBFV_{mean} in acute stroke.^{10,26,27} Wojner et al. found 20% CBFV_{mean} increase on average in the supine position in 20 patients with an acute MCA occlusion. However, a wide range of individual flow improvements was present (5% to 96% from baseline), with no data from the unaffected hemisphere being available.¹⁰ A small study with 8 subjects found important postural flow changes in 4 severely affected patients with incomplete MCA recanalization on 24 h follow-up imaging (affected hemisphere).²⁶ A more than 15% higher MCA flow in the supine position in 18 large stroke patients with intracranial pressure (ICP) monitoring on the ICU was found. This effect was only present in the affected hemisphere.²⁷ Our study did not show relevant postural changes despite the larger position changes (70° instead of 30°). This is probably largely due to our predominant focus on mild to moderately affected stroke patients. Also, in our study changes in all variables were related to the individual baseline supine level (by normalization), reducing the effects of large variation of measured parameters and difficulties with standardization of the used techniques (TCD, NIRS and BP). In none of the 3 studies, flow data were recorded simultaneously with NIRS and $etCO_2$. Furthermore, there might be an effect of anesthesia, vasopressors, hypothermia and decompressive craniectomy on cerebral vasoregulation used in the ICP monitoring stroke positioning study.²⁸ Our results are in line with subarachnoid hemorrhage patients in whom MCA CBFV_{mean} remained constant in supine and 45° HOB positions, regardless of the development of vasospasm.²⁹

Cerebral blood flow and autoregulation

Early upright positioning of stroke patients might challenge autoregulation.⁹ We show that the impact of this on cerebral hemodynamics and neurological status is limited. This observation, however, does not allow a conclusion on whether cerebral CA is disturbed. Because a formal evaluation of static (pressure) CA is unfeasible in the stroke unit setting, we used an alternative method of assessing CA. For assessment of dynamic CA, phase relation or transfer magnitude (gain) or both between BP and CBF are computed using spontaneous BP fluctuations. These techniques are based on a high-pass filter model of CA, which assumes that (spontaneous or induced) variations in CBF caused by changes in BP are effectively damped in the LF range but not in the high-frequency range, in which changes in pressure are directly transferred to changes in CBF. Using the transfer function method in the baseline supine position, we were able to show bilateral impairment of dynamic CA in the (sub) acute phase of stroke. However, this was not correlated with the relative MCA CBFV_{mean} changes upon sitting. The gain estimates were not different between strokes and controls but this discrepancy has been reported before.¹⁹ A more global dynamic autoregulatory dysfunction has been demonstrated in the first days after ischemic stroke.^{9,30} Such changes were not uniformly detected for static CA.³¹ The reasons for this general dynamic impairment is not clear but it is not likely to be a direct or exclusive effect of the acute infarction.³⁰ It rather reflects pre-existing endothelial dysfunction with multiple vascular risk factors. This may exacerbate shortly after larger cortical stroke. It would lead to the conclusion that dynamic CA is disturbed in most strokes but fortunately the hemodynamic and practical consequences of this seem limited with upright positioning.

With the upright position there was a consistent decrease in etCO₂. This decrease in etCO₂ is a common finding that might be a consequence of maintained alveolar ventilation with reduced CO₂ return to the lungs as venous return decreases with tilt. It is well established that reductions in arterial etCO₂ will cause an increase in vascular resistance. Thus, regulation of CBF on going to the head-up position is the sum of the complex interactions of altered pressure gradient, cerebral vessel dilation to counter the reduction in perfusion pressure, increased cerebral venous return, and vasoconstriction resulting from lower arterial etCO₂. Patients had lower etCO₂ levels in the baseline supine position. However, several studies reported improved dynamic and static CA with hypocapnia and therefore seems unlikely to explain the found differences.³²

Upright positioning in acute stroke

It is widely believed that a sudden BP reduction can affect CBF and render elderly subjects or patients with cerebrovascular disease vulnerable to orthostatic symptoms.³³ Especially with impaired cerebral CA, the sitting position is thought to be dangerous to acute stroke patients because of susceptibility of the penumbral regions to local hypoperfusion. However, our results indicate that sitting is well tolerated in mildly to moderately affected patients with acute stroke and seems independent of dynamic autoregulatory impairment. This

may be due to the counterbalancing effects of BP elevation (with adequate hydration), ICP reduction and increased venous return to stabilize cerebral perfusion pressure in the acute phase of stroke. There is also evidence for increased sympathetic activation in acute stroke patients.³⁴⁻³⁶ Replication of this study should be considered using more sophisticated and direct methods that measure CBF and cerebral oxygen metabolism.³⁷ Follow-up studies several days after stroke may be warranted because systemic compensatory mechanisms may become exhausted or cerebral autoregulation may deteriorate.³⁸ Our results do not hold for early sitting to the standing (out of bed) mobilisation, which may provoke different (probably larger) hemodynamic responses.³ In the paucity of results for the early out of bed mobilisation stroke trials,³⁹ we suggest to continue early upright positioning of stroke patients in the stroke unit and propose that continuous CBF measurements during early activity out of bed could be the next investigation to reassure safe stroke unit early mobilisation.

CONCLUSION

In conclusion, upright positioning in mildly to moderately affected ischemic stroke patients in the stroke unit appears to be safe during the first 3 Days on the stroke unit, despite suggestions of a disturbed dynamic CA. Supine or Trendelenburg positioning seems not to augment MCA CBFV_{mean} or improve neurological status.

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Supplemental Table 1 Postural CBFV_{mean} and rSO₂ changes (normalized values) for stroke patients (n=47) on Day 1

Position Δ	CBFV _{mean} AH (95% CI)	CBFV _{mean} UH (95% CI)	Δ CBFV _{mean} UH (95% CI)	p value#	CBFV _{mean} UH (95% CI)	Δ CBFV _{mean} UH (95% CI)	p value#	rSO ₂ AH (95% CI)	Δ rSO ₂ AH (95% CI)	p value#	rSO ₂ UH (95% CI)	Δ rSO ₂ UH (95% CI)	p value#	
0°→15°	1.0 (0.99 to 1.03)	1.02 (0.99 to 1.04)	0.02 (-0.05 to 0.03)	1.0	1.0 (0.98 to 1.01)	1.01 (0.99 to 1.04)	0.01 (-0.05 to 0.02)	1.0	1.01 (1.01 to 1.01)	0.02 (0.01 to 0.04)	0.04	1.03 (1.01 to 1.04)	0.02 (0.01 to 0.04)	0.04
0°→45°	1.0 (0.99 to 1.03)	1.02 (0.99 to 1.04)	0.01 (-0.03 to 0.04)	1.0	1.00 (0.98 to 1.01)	0.99 (0.97 to 1.01)	-0.01 (-0.03 to 0.04)	1.0	0.99 (1.01 to 1.01)	-0.02 (-0.04 to -0.01)	0.01	0.99 (1.01 to 1.01)	-0.01 (-0.03 to 0.01)	0.56
0°→70°	1.0 (0.99 to 1.03)	0.97 (0.95 to 1.0)	-0.04 (-0.06 to -0.03)	0.005	1.00 (0.98 to 1.01)	0.98 (0.96 to 1.0)	-0.02 (-0.05 to 0)	1.0	0.99 (1.01 to 1.01)	-0.02 (-0.03 to -0.01)	0.006	0.99 (1.01 to 1.01)	-0.02 (-0.03 to -0.01)	0.009
45°→70°	1.02 (0.99 to 1.04)	0.97 (0.95 to 1.0)	-0.04 (-0.08 to -0.01)	0.05	0.99 (0.97 to 1.01)	0.98 (0.96 to 1.0)	-0.01 (-0.04 to 0.02)	1.0	0.99 (0.98 to 1.0)	0 (-0.02 to 0.02)	1.0	0.99 (0.98 to 1.0)	0 (-0.02 to 0.02)	1.0

AH indicates affected hemisphere; UH, unaffected hemisphere.
P values with (Bonferroni) correction for multiple comparisons.

Supplemental Table 2 Postural CBFV_{mean} and rSO₂ changes (normalized values) for stroke patients (n=33) on Day 3

Position Δ	CBFV _{mean} AH (95% CI)	CBFV _{mean} AH (95% CI)	Δ CBFV _{mean} AH (95% CI)	p value#	CBFV _{mean} UH (95% CI)	Δ CBFV _{mean} UH (95% CI)	p value#	rSO ₂ AH (95% CI)	Δ rSO ₂ AH (95% CI)	p value#	rSO ₂ UH (95% CI)	Δ rSO ₂ UH ² (95% CI)	p value#
0°→15°	1.01 (0.99 to 1.03)	1.02 (0.99 to 1.05)	0.01 (-0.04 to 0.06)	1.0	1.01 (1.0 to 1.03)	1.03 (1.0 to 1.05)	0.01 (-0.03 to 0.05)	1.03 (1.01 to 1.04)	0.06 (0.04 to 0.08)	0.001	1.05 (1.03 to 1.06)	0.02 (0.01 to 0.05)	0.03
0°→ 45°	1.01 (0.99 to 1.03)	0.97 (0.95 to 1.0)	-0.04 (-0.08 to 0.01)	0.38	1.01 (1.0 to 1.03)	0.98 (0.96 to 1.0)	-0.03 (-0.07 to 0.01)	1.03 (1.01 to 1.04)	0.99 (0.97 to 1.0)	<0.001	0.99 (0.98 to 1.0)	-0.03 (-0.06 to -0.01)	<0.001
0°→ 70°	1.01 (0.99 to 1.03)	0.94 (0.92 to 0.96)	-0.07 (-0.10 to -0.03)	<0.001	1.01 (1.0 to 1.03)	0.96 (0.94 to 0.98)	-0.05 (-0.08 to -0.02)	1.03 (1.01 to 1.04)	1.00 (0.99 to 1.01)	0.004	1.00 (0.99 to 1.01)	-0.02 (-0.04 to -0.01)	0.02
45°→ 70°	0.97 (0.95 to 1.0)	0.94 (0.92 to 0.96)	-0.03 (-0.08 to 0.02)	1.0	0.98 (0.96 to 1.0)	0.96 (0.94 to 0.98)	-0.02 (-0.06 to 0.02)	0.99 (0.97 to 1.0)	1.00 (0.99 to 1.01)	1.0	1.00 (0.99 to 1.01)	0.01 (-0.04 to 0.01)	1.0

AH indicates affected hemisphere; UH, unaffected hemisphere.
P values with (Bonferroni) correction for multiple comparisons.

Supplemental Table 3 Postural CBFV_{mean} and rSO₂ changes (normalized values) for healthy controls (n=20)

Position Δ	CBFV (95% CI) ^{mean}	CBFV (95% CI) ^{mean}	Δ CBFV (95% CI) ^{mean}	p value [#]	rSO ₂ (95% CI)	rSO ₂ (95% CI)	Δ rSO ₂ (95% CI)	p value [#]
0°→15°	0.98 (0.95 to 1.01)	0.98 (0.94 to 1.02)	0 (-0.06 to 0.06)	1.0	0.99 (0.98 to 1.01)	1.02 (1.0 to 1.03)	0.02 (0 to 0.05)	0.13
0°→45°	0.98 (0.95 to 1.01)	0.96 (0.92 to 1.0)	-0.02 (-0.08 to 0.04)	1.0	0.99 (0.98 to 1.01)	0.97 (0.96 to 0.99)	-0.02 (-0.04 to 0.01)	1.0
0°→70°	0.98 (0.95 to 1.01)	0.93 (0.90 to 0.97)	-0.04 (-0.08 to -0.01)	0.04	0.99 (0.98 to 1.01)	0.97 (0.95 to 0.98)	-0.03 (-0.05 to -0.01)	0.002
45°→70°	0.96 (0.92 to 1.0)	0.93 (0.90 to 0.97)	-0.02 (-0.08 to 0.06)	1.0	0.97 (0.96 to 0.99)	0.97 (0.95 to 0.98)	-0.01 (-0.04 to 0.02)	1.0

AH indicates affected hemisphere; UH, unaffected hemisphere.

[#] P values with (Bonferroni) correction for multiple comparisons.

Supplemental Table 4 Comparison of postural CBFV_{mean} and rSO₂ changes (normalized values) between Day 1 and 3 measurements

Position	CBFV _{mean} AH Day 1 (95% CI)	CBFV _{mean} AH Day 3 (95% CI)	Δ CBFV _{mean} AH (95% CI)	p value#	CBFV _{mean} Day 1 UH (95% CI)	CBFV _{mean} Day 3 UH (95% CI)	Δ CBFV _{mean} UH (95% CI)	p value#	rSO ₂ AH Day 1 (95% CI)	rSO ₂ AH Day 3 (95% CI)	Δ rSO ₂ AH (95% CI)	p value#	rSO ₂ UH Day 1 (95% CI)	rSO ₂ UH Day 3 (95% CI)	Δ rSO ₂ UH (95% CI)	p value#
-15°	1.02 (0.99 to 1.04)	1.02 (0.99 to 1.05)	0 (-0.05 to 0.06)	1.0	1.01 (0.99 to 1.04)	1.03 (1.0 to 1.05)	0.01 (-0.04 to 0.06)	1.0	1.03 (1.01 to 1.05)	1.06 (1.04 to 1.08)	0.03 (0 to 0.06)	0.15	1.03 (1.01 to 1.04)	1.05 (1.03 to 1.06)	0.02 (-0.01 to 0.05)	0.54
0°	1.01 (0.99 to 1.03)	1.01 (0.99 to 1.03)	0 (-0.03 to 0.03)	1.0	1.00 (0.98 to 1.01)	1.01 (1.0 to 1.03)	0.02 (-0.01 to 0.04)	1.0	1.01 (1.0 to 1.01)	1.03 (1.01 to 1.04)	0.01 (0 to 0.03)	0.13	1.01 (1.0 to 1.01)	1.02 (1.01 to 1.03)	0.02 (0.01 to 0.03)	0.01
45°	1.02 (0.99 to 1.04)	0.97 (0.95 to 1.0)	-0.04 (-0.08 to 0.01)	0.46	0.99 (0.97 to 1.01)	0.98 (0.96 to 1.0)	-0.01 (-0.06 to 0.04)	1.0	0.99 (0.98 to 1.0)	0.99 (0.97 to 1.0)	0 (-0.03 to 0.03)	1.0	0.99 (0.98 to 1.0)	0.99 (0.98 to 1.0)	0 (-0.03 to 0.02)	1.0
70°	0.97 (0.95 to 1.0)	0.94 (0.92 to 0.96)	-0.03 (-0.07 to 0.01)	0.29	0.98 (0.96 to 1.0)	0.96 (0.94 to 0.98)	-0.02 (-0.05 to 0.02)	1.0	0.99 (0.98 to 1.0)	1.0 (0.99 to 1.01)	0 (-0.03 to 0.02)	1.0	0.99 (0.98 to 1.0)	1.00 (0.99 to 1.01)	0.01 (-0.05 to 0.01)	1.0

AH indicates affected hemisphere; UH, unaffected hemisphere.
P values with (Bonferroni) correction for multiple comparisons.

Supplemental Table 5 Comparison of postural CBFV_{mean} and rSO₂ changes (normalized values) between affected and unaffected hemisphere on Day 1 (n=47)

Position Δ	CBFV _{mean} difference (95% CI)	CBFV _{mean} difference (95% CI)	Δ (95% CI)	p value [#]	rSO ₂ difference (95% CI)	rSO ₂ difference (95% CI)	Δ (95% CI)	p value [#]
0°→15°	0·01 (-0·01 to 0·03)	0 (-0·02 to 0·03)	-0·01 (-0·04 to 0·03)	1·0	0·01 (0 to 0·01)	0·01 (0 to 0·02)	0 (-0·02 to 0·02)	1·0
0°→45°	0·01 (-0·01 to 0·03)	0·02 (0 to 0·05)	0·01 (-0·03 to 0·05)	1·0	0·01 (0 to 0·01)	0 (-0·01 to 0·01)	-0·01 (-0·03 to 0·01)	1·0
0°→70°	0·01 (-0·01 to 0·03)	-0·01 (-0·03 to 0·02)	-0·02 (-0·05 to 0·02)	1·0	0·01 (0 to 0·01)	0 (0 to 0·01)	0 (-0·01 to 0·02)	1·0
45°→70°	0·02 (0 to 0·05)	-0·01 (-0·03 to 0·02)	0 (-0·02 to 0·07)	1·0	0 (-0·01 to 0·01)	0 (0 to 0·01)	0·01 (-0·01 to 0·03)	1·0

[#] P values with (Bonferroni) correction for multiple comparisons.

Supplemental Table 6 Comparison of postural CBFV_{mean} and rSO₂ changes (normalized values) between affected and unaffected hemisphere on Day 3 (n=33)

Position Δ	CBFV _{mean} difference (95% CI)	CBFV _{mean} difference (95% CI)	Δ (95% CI)	p value [#]	rSO ₂ difference (95% CI)	rSO ₂ difference (95% CI)	Δ (95% CI)	p value [#]
0°→15°	-0·01 (-0·03 to 0·02)	-0·01 (-0·04 to 0·03)	0 (-0·05 to 0·05)	1·0	0 (-0·01 to 0·01)	0·01 (0 to 0·03)	0·01 (-0·02 to 0·03)	1·0
0°→45°	-0·01 (-0·03 to 0·02)	-0·01 (-0·04 to 0·02)	0 (-0·05 to 0·04)	1·0	0 (-0·01 to 0·01)	0 (-0·01 to 0·01)	0 (-0·02 to 0·03)	1·0
0°→70°	-0·01 (-0·03 to 0·02)	-0·02 (-0·05 to 0)	-0·02 (-0·05 to 0·02)	1·0	0 (-0·01 to 0·01)	0 (-0·02 to 0·01)	0 (-0·03 to 0·01)	1·0
45°→70°	-0·01 (-0·04 to 0·02)	-0·02 (-0·05 to 0)	-0·01 (-0·06 to 0·04)	1·0	0 (-0·01 to 0·01)	0 (-0·02 to 0·01)	0 (-0·03 to 0·02)	1·0

[#] P values with (Bonferroni) correction for multiple comparisons.

Supplemental Table 7 Comparison of postural CBFV mean and rSO₂ changes (normalized values) between patients (n=47) and healthy controls (n=20) on Day 1

Position	CBFV _{mean} (95% CI)	CBFV _{mean} (95% CI)	Δ CBFV _{mean} (95% CI)	CBFV _{mean} (95% CI)	CBFV _{UH} (95% CI)	p value#	CBFV _{mean} (95% CI)	Δ CBFV _{mean} (95% CI)	CBFV _{UH} (95% CI)	p value#	rSO ₂ AH (95% CI)	Δ rSO ₂ (95% CI)	rSO ₂ UH (95% CI)	Δ rSO ₂ (95% CI)	p value#
-15°	1.02 (0.99 to 1.04)	0.98 (0.94 to 1.02)	0.04 (-0.11 to 0.05)	1.01 (0.99 to 1.04)	0.98 (0.94 to 1.02)	1.0	1.01 (0.99 to 1.04)	0.03 (-0.09 to 0.04)	1.03 (1.01 to 1.05)	1.0	1.02 (1.0 to 1.03)	0.02 (-0.02 to 0.05)	1.03 (1.01 to 1.04)	0.01 (-0.03 to 0.04)	1.0
0°	1.00 (0.99 to 1.03)	0.98 (0.95 to 1.01)	0.03 (-0.09 to 0.03)	1.00 (0.98 to 1.01)	0.98 (0.95 to 1.01)	1.0	1.00 (0.98 to 1.01)	0.02 (-0.07 to 0.03)	1.01 (1.0 to 1.01)	1.0	0.99 (0.98 to 1.01)	0.02 (-0.02 to 0.02)	1.01 (1.0 to 1.01)	0.01 (-0.04 to 0.01)	1.0
45°	1.03 (0.99 to 1.04)	0.96 (0.92 to 1.0)	0.06 (-0.13 to 0.02)	0.99 (0.97 to 1.0)	0.96 (0.92 to 1.0)	0.93	0.99 (0.97 to 1.0)	0.04 (-0.10 to 0.03)	0.99 (0.98 to 1.0)	1.0	0.97 (0.96 to 0.99)	0.01 (-0.05 to 0.02)	0.99 (0.98 to 1.0)	0.02 (-0.05 to 0.02)	1.0
70°	0.97 (0.95 to 1.0)	0.93 (0.90 to 0.97)	0.04 (-0.11 to 0.03)	0.98 (0.96 to 1.0)	0.93 (0.90 to 0.97)	1.0	0.98 (0.96 to 1.0)	0.05 (-0.10 to 0.01)	0.99 (0.98 to 1.0)	0.44	0.97 (0.95 to 0.98)	0.03 (-0.06 to 0.01)	0.99 (0.98 to 1.0)	0.02 (-0.05 to 0.01)	0.42

AH indicates affected hemisphere; UH, unaffected hemisphere.

P values with (Bonferroni) correction for multiple comparisons.

Supplemental Table 8 Comparison of postural CBFV_{mean} and rSO₂ changes (normalized values) between patients (n=33) and healthy controls (n=20) on Day 3

Position	CBFV _{mean} (95% CI)	CBFV _{mean} (95% CI)	Δ CBFV _{mean} (95% CI)	CBFV _{mean} (95% CI)	CBFV _{UH} (95% CI)	p value#	CBFV _{mean} (95% CI)	Δ CBFV _{mean} (95% CI)	CBFV _{UH} (95% CI)	p value#	rSO ₂ AH (95% CI)	Δ rSO ₂ (95% CI)	rSO ₂ UH (95% CI)	Δ rSO ₂ (95% CI)	p value#
-15°	1.02 (0.99 to 1.05)	0.98 (0.94 to 1.02)	0.04 (-0.12 to 0.05)	1.03 (1.01 to 1.05)	1.01 (0.99 to 1.03)	1.0	1.03 (1.01 to 1.05)	0.04 (-0.11 to 0.03)	1.03 (1.01 to 1.05)	1.0	1.02 (1.0 to 1.04)	0.04 (0.01 to 0.08)	1.02 (1.0 to 1.04)	0.03 (-0.01 to 0.07)	0.34
0°	1.01 (0.99 to 1.03)	0.98 (0.95 to 1.01)	0.03 (-0.09 to 0.03)	1.01 (0.99 to 1.03)	0.98 (0.95 to 1.01)	1.0	1.01 (0.99 to 1.03)	0.04 (-0.08 to 0.01)	1.03 (1.01 to 1.04)	0.66	0.99 (0.98 to 1.01)	0.03 (0.01 to 0.06)	0.99 (0.98 to 1.01)	0.03 (0.01 to 0.06)	0.005
45°	0.97 (0.95 to 1.0)	0.96 (0.92 to 1.0)	0.01 (-0.09 to 0.07)	0.98 (0.96 to 1.0)	0.96 (0.92 to 1.0)	1.0	0.98 (0.96 to 1.0)	0.02 (-0.09 to 0.04)	0.99 (0.97 to 1.0)	1.0	0.97 (0.96 to 0.99)	0.01 (-0.05 to 0.02)	0.99 (0.98 to 1.0)	0.01 (-0.05 to 0.02)	1.0
70°	0.94 (0.92 to 0.96)	0.93 (0.90 to 0.97)	0.01 (-0.08 to 0.06)	0.96 (0.94 to 0.98)	0.93 (0.90 to 0.97)	1.0	0.96 (0.94 to 0.98)	0.03 (-0.08 to 0.03)	0.97 (0.95 to 0.98)	0.12	0.97 (0.95 to 0.98)	0.03 (-0.06 to 0)	0.97 (0.95 to 0.98)	0.04 (-0.07 to 0)	0.09

AH indicates affected hemisphere; UH, unaffected hemisphere.

P values with (Bonferroni) correction for multiple comparisons.

Supplemental Table 9 Postural systemic hemodynamic and ventilation changes (normalized values) for stroke patients (n=47) on Day 1

Position Δ	Mean Arterial Pressure (95% CI)	Δ Mean Arterial Pressure (95% CI)	p value #	Heart Rate (95% CI)	Δ Heart Rate (95% CI)	p value #	etCO ₂ (95% CI)	Δ etCO ₂ (95% CI)	p value #
0°→15°	1.05 (1.02 to 1.07)	1.17 (1.13 to 1.20)	<0.001	1.0 (0.99 to 1.02)	1.02 (1.0 to 1.04)	1.0	1.0 (0.98 to 1.01)	0 (-0.03 to 0.03)	1.0
0°→45°	1.05 (1.02 to 1.07)	0.90 (0.87 to 0.93)	<0.001	1.0 (0.99 to 1.02)	1.01 (0.99 to 1.03)	1.0	0.98 (0.97 to 1.0)	-0.01 (-0.04 to 0.01)	1.0
0°→70°	1.05 (1.02 to 1.07)	0.90 (0.87 to 0.93)	<0.001	1.0 (0.99 to 1.02)	1.04 (1.02 to 1.05)	<0.001	0.97 (0.95 to 0.98)	-0.03 (-0.05 to -0.01)	<0.001
45°→70°	0.90 (0.87 to 0.93)	0.90 (0.87 to 0.93)	0.92	1.01 (0.99 to 1.03)	1.04 (1.02 to 1.05)	0.27	0.97 (0.97 to 1.0)	-0.02 (-0.05 to 0.01)	1.0

P values with (Bonferroni) correction for multiple comparisons.

Supplemental Table 10 Postural systemic hemodynamic and ventilation changes (normalized values) for stroke patients (n=33) on Day 3

Position Δ	Mean Arterial Pressure (95% CI)	Δ Mean Arterial Pressure (95% CI)	p value #	Heart Rate (95% CI)	Δ Heart Rate (95% CI)	p value #	etCO ₂ (95% CI)	Δ etCO ₂ (95% CI)	p value #
0°→15°	1.05 (1.02 to 1.08)	1.17 (1.13 to 1.21)	<0.001	1.01 (0.99 to 1.02)	1.0 (0.98 to 1.02)	1.0	0.98 (0.97 to 0.99)	0.01 (-0.04 to 0.03)	1.0
0°→45°	1.05 (1.02 to 1.08)	0.88 (0.84 to 0.92)	<0.001	1.01 (0.99 to 1.02)	1.02 (1.0 to 1.05)	1.0	0.97 (0.96 to 0.99)	-0.01 (-0.04 to 0.03)	1.0
0°→70°	1.05 (1.02 to 1.08)	0.88 (0.85 to 0.91)	<0.001	1.01 (0.99 to 1.02)	1.05 (1.04 to 1.08)	<0.001	0.94 (0.92 to 0.95)	-0.04 (-0.07 to -0.02)	<0.001
45°→70°	0.88 (0.84 to 0.92)	0.88 (0.85 to 0.91)	1.0	1.02 (1.0 to 1.05)	1.05 (1.04 to 1.07)	1.0	0.94 (0.92 to 0.95)	-0.04 (-0.07 to -0.01)	0.02

P values with (Bonferroni) correction for multiple comparisons.

Supplemental Table 11 Postural systemic hemodynamic and ventilation changes (normalized values) for healthy controls (n=20) on Day 3

Position Δ	Mean Arterial Pressure (95% CI)	Mean Arterial Pressure (95% CI)	Δ Mean Arterial Pressure (95% CI)	<i>p</i> value #	Heart Rate (95% CI)	Heart Rate (95% CI)	Δ Heart Rate (95% CI)	<i>p</i> value #	etCO ₂ (95% CI)	etCO ₂ (95% CI)	Δ etCO ₂ (95% CI)	<i>p</i> value #
0° \rightarrow 15°	1.02 (0.99 to 1.06)	1.14 (1.09 to 1.20)	0.12 (0.04 to 0.20)	<0.001	0.98 (0.96 to 1.0)	0.98 (0.95 to 1.01)	0 (-0.05 to 0.05)	1.0	0.98 (0.96 to 1.0)	1.00 (0.97 to 1.02)	0.02 (-0.03 to 0.06)	1.0
0° \rightarrow 45°	1.02 (0.99 to 1.06)	0.84 (0.79 to 0.89)	-0.18 (-0.26 to -0.10)	<0.001	0.98 (0.96 to 1.0)	1.01 (0.98 to 1.04)	0.02 (-0.02 to 0.07)	1.0	0.98 (0.96 to 1.0)	0.97 (0.95 to 0.99)	-0.01 (-0.05 to 0.03)	1.0
0° \rightarrow 70°	1.02 (0.99 to 1.06)	0.85 (0.81 to 0.89)	-0.17 (-0.24 to -0.11)	<0.001	0.98 (0.96 to 1.0)	1.04 (1.02 to 1.06)	0.06 (0.02 to 0.09)	<0.001	0.98 (0.96 to 1.0)	0.95 (0.93 to 0.97)	-0.03 (-0.06 to 0)	0.15
45° \rightarrow 70°	0.84 (0.79 to 0.89)	0.85 (0.79 to 0.89)	0.01 (-0.09 to 0.08)	1.0	1.01 (0.98 to 1.04)	1.04 (1.02 to 1.06)	0.03 (-0.02 to 0.08)	1.0	0.97 (0.95 to 0.99)	0.95 (0.93 to 0.97)	-0.02 (-0.06 to 0.02)	1.0

P values with (Bonferroni) correction for multiple comparisons.



CHAPTER 9

NEAR INFRARED SPECTROSCOPY FOR THE DETECTION OF DESATURATIONS IN VULNERABLE ISCHEMIC BRAIN TISSUE: A PILOT STUDY AT THE STROKE UNIT BEDSIDE

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ABSTRACT

Background and purpose

There is uncertainty whether bilateral near-infrared spectroscopy (NIRS) can be used for monitoring of acute stroke patients.

Methods

The NIRS responsiveness to systemic and stroke-related changes was studied overnight by assessing the effects of brief peripheral arterial oxygenation (SpO_2) and mean arterial pressure (MAP) alterations in the affected versus nonaffected hemisphere in 9 patients with acute stroke.

Results

Significantly more NIRS drops were registered in the affected compared to the nonaffected hemisphere (477 drops versus 184, $p < 0.001$). In the affected hemispheres nearly all SpO_2 drops ($n = 128$; 96%) were detected by NIRS; in the nonaffected hemispheres only 23% ($n = 30$; $p = 0.17$). Only a few MAP drops were followed by a significant NIRS drop. This was however significantly different between both hemispheres (32% versus 13%, $p = 0.01$).

Conclusions

This pilot study found good responsiveness of NIRS signal to systemic and stroke related changes at the bedside but requires confirmation in a larger sample.

INTRODUCTION

In patients on stroke units, parameters like blood pressure (BP) and peripheral arterial oxygenation (SpO₂) are continuously monitored. It would probably be more relevant to be informed bedside on cerebral perfusion and metabolism. Near-infrared spectroscopy (NIRS) allows noninvasive measurement of regional cerebral oxygen saturation (rSO₂) with high time resolution. NIRS measurements are derived from a sample volume of one third of arterial blood and intra- or extracellular tissue, and two thirds of venous blood. Relative contributions vary depending on several systemic (e.g., BP and oxygenation) and local stroke related factors (e.g., ischemia and autoregulation).¹ As such, NIRS may provide a useful summary measure of factors that determine blood oxygenation in the early cerebral venous phase. A first requirement for use of NIRS in stroke unit monitoring would be that NIRS measurements are responsive to such systemic and stroke-related changes.

In this pilot study, NIRS responsiveness was studied by assessing the effects of brief SpO₂ and BP alterations in the affected versus nonaffected hemisphere. Obstructive sleep apnea syndrome, highly prevalent in acute stroke patients, serves as an attractive in vivo model for such changes. Questions addressed in this study in the first 24 hours after stroke are: (1) does bilateral frontal NIRS change after nocturnal SpO₂ change and relative hypotension (responsiveness to systemic changes) (2) can NIRS demonstrate differences between affected and nonaffected hemispheres after SpO₂ and BP changes (responsiveness to stroke related changes)?

METHOD

Patients

After local ethics committee approval and with informed consent, 9 patients were studied overnight within 24 hours after anterior circulation stroke. Patients with severe aphasia and hemodynamic instability were excluded. All patients received standard stroke unit care and work-up including ultrasound examination of extracranial vessels. Measurements were started from 10.00 pm onwards, ending the next morning or at the patient's request.

Near-infrared spectroscopy

The INVOS 5100C device (Somanetics Corp, Detroit, MI) was used with a sampling frequency of 0.2 Hz. Adhesive optodes were placed on each side of the forehead according to the manufacturer's recommendations. NIRS was incorporated into a continuous overnight monitoring system with noninvasive BP (Portapres; Finapres Medical Systems, Amsterdam, The Netherlands) and SpO₂ measurement (derived from Vitaport 4; TEMEC Instruments, the Netherlands). Data signals were digitized and collected at 40 Hz (Labview, National Instruments, Texas, USA). BP was measured unilaterally using 2 finger cuffs in alternation.

Beat-to-beat values were normalized over the period of 1 finger measurement (15 minutes) to overcome variance caused by cuff switch. For NIRS and SpO₂, a drop of 4% was defined as significant, for mean arterial pressure (MAP) a drop of 20%.² The correlations between significant NIRS signal decrease and BP or SpO₂ decreases were evaluated at or up to 30 seconds prior to the NIRS drop. All patients received overnight polygraphy including nasal airflow, thoracoabdominal movement and SpO₂ measurement (Vitaport 4, TEMEC Instruments, The Netherlands) to screen for periods of hypopnea or apnea. NIRS hemispheric signals were compared by Wilcoxon Rank sum tests.

RESULTS

Nine patients were included with a total overnight recording time of 2.898 minutes (range, 115-580 minutes) representing 49 hours. Patient characteristics are presented in Table 1. Ultrasound bedside examination demonstrated flow in both middle cerebral arteries insonated at a depth of 40 to 50 mm in all patients. Table 2 provides individual nocturnal

Table 1 Patient characteristics (n = 9)

Variable	
Gender: male	3 (33)
Admission median NIHSS [IQR]	6 [3-13]
Age, y, mean ± SD	71 ± 10
rSO ₂ %, mean ± SD Affected hemisphere Nonaffected hemisphere	68.4 ± 6 72.6 ± 7
MAP, mmHg, mean ± SD Heart rate, beats/minute, mean ± SD SpO ₂ %, mean ± SD	88.1 ± 18 77.1 ± 17 94.9 ± 2
Stroke subtype Large artery atherosclerosis Cardioembolism Small vessel occlusion	1 (11) 4 (44) 4 (44)
Carotid artery abnormalities	1 (11)
BMI, mean ± SD	30 (6)
Median O ₂ supply overnight, l/min [IQR]	2 [1-2]
Modified Rankin Score at 3 mo 0-2 3-6	5 (56) 4 (44)
Apnea-Hypopnea Index, N/h# < 5 5-15 > 15	4 (50) 0 4 (50)

Values are numbers (%), unless otherwise indicated.
Abbreviations: NIHSS indicates national institutes of health stroke scale; IQR, interquartile range; MAP, mean arterial pressure; BMI, body mass index; SD, standard deviation
In 1 patient, the polygraphy data were lost.

changes in NIRS and its relation with significant SpO₂ and MAP drops. Two patients had problematic SpO₂ measurements. Overall, 133 significant SpO₂ and 414 significant MAP drops were recorded. Significantly more NIRS drops were registered in the affected compared to the nonaffected hemisphere (477 drops versus 184, $p < 0.001$). In the affected hemispheres 96% of 133 SpO₂ drops were detected by NIRS; in the nonaffected hemispheres only 23% of 133 ($p = 0.17$). Only a few MAP drops were followed by a significant NIRS drop; 32% in affected versus 13% in nonaffected hemisphere ($p = 0.01$; Table 2). In comparison to lacunar stroke, the difference in NIRS drops between affected and nonaffected hemisphere was more pronounced in cortical stroke (127 versus 70 and 350 versus 114 drops, respectively). No correlation between overnight disability score change and NIRS drops was found (Table 2).

Table 2 Nocturnal changes in NIRS and the relationship with significant MAP and SpO₂ drops (n = 9)

Patient No.	Recording Time, min	Stroke Subtype	Overnight NIHSS Improvement	Total SpO ₂ Drop (>4%)	Total MAP drop (> 20%)	Hemisphere	Total NIRS drop (>4%)	SpO ₂ Drop (>4%) Detected by NIRS (%)	MAP Drop (>20%) Detected by NIRS (%)
1	343	PACI	0	33	AH NAH	2 5	1 (3) 1 (3)
2	139	LACI	0	11	28	AH NAH	23 9	6 (55) 6 (55)	6 (21) 5 (18)
3	115	PACI	0	3	2	AH NAH	17 26	3 (100) 3 (100)	0 (0) 1 (50)
4	163	LACI	0	16	AH NAH	14 8	4 (25) 3 (19)
5	424	LACI	2	2	6	AH NAH	85 43	2 (100) 2 (100)	3 (50) 5 (83)
6	400	TACI	1	0	52	AH NAH	13 2	13 (25) 0 (0)
7	283	LACI	0	0	19	AH NAH	5 10	0 (0) 3 (16)
8	451	PACI	0	16	56	AH NAH	122 39	16 (100) 10 (63)	14 (25) 5 (9)
9	580	TACI	0	101	202	AH NAH	196 42	101 (100) 9 (9)	90 (45) 31 (16)
Total	2.898			133	414	AH NAH	477 184	128 (96) 30 (23)	131(32) 54 (13)

Values are numbers (%).

Abbreviations: NIRS indicates near-infrared spectroscopy; AH, affected hemisphere; NAH, nonaffected hemisphere; SpO₂, peripheral arterial oxygen; MAP, mean arterial pressure; TACI, total anterior circulation infarction; PACI, partial anterior circulation infarction; LACI, lacunar circulation infarction; NIHSS, national institutes of health stroke scale.

DISCUSSION

In this pilot study, 96% of systemic desaturations were rapidly followed by local cerebral desaturations as measured by NIRS. Also, BP drops were more likely to be followed by NIRS drops in the affected than in the nonaffected hemisphere. Local nocturnal cerebral desaturations were more than twice as likely in the affected hemisphere.

NIRS is noninvasive and easy to employ in a stroke unit setting, although experience in acute stroke is limited. In 1 study, different rSO_2 patterns in both hemispheres were demonstrated for patients with space-occupying stroke. Real-time NIRS assessment may be used to manage brain swelling and planning of hemicraniectomy.³ Our results suggest that NIRS can also be employed for detection of less severe complications, such as systemic events that could harm the ischemic brain. Nearly all SpO_2 drops (96%) were detected by NIRS. A similar positive correlation between SpO_2 changes and cerebral rSO_2 during sleep has been reported in OSA patients with clear improvement after CPAP treatment.⁴ These results support the sensitivity of NIRS to SpO_2 in an acute stroke population. Our data suggest that NIRS measurements reflect responses that are specific to the affected hemisphere, especially for cortical stroke. This responsiveness to stroke related changes makes NIRS an attractive technique when studying vulnerability of ischemic brain tissue to changes in the internal environment.

A limitation of our study is the small patient sample. Also, a large proportion of the NIRS drops was not explained by periods of SpO_2 drop and/or relative hypotension, pointing to the complex multifactorial contributions to the NIRS signal.⁵ More studies are needed to understand the interplay between local rSO_2 changes and cerebral perfusion pressure, SpO_2 , intrathoracic pressure changes, CO_2 levels, collateral flow and local oxygen consumption and distribution patterns.

In summary, this pilot study found good responsiveness of NIRS signal to systemic challenges and stroke related changes albeit in a small sample. After confirmation in a larger sample, further studies would need to (1) delineate the exact meaning and prognostic significance of NIRS changes in ischemic brain and (2) elucidate the mechanisms behind NIRS changes not explained by systemic desaturations.

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CHAPTER 10

CONTINUOUS MONITORING OF CEREBROVASCULAR REACTIVITY USING PULSE WAVEFORM OF INTRACRANIAL PRESSURE

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ABSTRACT

Background

Guidelines for the management of traumatic brain injury (TBI) call for the development of accurate methods for assessment of the relationship between cerebral perfusion pressure (CPP) and cerebral autoregulation and to determine the influence of quantitative indices of pressure autoregulation on outcome. We investigated the relationship between slow fluctuations of arterial blood pressure (BP) and intracranial pressure (ICP) pulse amplitude (an index called PAX) using a moving correlation technique to reflect the state of cerebral vasoreactivity and compared it to the index of pressure reactivity (PRx) as a moving correlation coefficient between averaged values of BP and ICP.

Methods

A retrospective analysis of prospective 327 TBI patients (admitted on neurocritical care unit of a university hospital in the period 2003 to 2009) with continuous BP and ICP monitoring.

Results

PAX was worse in patients who died compared to those who survived (-0.04 ± 0.15 vs -0.16 ± 0.15 , $\chi^2 = 28$, $p < 0.001$). In contrast to PRx, PAX was able to differentiate between fatal and nonfatal outcome in a group of 120 patients with ICP levels below 15 mmHg (-0.04 ± 0.16 vs -0.14 ± 0.16 , $\chi^2 = 6$, $p = 0.01$).

Conclusions

PAX is a new modified index of cerebrovascular reactivity which performs equally well as established PRx in long-term monitoring in severe TBI patients, but importantly is potentially more robust at lower values of ICP. In view of establishing an autoregulation-oriented CPP therapy, continuous determination of PAX is feasible but its value has to be evaluated in a prospective controlled trial.

INTRODUCTION

The latest Brain Trauma Foundation guidelines for the management of traumatic brain injury (TBI) call for the development of ‘minimally invasive, efficient and accurate methods for determining the relationship between cerebral perfusion pressure (CPP) and cerebral autoregulation’ and conclude ‘there is a need for randomised trials of the influence on outcome of basing optimal CPP [...] on quantitative indices of pressure autoregulation’.¹

Among such indices of cerebral autoregulation, the most commonly used in neurocritical care units (NCCU) is the pressure reactivity index (PRx), which reflects the capability of smooth muscle tone in the wall of cerebral arterioles to react to changes in transmural pressure.^{2,3} Several studies confirmed the prognostic significance of PRx and highlighted the opportunity of individualised optimisation of CPP based on bedside PRx monitoring.⁴ The PRx technology is based on continuous monitoring of the robust signals intracranial pressure (ICP) and arterial blood pressure (BP) and their computer integration by means of a simple calculation algorithm. The physiological principle of PRx is based on the following: when cerebral pressure reactivity is intact, a slow increase in BP will lead to vasoconstriction, with a subsequent reduction in cerebral blood volume (CBV) and therefore a decrease in ICP. Or to put in other words, when cerebral pressure reactivity is intact, BP and ICP are negatively correlated. On the other hand, when cerebral pressure reactivity is compromised, cerebral vessels dilate or collapse passively in response to changes in BP, and therefore ABP and ICP are positively correlated. The calculation is based on a major assumption: that changes in cerebrovascular resistance must be reflected in changes in CBV and, more importantly for the paper at hand, that changes in CBV must be reflected in changes in ICP.^{5,6} This assumption holds true when intracranial compliance is low, which is the case for higher ICP values. Yet, what happens when intracranial compliance artificially increases due to medical therapies or, much more dramatically, by surgical interventions such as decompressive craniectomy? The limited evidence available showed that PRx initially worsened after decompressive craniectomy.^{3,7} This finding could either be a genuine account of changes in cerebrovascular dynamics following decompression or, equally likely, could be an artefact caused by the fact that changes in CBV are not reflected in changes in mean ICP.^{8,9}

The pulsatile component of ICP (often referred to as ICP pulse amplitude) reflects beat-to-beat changes in CBV and carries significant clinical and pathophysiological information.¹⁰⁻¹³ Cardiac pulses in BP produce pulsatile expansions of the walls of the cerebral arteries (and thus pulsation in CBV) which in turn are the cause of the pulsatile component of pressure in the surrounding brain and cerebral spinal fluid (CSF). This transmission depends most of all on the compliance of the cerebral vessels, which is a function of the vascular tone and therefore is modulated by the state of the cerebrovascular reactivity. Therefore, it is assumed that even with low levels of ICP changes in vascular tone brought about by slow waves in BP will be reflected by changes in the BP to ICP pulse transmission. In a recent study with 293 TBI patients with intermittent transcranial Doppler (TCD) recordings the autoregulation

index Mx correlated strongly with a new index, termed PAX, reflecting pressure reactivity via the correlation coefficient between fluctuations of BP and ICP pulse amplitude, using a technique similar to the one used for the PRx index.¹⁴

In this study the relationship between the PAX and PRx indices was investigated in TBI patients with long-term monitoring. We hypothesised that the PAX index would reflect the state of cerebral vasoreactivity in a similar way to PRx, but would be more robust at low values of ICP. To this end a large database of patients with severe TBI over a 7-year period was retrospectively analysed.

METHODS

Material

We analysed retrospectively recordings of BP and ICP waveforms from 327 patients with severe TBI, admitted to the NCCU of Addenbrooke's hospital in Cambridge in the period 2003 to 2009. Anonymised digital recordings of physiological parameters and clinical outcomes were stored in a password-protected computer database. During monitoring all patients were sedated, intubated and mechanically ventilated with etCO₂ maintained in the mild hypocapnia range (4-4.5 kPa). A CPP/ICP driven protocol was used aiming for a CPP around 65 - 70 mmHg and ICP below 25 mmHg.¹⁵ The baseline neurological status of each patient was determined using the Glasgow Coma Score (GCS). The post resuscitation GCS was used in patients who allowed sedation discontinuation immediately following hospital admission.¹⁶ In patients who were deemed too unstable to undergo formal neurological assessment on admission the GCS collected on scene was used. Clinical outcome was assessed at 6 months using the Glasgow Outcome Scale (GOS). All data were recorded as part of standard clinical care. Patient's representatives were individually consented for using computerized data recorded with approval of our Local Ethical Committee and the permission to use anonymized clinical audit data was obtained from the NCCU User's Group.

Methods

BP was monitored invasively through radial or femoral artery using a standard pressure monitoring kit (Baxter Healthcare Corp, CardioVascular Group, Irvine, CA USA). ICP was monitored using an intraparenchymal probe (Codman ICP MicroSensor, Codman & Shurtleff Inc., Raynham, MA, USA) inserted via a cranial access device (triple bolt).¹⁷ All signals were digitised using an A/D converter (DT9800 series, Data Translation, Marlboro, Mass. USA), sampled at a frequency of 100 Hz and recorded using a laptop PC with ICM+ software (Cambridge Enterprise, Cambridge, UK, <http://www.neurosurg.cam.ac.uk/icmplus>). The same software was used for the retrospective analysis of physiological monitoring data. Time-averaged values of ICP, BP and CPP (CPP = ICP - ABP) were calculated using waveform time integration over 60 second intervals.

Cerebrovascular reactivity indices

PRx was calculated as a short-term moving Pearson correlation coefficient between changes in 30 consecutive, 10 second averages of BP and corresponding ICP signals (with 80% overlap of data).² Averaging over 10 seconds was used to suppress influence of the pulse wave and the respiratory wave. The same algorithm was used for PAr calculation except that mean ICP was replaced by pulse amplitude of the ICP signal. The ICP pulse amplitude was calculated as the fundamental harmonic of the pulse component in a fast Fourier Transform decomposition of the ICP signal.

Statistical analysis

All the data were expressed as mean or median values with their range or standard deviation (SD) where appropriate. To evaluate the relationship between CPP, ICP and the vasoreactivity indices in all patients, 1 hour averages were used. For correlation with outcome analysis, one mean value of the variables PRx, PAr, CPP and ICP was calculated for each patient. Nonparametric statistical methods were used where variables failed the normality test. Partial rank-correlation coefficients as well as analysis of variance (ANOVA, Kruskal-Wallis test) were used to investigate statistical relationships between the studied (continuous) variables: baseline GCS, patients' age and GOS at 6 months. Multivariate logistic regression analysis was used to identify independent associations between the pressure indices and outcome. A receiver operating characteristic (ROC) curve was calculated to compare the accuracy in predicting mortality using PRx, PAr and ICP using non-parametric methods for estimating standard errors (SE) and applying the method described by DeLong et al. for comparisons between two (correlated) parameters.¹⁸ Tests were considered statistically significant for values $p < 0.05$. Statistical analysis was performed using SPSS (version 16.0; IBM Inc., Chicago IL, USA).

RESULTS

Patients

The database population included 327 patients, (246 males, 75%), ranging in age from 15 to 87 year old (median age: 36 years). The median baseline GCS score was 6 and ranged from 3 to 15; 25% of patients had a baseline GCS > 8 , but their condition subsequently deteriorated, requiring neurocritical care and warranting invasive monitoring. The initial GCS score and GOS score were missing in 7 (2%) and 5 (1.5%) patients, respectively. Outcomes were grouped as follows: good recovery, $n = 51$ (16%); moderate disability, $n = 82$ (25%), severe disability, $n = 105$ (32%), persistent vegetative state, $n = 9$ (3%) and death, $n = 75$ (23%). Patients in persistent vegetative state were excluded from further outcome analysis because this group is disproportionately smaller than other outcome groups, leaving 313 patients for outcome analysis. Duration of data recording ranged between 1 and 28 days per patient with a mean of 4 days.

Table 1 Spearman partial Rank correlation coefficients and their significance levels calculated between the analyzed parameters (n = 327)

	Age	GCS	CPP	ICP	BP	PRx
GCS	0.17 $p = 0.004$					
CPP	0.07 $p = 0.23$	0.07 $p = 0.24$				
ICP	-0.08 $p = 0.16$	0.01 $p = 0.82$	-0.56 $p < 0.001$			
BP	0.03 $p = 0.66$	0.09 $p = 0.13$	0.91 $p < 0.001$	0.29 $p < 0.001$		
PRx	0.17 $p = 0.004$	0.03 $p = 0.58$	-0.11 $p = 0.05$	0.16 $p = 0.004$	-0.02 $p = 0.71$	
PAX	0.35 $p < 0.001$	0.06 $p = 0.27$	-0.15 $p = 0.008$	0.17 $p = 0.004$	-0.1 $p = 0.09$	0.63 $p < 0.001$

Control variables used for partial correlation test: age, GCS, ICP, ABP and PRx (or PAX).

Abbreviations: GCS indicates Glasgow Coma Scale; CPP, cerebral perfusion pressure; ICP, intracranial pressure; BP, blood pressure.

General exploratory correlations

Spearman partial rank correlation coefficients between averaged (for every patient) values of PRx, PAX, ICP, ABP, CPP, baseline GCS, and age are presented in Table 1. Lower baseline GCS was significant associated with lower age. There was no correlation between baseline GCS and any of the other variables. Higher age correlated only with higher PRx (0.17, $p = 0.004$) and PAX (0.35, $p < 0.001$). PRx and PAX correlated positively with ICP, negatively with CPP and ABP. Patients who died had significant higher ICP (22.6 ± 14 versus 15.8 ± 5 , $\chi^2 = 21$, $p < 0.001$) and lower CPP (73.6 ± 12.2 versus 78.4 ± 6.6 , $\chi^2 = 12$, $p = 0.001$).

Comparison between PAX and the PRx

Mean PRx was 0.03 (SD 0.17, range 1.11) and mean PAX -0.13 (SD 0.16, range 1.07). PAX showed a significant correlation with PRx ($R = 0.63$, $p < 0.001$) (Table 1). The correlation decreased somehow in patients with mean ICP below 15 mmHg ($R = 0.59$, $p < 0.001$, $n = 120$) and improved in patients with ICP levels above 15 mmHg ($R = 0.68$, $p < 0.001$, $n = 207$). Both indices presented similar changes during recording intervals. In an example of refractory intracranial hypertension, both PAX and PRx were capable of detecting severe (not reversible) impairment of vasoreactivity (Figure 1a). During plateau waves in ICP both indices of PAX and PRx were temporarily assuming values close to +0.5, indicating impairment of vasoreactivity (Figure 1b). Figure 1c shows an example of ICP, CPP and vasoreactivity indices before and after decompressive craniectomy. PAX improved immediately after surgery and seemed more stable in comparison to PRx (Figure 1c).

Figure 1a

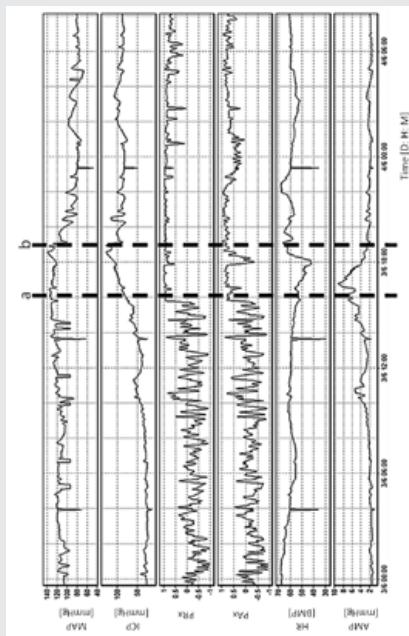


Figure 1b

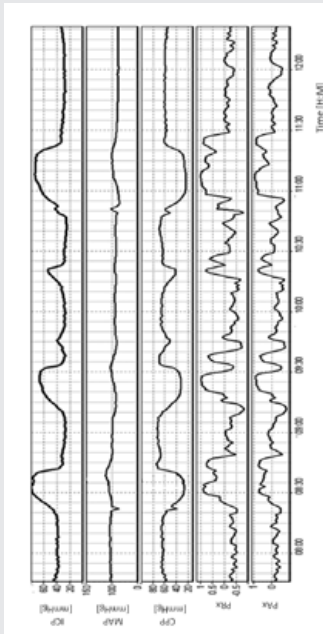
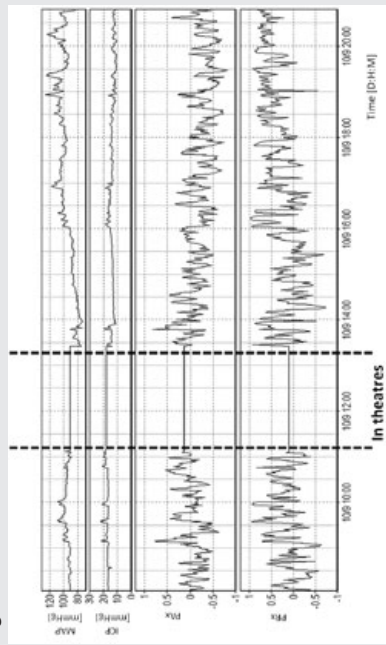


Figure 1c



Example of continuous monitoring of PAX and PRx in a patient developing suddenly refractory intracranial hypertension (Figure 1a). The values of both indices increased to > 0.5 past line *a*. Three hours later brainstem herniation was indicated by drop in mean arterial pressure (line *b*). The sudden drop in ICP pulse amplitude at very high ICP represents the upper breakpoint of the ICP pulse amplitude-ICP relationship. Example of PAX and PRx calculated continuously and changing over time (Figure 1b). During plateau waves in ICP both indices have temporarily values > 0.5 , indicating active vasodilatation at the onset and exhausted vasoreactivity during the wave. Graph of a patient's PRx and PAX before and after secondary decompressive craniectomy (Figure 1c). The mean ICP level is around 20 mmHg before surgery with worsening of the vasoreactivity parameters. After the craniectomy ICP decreased to approximately 12 to 15 mmHg and CPP increased to levels around 100 mmHg. PRx improved postoperatively to values around 0 but deteriorated later to positive values around 0.5. PAX levels slowly decreased to -0.5 indicating stable improved vascular reactivity after surgery.

Figure 2a

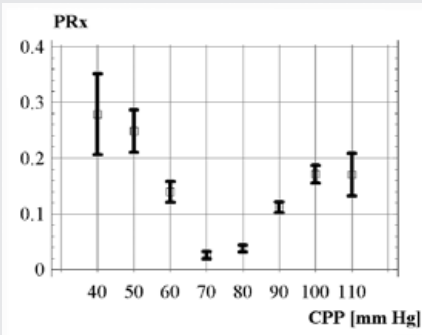
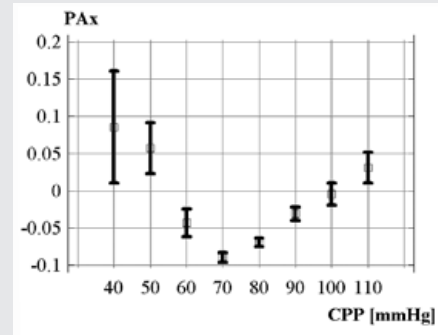
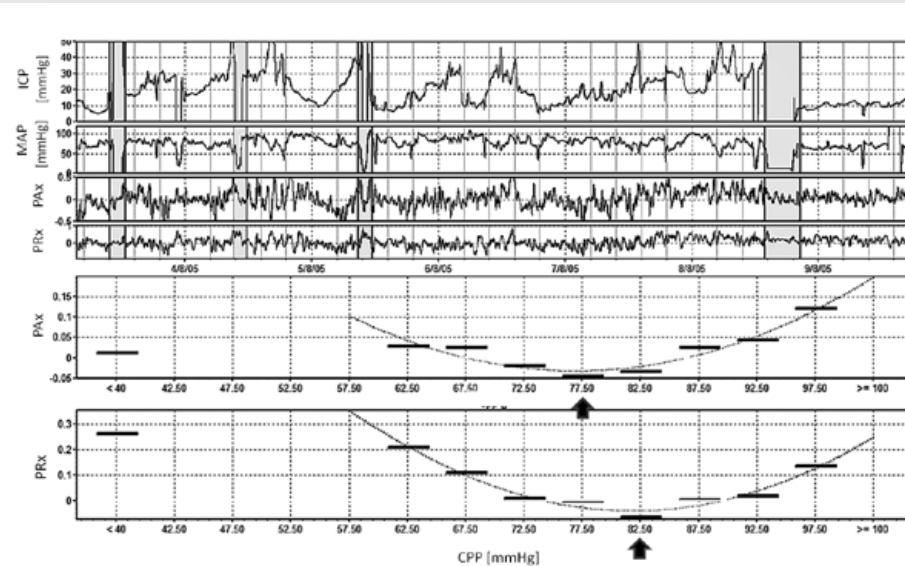


Figure 2b



Pressure reactivity indices (PRx and PAX) versus cerebral perfusion pressure ($n = 327$). Below 60 and above 80 mmHg the cerebrovascular pressure reactivity deteriorates. Error bars represent 95% confidence intervals.

Figure 3



This figure shows ICP and CPP recordings for several days in a severe TBI patient. The PRx/CPP and PAX/CPP plot allows retrospective assessment of optimal CPP, i.e. the CPP value for which pressure reactivity (PRx or PAX) has the most negative value. For this patient the optimal CPP seems to be between 77.5 and 82.5 mmHg (arrows).

Comparison of pressure indices with CPP

ANOVA plots of PRx and PAX versus mean CPP are presented in Figure 2. Looking at both PRx and PAX the lowest (optimal) pressure reactivity is achieved around a CPP of 70 mmHg in

Figure 4a

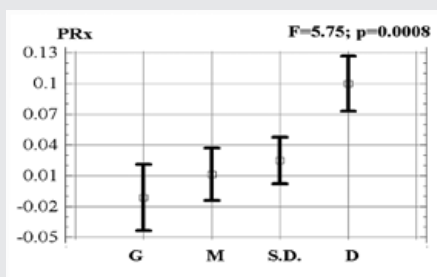
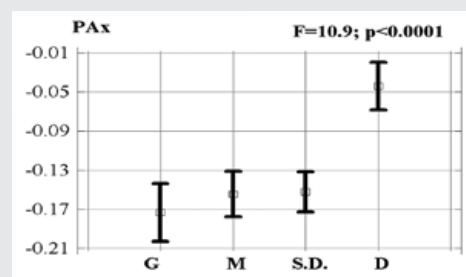


Figure 4b



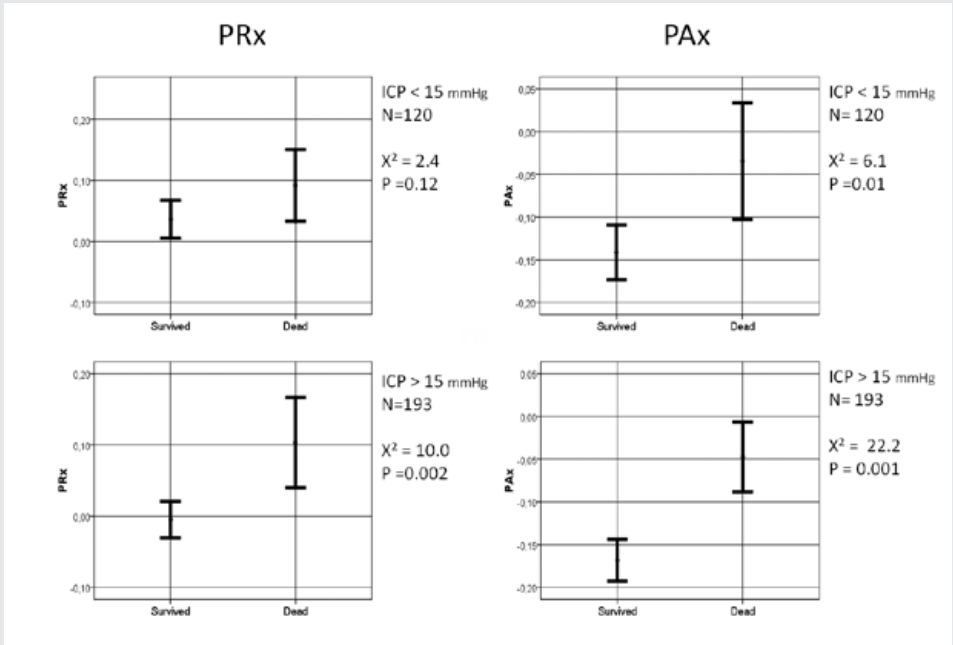
Distribution of PRx and PAX across different outcome groups ($n = 313$). Outcome was assessed 6 months after the injury. Vertical bars represent 95% confidence intervals. Outcome: G Good; M Moderate; S.D. Severe Disability; D Dead. A. The PRx values increased with worse outcome (ANOVA, $F = 5.75$, $p < 0.001$). B. The mean PAX value is the same in all outcome groups with the exception of patients who died (ANOVA, $F = 10.9$, $p < 0.001$).

our patient cohort. For both PRx and PAX a nearly linear association between worse pressure reactivity and higher CPP levels, starting from 80 mmHg, can be seen. At low CPP levels (< 60 mmHg) a sharp increase in the both PRx and PAX values is seen with higher absolute mean values. Figure 3 shows an example of a pressure reactivity index (using both PRx and PAX) versus CPP plot in a patient recording of several days that allows determination of the individual optimal CPP (retrospectively).

Comparison of pressure indices with outcome

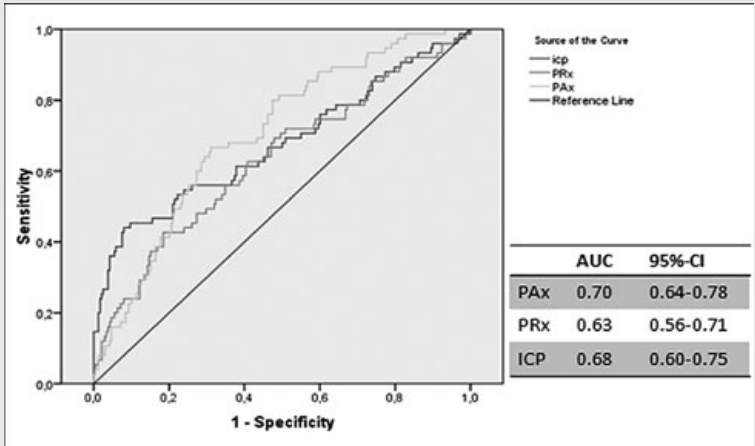
Figure 4 demonstrates distributions of PRx (a) and PAX (b) across the four outcome groups. Mean PRx was worse in patients who died compared to those who survived (0.10 ± 0.21 vs 0.01 ± 0.15 , respectively; $\chi^2 = 12$, $p = 0.001$). The same was true for PAX but the association was stronger (-0.04 ± 0.15 versus -0.16 ± 0.15 , $\chi^2 = 28$, $p < 0.001$). Figure 5 demonstrates that in contrast to PRx, PAX is still able to differentiate between fatal and non-fatal outcome in patients with mean ICP levels below 15 mmHg (-0.04 ± 0.16 versus -0.14 ± 0.16 , $\chi^2 = 6$, $p = 0.01$, $n = 120$). In a stepwise multivariate analysis, PAX (odds ratio (OR) 114, 95%-confidence interval (CI) 9.0-1418, $p < 0.001$) and PRx (OR 9.8, 95%-CI 1.5-64, $p < 0.001$) were very strong independent predictors of mortality. Other independent predictors for mortality were higher age, higher ICP and lower GCS score, while low CPP was not. In the model with PAX or PRx only ICP and baseline GCS were independent predictors of favorable outcome defined as good recovery and moderate disability (GOS 4-5). Estimating the area under the curve in ROC analysis, PAX had the highest diagnostic value for mortality in comparison to PRx and ICP (Figure 6). The differences were small and only for the comparison between PAX and PRx significant (differences between areas 0.07, 95%-CI 0.005-0.13, $p = 0.04$).

Figure 5



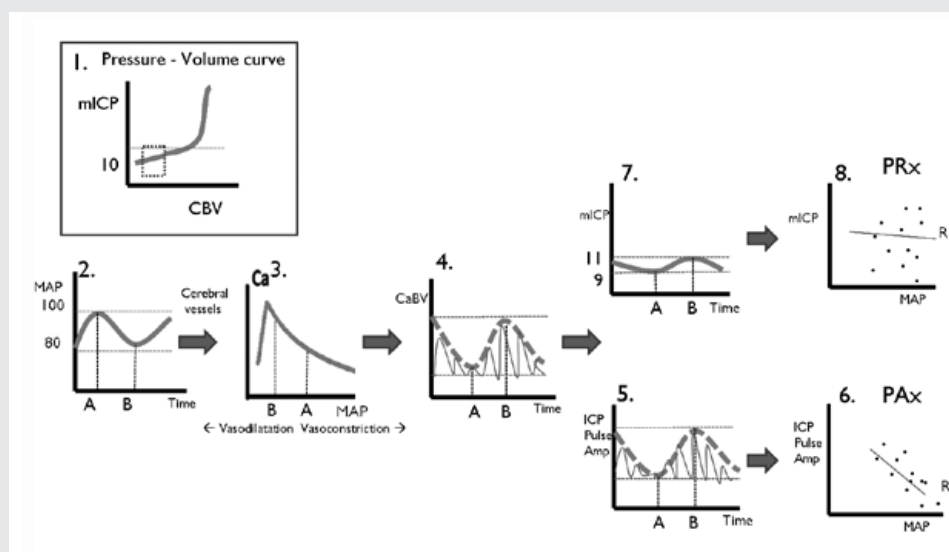
Error bar plots of dichotomized (fatal) outcome using PRx and PAX for patients with low to normal (< 15 mmHg) and intermediate to high (> 15 mmHg) mean ICP levels. In contrast to PRx, PAX is able to differentiate between the two outcome groups independent of the level of ICP. Statistics were calculated using the Kruskal-Wallis test.

Figure 6



Receiver Operating Characteristic analysis of predictive power of ICP, PRx and PAX for mortality showing highest AUC (area under the curve) values attributed to PAX and thus confirming its strongest link to mortality.

Figure 7



Explanation of the mechanism how PAX can express cerebrovascular reactivity at lower mean ICP (mICP) levels (flat part of the pressure-volume curve) (1). The hypothesized mechanism is that slow changes in mean arterial pressure (MAP), with reactive vessels (2), produce proportional changes in arterial smooth muscle tension, therefore causing an inverse change in the arterial compliance (Ca) (3). Changes in the compliance results in direct change of passive transmission of MAP pulse to ICP pulse amplitude (ICP pulse AMP). In this way, with reactive vessels, slow decrease in MAP produces increase in the compliance of cerebral arteries (vasodilatation with increasing arterial blood volume (CaBV) at time point B.) promoting stronger passive transmission of the pulse wave to ICP (4, 5), indicating a negative correlation index PAX (6). For PRx at the same levels of mICP the correlation between mICP and MAP changes may be less predictable (flat pressure-volume curve) (7, 8).

DISCUSSION

In this retrospective analysis, we tested the hypothesis that PAX, a novel index for the continuous assessment of cerebral vasoreactivity based on the analysis of ICP pulse amplitude, was more robust than the established parameter PRx. The results showed that in this series of more than 300 TBI patients with continuous bedside monitoring PAX was indeed a stronger independent predictor of fatal outcome than PRx. In contrast to PRx, PAX could also differentiate between fatal and non-fatal outcome in patients with normal to low ICP levels (Figure 5).

Background of PAX

Despite being widely validated,^{3,19} a potential limitation of the PRx methodology is in its dependence on the pressure-volume characteristic of the brain. Essentially, fluctuations in

ICP are treated as surrogates of fluctuations in CBV, which in turn respond to changes in BP. When the pressure-volume curve is flat (such as in the case of decompressive craniectomy or, in general, with elevated intracranial compliance) vasogenic changes in CBV may not result in sufficiently significant changes in ICP to warrant reliable calculation of PRx.^{8,9} In order to overcome the problem of weak transmission of volume to pressure at low ICP values, a feature of ICP signal was studied which more directly reflects the vascular tone, its pulse amplitude. When the pressure-volume curve is steep (at higher ICP values with low intracranial compliance), ICP pulse amplitude changes in the same direction as mean ICP changes (linear behaviour).^{8,9,20} and therefore we expect P_{Ax} to behave in the same way as PRx.

On the other hand, we hypothesized, that at low levels of ICP, when the link between mean BP and mean ICP is diminished by the flat pressure-volume curve, the relationship between mean BP and ICP pulse amplitude should be maintained by the active adjustment of the vascular compliance. Our model is explained in Figure 7. With reactive vessels, a significant decrease in mean BP will lead to active smooth muscle relaxation and subsequent increase of the vascular compliance (less stiff vessels). Increased compliance of the cerebral vessels augments transmission of BP pulse to ICP pulse and as a result ICP pulse amplitude increases with decreasing BP.^{21,22} This dynamic relationship does not rely on the pressure-volume characteristic of the brain and therefore is independent of the level of ICP. For non-reactive vessels the negative relationship between mean BP and ICP pulse amplitude is abolished due to the inability of cerebral vessels to actively change their tone, and therefore vascular compliance as a response to fluctuations of BP.^{6, 21}

P_{Ax} compared to PRx

A linear relationship between ICP pulse amplitude and mean ICP has been found in healthy animals and humans, at least up to mean ICP between 30 and 60 mmHg,^{8,20,23} so we were not surprised to find a good correlation between PRx and P_{Ax}, particularly at higher ICP levels. Similarly to PRx, P_{Ax} when plotted against CPP forms a U-shaped curve defining a CPP value at which pressure reactivity is optimal or in other words that too low or too high CPP values are unsuitable to maintain adequate cerebral blood flow (Figure 2). Interestingly, higher (more positive) absolute values of both PRx and P_{Ax} are seen with lower CPP levels compared to high CPP levels, which suggests that cerebral vessels compensate hypertension more easily than hypotension (Figure 2). Similarly to PRx, P_{Ax} allows for the identification of individual optimal CPP ranges (Figure 3). Both indices identified consistent values of optimal CPP. P_{Ax} correlates with outcome after severe TBI. It differentiates patients with fatal outcome from those who survive at 6 months. In contrast to PRx, this correlation seemed to be maintained for P_{Ax} in patients with mean normal to low ICP levels (Figure 5). This finding could suggest that P_{Ax} is a more robust estimator of cerebrovascular pressure reactivity in TBI patients. The correlation of P_{Ax} with patient outcome is independent of mean ICP: in the multivariate analysis both variables were included in the model.

Why a new index?

Several ‘autoregulation’ and ‘vascular reactivity’ indices were reported in the past. With intermittent TCD monitoring, autoregulation can be assessed, according to its definition, as a correlation between blood flow velocity and CPP. Unfortunately, with current TCD probe holders, monitoring over longer period is not feasible. Techniques involving near-infrared spectroscopy (NIRS) are easier for continuous monitoring but still need more accurate evaluation.²⁴ Their link to outcome following TBI is still not very well established. Unknown limited sample volume (hypothetically frontal cortical tissue) makes interpretation of the data difficult in cases of multifocal injuries. Indices derived from ICP and BP signals seem to be more robust. These modalities, fundamental in brain monitoring and management of TBI, are relatively artefact-free and can be monitored over long period. PRx has been accepted in many different centres and its analysis, particularly for assessing ‘optimal’ CPP seems feasible in many scenarios.⁴ Unfortunately the index is rather ‘noisy’. This may be partially due to the pressure-volume curve dependent link between CBV and mean ICP. Thus in scenarios involving high brain compliance, such as for example after decompressive craniectomy, P_{Ax} monitoring should potentially work better and be studied in near future.

Limitations

Several limitations deserve to be mentioned. Prospective data on a pressure reactivity-guided intensive care therapy are missing from the literature. This is also a major limitation of our own results given that all the analyses were performed retrospectively and some data like pupil reactivity on admission (as a strong prognostic factor for outcome of TBI) were not recorded. A further limitation of this study is the use of a very specific, although standard, intensive care management strategy with patients having different monitoring periods. Furthermore, we cannot rule out the impact of treatment on cerebral dynamics in the patients, in whom medications impacting vascular dynamics are commonly used. In such a large database, it is difficult to analyse changes caused by alterations in specific medications, regime of ventilation, core temperature control, and an influence of all complex environment of highly technologically dependent NCCU. These variables should be thus treated as unavoidable ‘background noise’ and the only remedy to minimize its influence is averaging large volumes of data. Furthermore, the present study did not have data regarding any ‘static’ autoregulatory measures with (BP) interventions, so validation of bedside P_{Ax} with more complex static rate of autoregulation is lacking at the moment.

CONCLUSION

P_{Ax} is a new modified index of cerebrovascular reactivity which performs equally well as established PRx in long-term monitoring in severe TBI patients, but importantly is potentially independent of the level of ICP.

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CHAPTER 11

CONTINUOUS DETERMINATION OF OPTIMAL CEREBRAL PERFUSION PRESSURE IN TRAUMATIC BRAIN INJURY

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ABSTRACT

Objectives

We have sought to develop an automated methodology for the continuous updating of optimal cerebral perfusion pressure (CPP_{opt}) for patients after severe traumatic head injury (TBI) using continuous monitoring of cerebrovascular pressure reactivity. We then validated the CPP_{opt} algorithm by determining the association between outcome and the deviation of actual CPP from CPP_{opt} .

Design and setting

Retrospective analysis of prospectively collected data. Neurosciences critical care unit of a university hospital.

Patients

A total of 327 TBI patients admitted between 2003 and 2009 with continuous monitoring of arterial blood pressure (BP) and intracranial pressure (ICP).

Measurements and Main Results

BP, ICP, and CPP were continuously recorded and pressure reactivity index (PRx) was calculated online. Outcome was assessed at 6 months. An automated curve fitting method was applied to determine CPP at the minimum value for PRx (CPP_{opt}). A time trend of CPP_{opt} was created using a moving 4-hr window, updated every minute. Identification of CPP_{opt} was, on average, feasible during 55% of the whole recording period. Patient outcome correlated with the continuously updated difference between CPP and CPP_{opt} ($\chi^2 = 45$, $p < 0.001$; outcome dichotomized into fatal and nonfatal). Mortality was associated with relative 'hypoperfusion' ($CPP < CPP_{opt}$), severe disability with 'hyperperfusion' ($CPP > CPP_{opt}$) and favorable outcome was associated with smaller deviations of CPP from the individualized CPP_{opt} . While deviations from global target CPP values of 60 and 70 mmHg were also related to outcome, these relationships were less robust.

Conclusions

Real-time CPP_{opt} could be identified during the recording time of majority of the patients. Patients with a CPP close to CPP_{opt} were more likely to have a favorable outcome than those in whom mean CPP was widely different from CPP_{opt} . Deviations from individualized CPP_{opt} were more predictive of outcome than deviations from a common target CPP. CPP management to optimize cerebrovascular pressure reactivity should be the subject of future clinical trial in severe TBI patients.

INTRODUCTION

Survival after traumatic brain injury (TBI) is dependent on the control of intracranial hypertension and the provision of hemodynamic support to achieve an 'adequate' cerebral perfusion pressure (CPP). However, the idea of a single value (or even a single range) of CPP being adequate for the diverse group of TBI patients is an oversimplification.¹⁻³ Age and pre-morbid arterial blood pressure (BP) are examples of factors likely to influence individual CPP targets, with elderly, hypertensive patients requiring a higher CPP compared to young, normotensive patients. Although multimodal brain monitoring, including continuous brain tissue oxygenation, near-infrared spectroscopy, transcranial Doppler ultrasonography and microdialysis provide valuable information at the bedside regarding the adequacy of CPP, these technologies are costly and restricted to a relatively small number of specialised neurocritical care units (NCCU). The 2007 Brain Trauma Foundation guidelines advocated randomized controlled trials to verify the feasibility and the impact on outcome of strategies based on individualised CPP management following severe TBI.⁴ A method for individualization of CPP oriented management based on determination of cerebrovascular reactivity (using the pressure reactivity index (PRx); a moving correlation coefficient between slow waves of intracranial pressure (ICP) and BP)⁵ was proposed in 2002.⁶ It was shown that a narrow CPP target (CPP_{opt}) could be identified by defining the level of best cerebrovascular reactivity using PRx. The deviation from CPP_{opt} was associated with worse outcome. However, the CPP_{opt} range was calculated retrospectively from recordings of the whole period of ICP monitoring. The findings, therefore, are not necessarily applicable to a prospective interventional strategy, which would require more rapid and repetitive assessments of CPP_{opt}. Further, the determination of CPP_{opt} in that study was done by visual inspection of PRx measurements stratified across CPP ranges, an impediment to regular updating.

The objective of this study was to develop and validate an algorithm for the objective, automated and continuous updating of CPP_{opt}, derived from a clinically useful time window of 4 hrs. Such an algorithm is necessary for a prospective trial of PRx monitoring to guide individualized CPP management after TBI. The algorithm presented in this manuscript was validated by measuring the observed association between outcome and continuous deviation of CPP from calculated CPP_{opt}.

MATERIALS AND METHODS

Monitoring of BP and ICP in patients following TBI has been an integral part of the routine clinical management. The computerised data storage protocol was reviewed and approved by the local ethics committee of Addenbrooke's Hospital, Cambridge University and the NCCU User's Group. With individual consents from patient representatives, we retrospectively

analysed anonymized digital recordings of BP and ICP waveforms from 327 consecutive patients with severe TBI, admitted to the NCCU at Addenbrooke's Hospital between 2003 and 2009. All patients were sedated, intubated, and mechanically ventilated during the recording period. A CPP/ICP-oriented protocol for management of head injury was used with CPP maintained > 60 mmHg and ICP < 20 mmHg.⁷ The baseline neurological status of each patient was determined using the Glasgow Coma Score (GCS). The postresuscitation GCS was used in patients who had sedation discontinuation immediately following hospital admission. In patients who were deemed too unstable to undergo formal neurological assessment on admission the GCS collected on scene was used. The clinical outcome was assessed at 6 months using the Glasgow Outcome Scale (GOS).⁸ All monitoring modalities recorded in the study were used as standard clinical care.

Data acquisition and Processing

BP was monitored invasively through the radial or femoral artery using a standard pressure monitoring kit (Baxter Healthcare Corp, CardioVascular Group, Irvine, CA USA). BP was zeroed at the level of the right atrium. ICP was monitored using an intraparenchymal probe (Codman ICP MicroSensor, Codman & Shurtleff Inc., Raynham, MA, USA) inserted into the frontal cortex. All signals were digitised using an A/D converter (DT9801, Data Translation, Marlboro, Mass. USA), sampled at a frequency of 100 Hz and recorded using a laptop PC with ICM+ software (University of Cambridge, Cambridge Enterprise, Cambridge, United Kingdom, <http://www.neurosurg.cam.ac.uk/icmplus>). The same software was later used for the retrospective analysis of all stored signals. Time-averaged values of ICP, BP and CPP (CPP = BP - ICP) were calculated using waveform time integration over 60-sec intervals. Cerebrovascular pressure reactivity (PRx) was calculated as a moving Pearson correlation coefficient between 30 consecutive, 10-sec averaged values of BP and corresponding ICP signals (with 80% overlap of data).⁹ Averaging over 10 secs was used to suppress the influence of the pulse- and respiratory-frequency wave components. Positive correlation between BP and ICP at low frequency is indicative of passive cerebral vasculature and impaired autoregulation. Zero or negative correlation between BP and ICP at the same frequency is indicative of reactive vasculature and intact autoregulation.¹⁰⁻¹² Artefacts were identified and excluded manually from analysis after the data collection.

Data analysis

For determination of CPP_{opt} in individual patients, a 5-min median CPP time trend was calculated alongside PRx. These PRx values were divided and averaged into CPP bins spanning 5 mmHg. An automatic curve fitting method (see Appendix for details) was applied to the binned data to determine the CPP value with the lowest associated PRx value. A time trend of CPP_{opt} calculated in this way, was recorded from a moving 4-hr time window (so called CPP_{opt}) updated every minute. The first CPP_{opt} curve could be generated when at least 50% of the required data points of PRx were available, i.e., after a minimum of 2 hrs of monitoring.

An illustrative example from an individual patient is shown in Figure 1. Note that when the fitted curve does not include the convex point the estimated 'optimal' value will be either underestimated (ascending curve) or overestimated (descending curve) depending on the shape of the fitted part (Figure 1B and C). In addition, the optimal CPP for the whole monitoring period (so called $CPP_{opt\ total}$, as in Steiner et al) was calculated.⁶ For exploratory analysis (Table 1), values of measured variables from each patient were averaged over the whole monitoring period, so every patient was represented by one set of data containing mean arterial pressure (MAP), ICP, CPP, and PRx. In individual patients, the differences between CPP_{opt} and median CPP for the moving window periods were calculated continuously ($\Delta CPP = \text{median CPP} - CPP_{opt}$). The ΔCPP was averaged for every patient for the whole monitoring period, separately for CPP above and below CPP_{opt} . Additionally, the difference between $CPP_{opt\ total}$ and median CPP for the whole monitoring period was calculated ($\Delta CPP_{total} = \text{median CPP}_{total} - CPP_{opt\ total}$). We calculated the number of patients with $CPP_{opt\ total}$ values above, below or close (± 5 mmHg) to the median CPP.

Outcome was dichotomized in two ways: First as favorable (good recovery, moderate disability) vs unfavorable outcome (severe disability, persistent vegative state, and death), second as fatal outcome (death) versus nonfatal outcome (persistent vegetative state, severe disability, moderate disability and good recovery). Groups were compared using the nonparametric Kruskal-Wallis test because the values in the majority of groups were not normally distributed.

Figure 1a

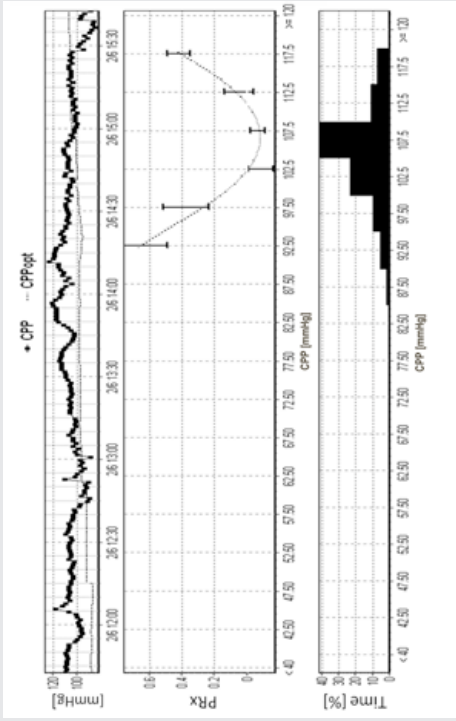


Figure 1b

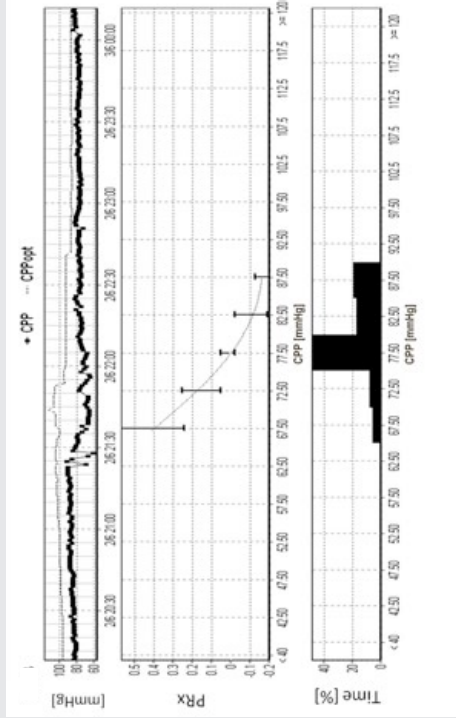
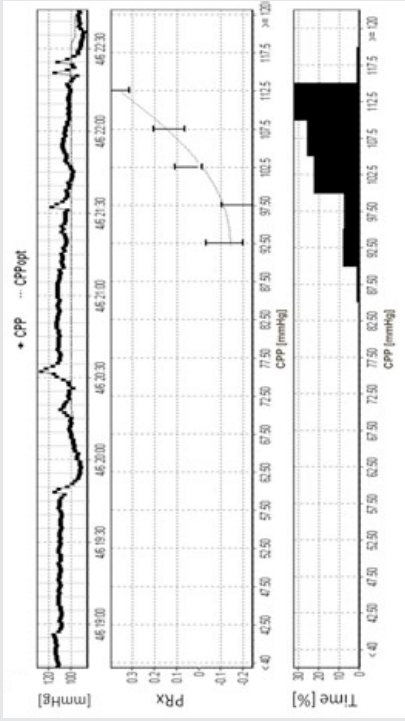


Figure 1c



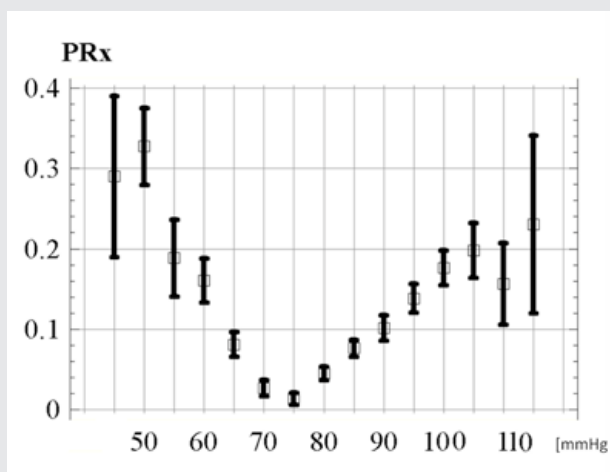
Screenshots showing (top) cerebral perfusion pressure (CPP) trend over a 4-hr period, (middle) pressure reactivity index (PRx) - CPP plot indicating an extraordinarily high optimal CPP (CPP_{opt}) at approximately 106 mmHg and (bottom) percentage of time spent within individual CPP ranges. Although in the majority of cases CPP_{opt} will be within or close to the 50 - 70 mmHg CPP range proposed by current guidelines, occasionally - such as in the example (A) shown here - CPP_{opt} will be much higher. This has been most commonly observed in patients developing vasospasm following aneurysmal subarachnoid hemorrhage;³⁷ B. Example of CPP_{opt} calculated with a descending-shaped curve; C. Example with CPP_{opt} calculated with a ascending-shaped curve.

RESULTS

Demographics and grand averages of monitored modalities

The database population included 327 patients with 246 male (75%), ranging in age from 15 to 87 yrs old (median age, 36 yrs). The median GCS score at the scene was 6 and ranged from 3 to 15; 25% of patients had an initial score > 8, but their condition subsequently deteriorated, requiring intubation and neurocritical care. The initial GCS score and GOS score were missing in 7 (2%) and 5 (1.5%) patients, respectively. The outcome was distributed as follows: good recovery, $n = 51$ (16%), moderate disability, $n = 82$ (25%), severe disability, $n = 105$ (32%), persistent vegetative state, $n = 9$ (3%) and death, $n = 75$ (23%). Patients in persistent vegetative state were excluded from further outcome analysis because this group is disproportionately smaller than other outcome groups. Sixteen patients were excluded because they had recordings shorter than 6 consecutive hours making CPP_{opt} calculation unreliable. Finally, data of 299 patients were available for outcome analysis (Table 1).

Figure 2



Pressure reactivity index (PRx) versus cerebral perfusion pressure using 1-hr averages for all patients ($n = 327$).

PRx-CPP relationship in the whole cohort

Figure 2 shows the relationship between PRx and CPP with 1-hr averages of CPP plotted in 10-mmHg bins for 327 patients monitored continuously. The U-shaped plot suggests that both too-low (ischemia) and too-high CPP (hyperemia and secondary increase in ICP) are associated with worse pressure reactivity. The plot suggests that, for our TBI cohort as a whole, CPP_{opt} would be around 75 mmHg (Figure 2). The 'U'-shape is asymmetrical, suggesting that a CPP below the averaged optimal level can impair cerebral pressure reactivity much more than CPP above the averaged optimal level.

Table 1 Patient demographics, clinical variables, and outcome (GOS, n = 299)

GOS	N	Age*	M/F	GCS*	MAP	ICP*	CPP*	PRx*
Death	71	46 (17)	59/12	6 (3)	96 (9)	21 (11)	75 (10)	0.10 (0.19)
Persistent vegetative state	0	-	-	-	-	-	-	-
Severe disability	101	39 (15)	74/27	6 (3)	95 (7)	16 (4)	78 (6)	0.02 (0.16)
Moderate disability	79	33 (14)	66/13	8 (4)	94 (7)	15 (4)	79 (6)	0.01 (0.14)
Good recovery	48	34 (17)	31/18	7 (3)	95 (6)	16 (4)	79 (7)	-0.01 (0.13)
Total	299	38 (16)	230/70	7 (3)	95 (7)	17 (7)	78 (8)	0.03 (0.16)

Values are shown as means (standard deviation). MAP, ICP, CPP and PRx were averaged in each patient over the whole monitoring period.

Abbreviations: GOS indicates Glasgow outcome scale; M/F, males/females; GCS, Glasgow coma score at the scene; MAP, mean arterial pressure; ICP, intracranial pressure; CPP, cerebral perfusion pressure; PRx, pressure reactivity index.

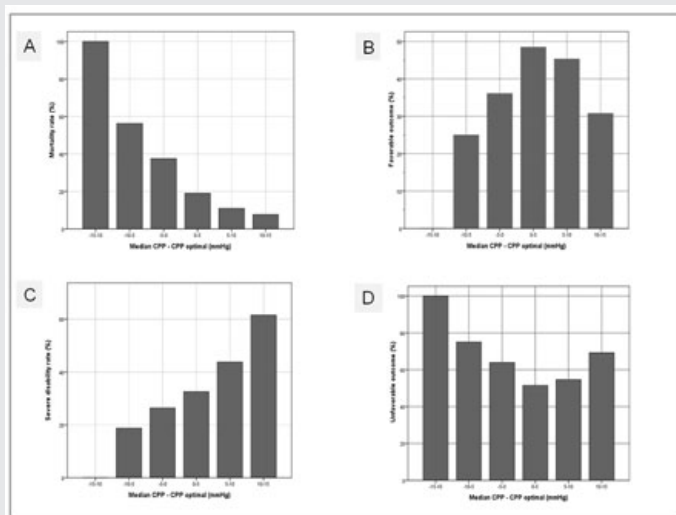
* Significant difference ($p < 0.001$) between groups of GOS (analysis of variance).

CPP optimal with 4 hours moving window in individual patients

The mean recording time per patient after artefact removal was 4 days (range, 1 day - 28 days). Overall determination of an individual CPP_{opt} was possible in all 299 patients. A CPP_{opt} curve was on average present during 55% (range, 1% - 91%) of the whole recording period. In 10 patients determination of the CPP_{opt} curve was impossible for > 20% of the recording time. In 69% of time a U-shaped curve was present, and in 22% and 9% ascending and descending curves were generated, respectively. On average, per patient, in our retrospective data set CPP_{opt} stayed below the actual CPP values during 62% (range 0 - 100) of total recording time (thus suggesting potential hyperperfusion), while in 38% (range 0 - 100) of the recording time the patients were potentially hypoperfused (CPP_{opt} above the actual CPP level).

Figure 3 demonstrates the relationship between the mortality rate (GOS score 1), favorable outcome (GOS score 4-5), unfavorable outcome (GOS score 1 and 3) and the severe disability rate (GOS 3) and continuous median CPP-CPP_{opt} difference. The mortality increased steadily with the median CPP shifting below the threshold of CPP_{opt} and decreases slightly with values above CPP_{opt} (Figure 3 A). The likelihood of severe disability increased monotonically when CPP was above CPP_{opt} (Figure 3 C). An asymmetrical inversed U-shaped curve with the highest favorable outcome rate with CPP approaching CPP_{opt} is seen (Figure 3 B). Respectively, unfavorable outcome showed U-shaped curve, with a rate increasing below and above CPP optimal (Figure 3 D). Additional analysis was performed with fatal versus nonfatal outcome dichotomization. Using CPP_{opt} as an individual threshold, the rate of fatal outcome was < 20% in patients with median CPP values around or above CPP_{opt} (median CPP > CPP_{opt} - 2 mmHg) ($\chi^2 = 45$, $p < 0.001$). In comparison, for fixed CPP thresholds of 60 or 70 mmHg, suggested by current guidelines, less discriminative values were obtained ($\chi^2 = 13$, $p < 0.001$ and $\chi^2 = 21$, $p < 0.001$, respectively). All above comparisons were repeated using a 12-hr moving time window, yielding similar results.

Figure 3



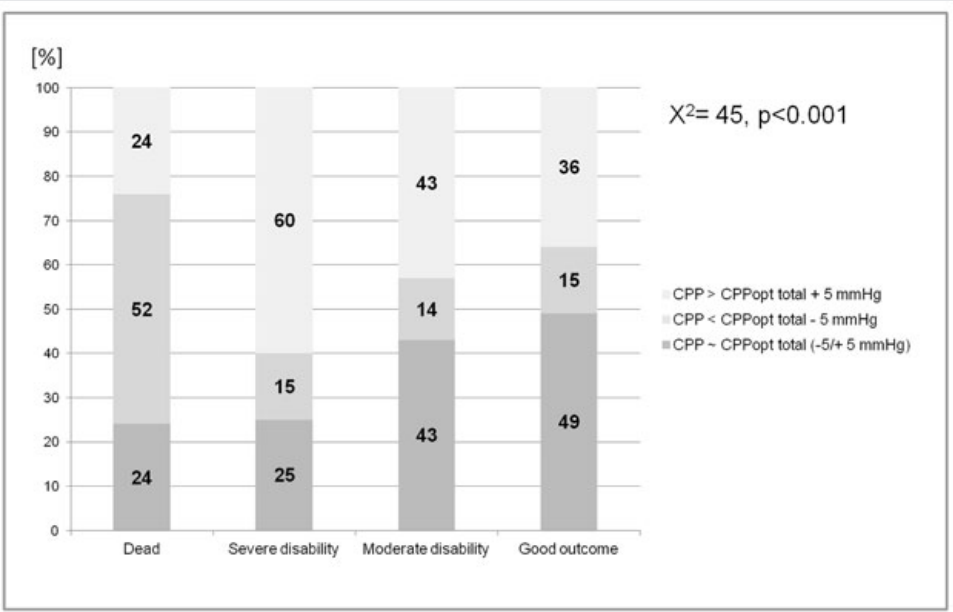
Graphs of the relationship between mortality rate (Glasgow outcome Scale (GOS) score 1), unfavorable outcome (GOS scores 1 - 3), severe disability rate (GOS score 3) and difference between continuous calculation of median cerebral perfusion pressure (CPP) and CPP_{opt} using the moving window of 4 hrs (n = 299); **A**. The mortality increases steadily when CPP is increasingly below the threshold of CPP_{opt}, and decreases slightly with increasing values above CPP_{opt}; **B**. This graph shows the asymmetrical inversed U-shaped curve between favorable outcome and the difference between the median CPP - CPP_{opt}; **C**. A nearly linear relationship between median CPP values above the CPP_{opt} threshold and severe disability rate can be seen; **D**. A U-shaped curve demonstrating that the smallest incidence of unfavorable outcome was associated with median CPP around CPP_{opt}.

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CPP optimal for total monitoring period in individual patients

Determination of an individual CPP_{opt total} was possible in 249 patients (83%) with 172 (70%) patients demonstrating a U-shaped curve, 53 (21%) and 24 (9%) demonstrating ascending and descending curves, respectively. The proportion of patients in whom no CPP_{opt total} was detected did not differ significantly between the categories of outcome. In 100 patients (40%) median CPP_{total} was below CPP_{opt total} and in 149 patients (60%) was above CPP_{opt total}. Figure 4 shows the distribution of patients (%) into the categories of the GOS with median CPP_{total} above, below, or close to the CPP_{opt total} for the whole recording period. The distribution was significantly different between the outcome groups ($\chi^2 = 45$, $p < 0.001$). More patients with good recovery and moderate disability were treated close to the individualized CPP_{opt total}. Around 50% of patients with fatal outcome were treated below CPP_{opt total} (median CPP_{total} < CPP_{opt total} - 5 mmHg). Patients treated above the CPP_{opt total} threshold (median CPP_{total} > CPP_{opt total} + 5 mmHg) (Figure 4) were more likely severely disabled (60%) than patients with lower median CPP_{total}.

Figure 4



Distribution of patients (%) into the categories of the Glasgow Outcome Score with median cerebral perfusion pressure (CPP) above, below, or close to a mean CPP_{opt} for the whole recording period.

DISCUSSION

We have developed and validated an automated methodology for the continuous calculation of optimal CPP using pressure reactivity monitoring. The method presented is applicable to a randomized clinical trial of individualized CPP following severe TBI. We were able to calculate CPP_{opt} continuously during, on average, 55% of the ICP monitoring time. We confirmed a significant correlation between outcome and the difference between actual CPP and the calculated CPP_{opt}, supporting the concept and the feasibility of a trial evaluating individualized CPP optimization based on continuous monitoring of cerebrovascular reactivity following severe TBI. Given that CPP is a modifiable target in intensive care of TBI patients, a great deal of effort has been expended in optimizing CPP. The selection of an optimal CPP is possible in theory, as confirmed by our Figure 2, but in practice many uncertainties remain. Cerebral blood flow and metabolism are regionally and temporally heterogeneous after TBI. It is not known whether these differences in flow and metabolism also correspond to individual differences in the lower limit of autoregulation, or CPP-optimization ranges. Different regions of the brain may therefore require different levels of CPP and different levels of CPP may be needed at different time points after injury.¹ Although optimal CPP is essentially an imaginary number,

brain- monitoring techniques of pressure regulation provide complementary information about the lower and upper limits of CPP for an individual patient over time.

Our study confirms earlier findings of our group in a smaller cohort of 114 severe TBI patients in a different study period (1997-2000). By using the method of visual inspection of PRx curves demonstrated that patients with a mean CPP close to $CPP_{opt\ total}$ were more likely to have a favorable outcome than those whose mean CPP was different from $CPP_{opt\ total}$.⁶ In that article, we proposed to calculate CPP_{opt} as a moving average to guide treatment and shorten the period to define CPP_{opt} by artificial manipulation of MAP. In the present study, we adapted the software to calculate CPP_{opt} continuously at the bedside, and investigated whether spontaneous CPP changes over a period of 4 hrs would yield reliable values of CPP_{opt} . This method is more practical for the treating physicians and nurses allowing early initiation of CPP_{opt} targeted management after only 2 hrs of continuous ICP and BP recording. Additionally, the presented method allows adjustment of the target CPP according to the changing clinical state. In < 20% of our patients we were unable to define $CPP_{opt\ total}$. In contrast to Steiner et al, we also accepted ascending and descending curves (Figure 1 B and C) in addition to U-shaped curves. Both additional patterns allow identification of the best vasoreactivity (and thus approximation of CPP_{opt}) in the available CPP range. It is important to note that taking both edges of the curves instead of only the turning point (vertex) introduces some overestimation (with ascending curves) or underestimation (with descending curves) of CPP_{opt} in those cases. Furthermore, descending curves indicate the need to raise the CPP, with the converse being true for ascending curves. Therefore, the one-sided curve gives appropriate clinical guidance of CPP to some extent. Interestingly, the overall distribution of curve types was not different using the calculation window of 4, 12 hrs or total monitoring period, which might indicate that the current TBI CPP treatment regime at our centre does not allow for studying the full range of CPP values. Only when the data from all patients were pooled together the full autoregulatory range of CPP is revealed (Figure 2).

Optimal CPP as a threshold for autoregulation oriented therapy

The need to define optimal CPP for individual TBI patients has been stressed by several authors.^{1-4,13,14} The Brain Trauma Foundation guidelines (2007) for management of severe TBI recommended that CPP should be managed within the range of 50 - 70 mm Hg (level III evidence). The Foundation concluded that a critical threshold for ischemia generally lies in the realm of 50 - 60 mmHg and breaching such a threshold should be avoided.⁴ Furthermore, maintaining the CPP at levels that are too high (> 70 mm Hg) might also have a negative influence on outcome. A previous study of our group, including patients from the period 1992 to 2001, suggested that higher CPP levels were associated with increased severe disability rate.¹⁵ However, this was not found consistently and probably does not apply to all patients.¹⁶⁻¹⁹ Another evidence of a serious detrimental systemic effect of aggressive CPP therapy is acute respiratory distress syndrome.¹⁶

Because both inadequate and excessive CPP can be deleterious, it is necessary to study

not only the absolute difference between CPP and CPP_{opt} , but also to differentiate periods of hypoperfusion ($CPP < CPP_{opt}$) and hyperperfusion ($CPP > CPP_{opt}$). Our results show that using a value around CPP_{opt} ($CPP_{opt} - 2$ mmHg) as an individual lower threshold for CPP management has a better discriminative value than a fixed threshold of 60 or 70 mmHg. Furthermore, we demonstrated that mortality rate increased with relative 'hypoperfusion' ($CPP < CPP_{opt}$), severe disability with 'hyperperfusion' ($CPP > CPP_{opt}$) and thus favorable outcome was maximal with CPP around individualized CPP_{opt} (Figure 3). Based on these findings we propose that for clinical purposes CPP_{opt} should be used as a continuously adjusted individual target value for CPP management.^{2,6,16,17,19-28} In 2010 Jaeger et al demonstrated that CPP_{opt} represents the lower breakpoint of autoregulation on the classic S-shaped autoregulation curve, with the partial pressure of brain-tissue oxygen as a CBF surrogate.²⁹ Similar findings have been described in a recent experimental study in piglets.³⁰

However, treatment too far above this threshold will provide oxygen and CBF in excess of oxygen demand (hyperaemia) and may promote secondary transcapillary water leak aggravating, brain edema, elevated ICP and eventually neuronal death.^{16,31-33} Especially in patients with impaired autoregulation, the ICP response to BP elevations is less predictable and so attempts to maintain CPP at higher levels should be avoided.¹⁷⁻¹⁹

Limitations

Although this study has a large sample size, it is a retrospective observation. The limitations of optimal CPP estimation based on PRx monitoring include a range of artifacts that can degrade the signal to noise ratio of the data collected, and intrinsic, systematic limitations of the linear PRx methodology. Artifacts are either related to malfunction of probes or transducers, or are caused by active maneuvers such as ventricular draining, coughing and changes of ventilator parameters affecting carbon-dioxide levels. Although such artifact could be theoretically avoided in a prospective study (PRx calculation could be stopped during EVD draining or nursing maneuvers), these are in practice dealt by means of semi-automated artifact-recognition algorithms with acceptable success. On the other hand, the intrinsic limitations of the technology derive from a series of assumptions made in order to calculate PRx. First, PRx is a global index and therefore represents the grand-average of all intracranial vascular territories. It is not unreasonable to assume that different territories might require different perfusion pressures (i.e., uninjured brain requiring normal CPP, while pericontusional areas require perfusion pressures that are different from this 'normal' level). Second, it is assumed that slow ICP pressure waves are predominantly vasogenic in nature. This may not always be true. Thirdly, CPP may be too stable within the period of calculation and so not probing enough of the autoregulatory curve. Last, the calculation of PRx requires of the presence of spontaneous fluctuation of BP. While such fluctuations are present in the majority of patients following TBI, their magnitude may be insufficient to produce significant ICP changes. In such cases the value of PRx will be unreliable. However, this loss of precision can be compensated by the continuous nature of the recording.

Further prospective studies are needed to support our hypothesis that managing at about CPP_{opt} will be beneficial in severe TBI patients. This can be only done with a randomized multicenter prospective trial, and can only be done with standardized interventions for PRx monitoring results. Continuous calculation of CPP_{opt} with regular updating (i.e., hourly) is a necessary step to perform such standardization. In addition, performance of the proposed cerebrovascular pressure reactivity-guided optimization of CPP should be tested in specific TBI treatments like decompressive craniectomy, barbiturate coma, hyperventilation or therapeutic hypothermia.^{34,35} With our bedside method we were able to calculate CPP_{opt} in around 55% of monitoring time. Future attempts should be undertaken to increase these numbers by testing flexible individual time windows to extend the CPP ranges. Furthermore, our concept should be validated by analyzing its relationship with other brain-monitoring techniques and various patterns of injury on diagnostic imaging.^{1,3}

CONCLUSION

Our data suggest that online calculation of CPP_{opt} based on a 4-hr moving time window is feasible in severe TBI patients. We have also been able to show that there is an association between outcome and the difference between the CPP at which the patient was managed and the continuously calculated CPP_{opt} . Based on our results we suggest that the concept of CPP_{opt} as an individual target value should be tested in a prospective randomized CPP oriented therapy trial.

APPENDIX

The PRx data were first processed using Fisher Transform in order to achieve normal distribution eliminating the ceiling effect of the maximum PRx value of 1.0.³⁶ The data were then binned according to CPP values subdivided into 5-mmHg sections. CPP values < 40 mmHg and > 120 mmHg formed the two extreme bins. For each bin corresponding values of PRx were assembled. The mean value and standard deviation of each bin were then plotted against the bins' mean CPP values in order to create the error bar chart representing the relationship between PRx and CPP. Theoretically, this relationship should form a smooth U-shaped curve, i.e., with cerebrovascular pressure reactivity getting worse (PRx increasing) for CPP values further away from the curve center. An algorithm was therefore devised to fit such a curve to the PRx-CPP error bar plot to estimate the value of the 'optimal CPP', i.e., the CPP value for which PRx achieves the smallest value. A summary of the processing steps are listed below.

- 1 Discard the first and the last CPP bin, as these contain outlier values.
- 2 Discard CPP bins that contain < 2% of data points.
- 3 Identify the CPP bin with the minimum PRx value (labelled as ' CPP_{best} ')

- 4 Fit a second-order polynomial representing a convex parabola to the plot. The fitted curve must fulfil the following criteria:
 - a In the first attempt the curve part fitted is expected to include the convex point (i.e., point of sign change of the first derivative from negative to positive). If such a curve cannot be found or it does not fulfil all the remaining criteria then the monotonically ascending or descending part of the curve can be used. The curve must however follow the convex shape to some extent.
 - b The sequence of the mean PRx values of the last two bins at each edge of the curve must follow the correct, expected order depending on the part of the parabolic curve fitted (i.e., descending at the left edge and ascending on the right when fitting a parabolic curve including a clear minimum). The edge bins that do not fulfil this criterion are excluded and the fitting process is repeated.
 - c Data corresponding to the bins used in successful curve fitting (i.e., after various exclusions mentioned above) must represent at least: i. represent 50% of all the data points in the analysed window period, ii. cover at least 50% of the range of PRx data available in that period and iii. Represent 20 mmHg of CPP fluctuation, so the number of bins used for data fit must be at least 4.
 - d The fitted part of the curve must span the range of PRx values of at least 0.2, in other words curves that are too 'flat' are rejected.
 - e The fitted part of the curve must include the 'CPP_{best}' value as defined above.
- 5 If all the criteria/restrictions are fulfilled the fitting procedure is stopped and the 'optimal CPP' is automatically returned. This will be the value corresponding to the minimum point of the fitted curve that lies within the covered range of CPP values (range of CPP bins used for the fit). Note that when the fitted curve does not include the convex point (i.e., point of sign change of the first derivative from negative to positive) the estimated 'optimal' value will be either underestimated (ascending curve) or overestimated (descending curve) depending on the shaped of the fitted part.
- 6 If all attempts have been exhausted and no satisfactory curve was fitted, the procedure returns an invalid value (i.e., Not-A-Number value) for the selected period.

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CHAPTER 12

SUMMARY AND GENERAL DISCUSSION

INTRODUCTION

Advances in measurement techniques and methods have made it possible to study static and dynamic changes in blood pressure (BP) and cerebral blood flow (CBF). In this thesis these techniques have been further explored, with specific attention for their potential use in stroke and traumatic brain injury (TBI) subjects. First, we have outlined that measurements of BP, CBF, regional cerebral oxygen saturation (rSO₂) and intracranial pressure (ICP) and their interaction (called autoregulation or vasoregulation) are important in stroke and TBI research (chapter 2, 3 and 4). Second, we have considered that simple postural BP changes in the stroke unit could form a physiological challenge to the cerebral vasoregulation and vulnerable brain (chapter 5, 6 and 7). This will not only improve our knowledge of the complex autoregulation or vasoregulation process, but also directly relates it the pressing question regarding safe early upright positioning and early (in and out of bed) mobilisation of stroke patients (chapter 7 and 8). Third, vasoregulation or autoregulation results have been proposed to be capable of providing feedback to treatment interventions. We investigated new methods to calculate a continuous updated *target* cerebral perfusion pressure (CPP) in severe TBI patients with ICP monitoring that might result in better survival (chapter 10 and 11).

This chapter will provide a summary of the findings in this thesis, followed by a general discussion.

SUMMARY

PART 2. CLINICAL AND METHODOLOGICAL BACKGROUND

Chapter 2.

This chapter introduces the concept of cerebral vasoregulation/autoregulation. It provides a clinical background underlining its relevance in early detection of cerebral (hypo) perfusion at the individual level with follow up over time. Several methods to analyse and quantify cerebral vasoregulation/autoregulation and cerebral CO₂ vasoreactivity are described. Some vasoregulation techniques inform the clinician about subtle local regulation disorders ('snapshot assessment'). Other techniques are suitable for long term monitoring of vasoregulation ('monitoring assessment') where the updated results can serve as feedback for treatment interventions. We conclude that monitoring cerebral autoregulation/vasoregulation can be used in a variety of clinical scenarios and may be helpful in delineating optimal therapeutic strategies and prognostication. However, so far prospective research is lacking.

Chapter 3.

In the third chapter we consider the interaction between stroke and cerebral autoregulation.

Transcranial Doppler ultrasonography (TCD) in combination with continuous BP measurements allows non-invasive continuous bedside investigation with high temporal resolution of the dynamic and the steady-state components of cerebral autoregulation. We reviewed all relevant TCD studies on cerebral autoregulation in ischemic stroke. TCD studies have shown impairment of cerebral autoregulation in various subtypes of ischemic stroke with progressive deterioration in the first 5 days after stroke and recovery over the next 3 months. Impaired cerebral autoregulation was related to neurological deterioration, the necessity for decompressive surgery, and poor outcome. To improve the synthesis of data from various research groups, there is urgent need for standardization of methodology of TCD studies in cerebral autoregulation.

Chapter 4.

Calculation of dynamic cerebral autoregulation (dCA) estimates require slow BP fluctuations of sufficient amplitude. We tested if reproducibility and variability of three dCA estimates improved with a passive cyclic leg raising (PCLR) maneuver in 16 healthy subjects. Middle cerebral artery cerebral blood flow velocity (MCA-CBFV), BP and end-tidal CO₂ (etCO₂) were obtained twice at rest and twice during PCLR at 0.1 Hz. The maneuver significantly increased the power of BP fluctuations at 0.1 Hz. However, an increase in etCO₂ fluctuations around this frequency also occurred, as a result of irregular breathing. Reproducibility of dCA estimates phase and autoregulation index (ARI) was low and did not improve with the PCLR maneuver. Reproducibility of dCA gain increased significantly with the maneuver. Variability was not reduced by PCLR for all dCA estimates. We conclude that the utility of PCLR for autoregulation testing is limited because of the simultaneous changes in etCO₂. This limits reproducibility of the most important dCA estimates. Future research on reproducibility and variability of dCA parameters should therefore incorporate CO₂ variability or find methods to keep CO₂ constant.

PART 3. BLOOD PRESSURE, CEREBRAL PERFUSION AND VASOREGULATION IN DIFFERENT BODY POSITIONS IN ACUTE STROKE AND CRITICALLY ILL PATIENTS

Chapter 5.

This chapter introduces BP as one of the major vital parameters monitored in the stroke unit. Routine lateral turning of (critically) ill stroke patients has become an accepted standard of care to prevent complications of immobility. We investigated the effect of alternating body positions in relation to affected body side on the outcome and reliability of BP readings in 54 acute stroke patients. The indirect BP was measured in both arms in the supine back and both lateral decubitus positions (45°). Supine BP readings were similar in the right and left arms regardless of side of deficit. Measurements of BP in the lateral decubitus positions resulted in significantly lower BP readings in the uppermost arm (around 12 mmHg in both arms) and significantly higher readings in the right lowermost arm (around 6 mmHg) compared to

the supine position. This effect seemed less pronounced when the left lowermost arm was measured. There was no relation between change of BP readings in various lateral positions and side of stroke. We conclude that alternating lateral decubitus positions according to nursing standards in acute stroke patients lead to a mean 18 mmHg BP fluctuation. This may largely be explained by hydrostatic pressure effects, partly by anatomic factors in the left lowermost arm, but not by the side of stroke.

Chapter 6.

In intensive care routine lateral turning of critically ill patients has become an accepted standard of care to prevent complications of immobility. We studied the effect of these positions on intraarterial BP (with height correction), heart rate (HR) and peripheral arterial oxygenation saturation measurements in 20 general intensive care unit (ICU) patients. BP readings in the lateral positions were, on average, 5 mmHg higher than in the supine position ($p < 0.001$). There were no significant differences between BP recordings in the left and right lateral position ($p = 0.99$). No important differences in oxygenation saturation and HR were observed. After correction for covariates, the effects persisted. We conclude that there is an increase, albeit small, in BP in the lateral positions. Turning hemodynamically stable ICU patients has no important effects on intraarterial BP measurements when continuous hydrostatic height correction is applied.

Chapter 7.

In this chapter we extended the earlier postural BP data (chapter 5) by studying the effects of early upright positioning in the acute phase of ischemic stroke on both BP and functional outcome. The indirect BP, HR, and peripheral oxygen saturation in the supine, sitting, and (if attainable) active standing position 1, 2, and 3 days after acute stroke was measured in 167 patients. Approximately 60% of the patients were able to stand. On average the BP increased when patients moved from the supine to sitting (Day 1: Δ 3.9 mmHg; $p < 0.001$) and from sitting to an active standing position (Day 1: Δ 4.6 mmHg; $p < 0.001$). Changes were most pronounced within the first 24 hrs after a stroke. BP decreased significantly (orthostatic fall) on standing in 13% of patients and increased significantly (orthostatic rise) in 20% of the patients. The latter was independently associated with a favorable outcome ($p = 0.003$). We conclude that BP changes upon upright positioning are most pronounced in the first 24 hrs after stroke and that a significant BP rise during early upright positioning out of bed in patients with acute stroke is independently associated with a favorable outcome. No contraindication to early mobilization was found in this study.

Chapter 8.

In this study we assessed whether cerebral blood flow velocity (CBFV) changes significantly after upright positioning in bed of acute stroke patients and related this to changes in neurological status, functional outcome and dynamic cerebral autoregulation status. We

investigated postural changes in neurological status and simultaneously recorded bilateral TCD, near-infrared spectroscopy (NIRS), etCO_2 and non-invasive continuous BP data. We included 52 stroke patients and 20 controls. During the upright positioning, no neurological worsening or improvement (using motor NIHSS) was observed in any of the patients. The CBFV decrease upon sitting (70°) was not significantly different between healthy controls and stroke patients. This was most evident the first 24 hrs after stroke. No significant differences were found between affected and unaffected stroke hemispheres and between patients with unfavorable and favorable outcome. Dynamic cerebral autoregulation was impaired in patients with acute stroke, especially large vessel strokes. This disturbance was bilateral initially, and tended to improve over time in the unaffected hemisphere. These changes were not correlated to changes in mean CBFV upon sitting. We conclude that upright positioning in bed of mildly to moderately affected stroke patients appears to be safe during the first 3 days on the stroke unit, despite a bilaterally impaired dynamic cerebral autoregulation. Supine or Trendelenburg positioning did not seem to augment real time flow variables or improve neurological status.

PART 4. APPLICATIONS IN CLINICAL RESEARCH

Chapter 9.

In this chapter we evaluated whether bilateral NIRS can be used for monitoring of patients with acute ischemic stroke. Therefore, the NIRS responsiveness to systemic and stroke-related changes was studied overnight by assessing the effects of brief peripheral arterial oxygenation saturation and BP alterations in the affected versus nonaffected hemisphere in 9 patients with acute stroke. Significantly more NIRS drops were registered in the affected compared with the nonaffected hemisphere (477 versus 184 drops, $p < 0.001$). In the affected hemispheres, nearly all peripheral oxygenation saturation drops ($n = 128$; 96%) were detected by NIRS; in the nonaffected hemispheres only 23% ($n = 30$; $p = 0.17$). Only a few BP drops were followed by a significant NIRS drop. This was however significantly different between both hemispheres (32% versus 13%, $p = 0.01$). We conclude that these pilot data demonstrated good responsiveness of the NIRS signal to systemic and stroke-related changes at the bedside but requires confirmation in a larger sample. This responsiveness to stroke-related changes makes NIRS an attractive technique when studying vulnerability of ischemic brain tissue to changes in the internal environment.

Freeman *et al.* commented on our results in a 'Letter to the editor' to *Stroke*.¹ They recently demonstrated a strong correlation between bilateral frontal NIRS measurements and corresponding regional CBF on CT perfusion imaging. However, both techniques were not applied simultaneously (minutes to hours apart).² We responded that their findings would indicate that not only relative changes (like in our study), but also absolute (mean) regional cerebral oxygen saturation values might be of clinical use.³

Chapter 10.

Chapter 10 and 11 concern retrospective analyses in severe traumatic brain injury (TBI) patients to improve (perfusion) monitoring and outcome. In chapter 10 we investigated the relationship between slow fluctuations of BP and ICP pulse amplitude (a new index called PAX) using a moving correlation technique to reflect the state of cerebrovascular reactivity. The index was compared to the well established and validated PRx index as a moving correlation coefficient between averaged values of BP and ICP. Data of 327 patients with continuous BP and ICP monitoring were used. The index PAX was worse in patients who died compared to those who survived (-0.04 ± 0.15 vs. -0.16 ± 0.15 , $\chi^2 = 28$, $p < 0.001$). In contrast to PRx, PAX was able to differentiate between fatal and nonfatal outcome in a group of 120 patients with ICP levels below 15 mmHg (-0.04 ± 0.16 vs. -0.14 ± 0.16 , $\chi^2 = 6$, $p = 0.01$). We conclude that PAX is a new modified index of cerebrovascular reactivity which performs equally well as established PRx in long-term monitoring in severe TBI patients, but is potentially more robust at lower values of ICP. In view of establishing a vasoreactivity-oriented cerebral perfusion pressure therapy (CPP), continuous determination of PAX is feasible but its value has to be evaluated in a prospective controlled trial.

Chapter 11.

In this chapter we have sought to develop an automated methodology for the continuous updating of CPP_{opt} for patients after severe TBI, using continuous monitoring of cerebrovascular pressure reactivity. We then validated the CPP_{opt} algorithm by determining the association between outcome and the deviation of actual CPP from CPP_{opt} . Data of 327 patients with continuous BP and ICP monitoring were used. An automated curve fitting method was applied to determine CPP at the minimum value PRx (' CPP_{opt} '). A time trend of CPP_{opt} was created using a moving 4-hr window, updated every minute. Identification of CPP_{opt} was, on average, feasible during 55% of the whole recording period. Patient outcome correlated with the continuously updated difference between median CPP and CPP_{opt} ($\chi^2 = 45$, $p < 0.001$; outcome dichotomized into fatal and nonfatal). Mortality was associated with relative 'hypoperfusion' ($CPP < CPP_{opt}$), severe disability with 'hyperperfusion' ($CPP > CPP_{opt}$), and favorable outcome was associated with smaller deviations of CPP from the individualized CPP_{opt} . We conclude that real-time CPP_{opt} could be identified during the recording time of majority of the patients. Patients with a median CPP close to CPP_{opt} were more likely to have a favorable outcome than those in whom median CPP was widely different from CPP_{opt} . CPP management to optimize individual cerebrovascular pressure reactivity should be the subject of future clinical trial in severe TBI patients.

Salvatori *et al.* commented on our results in a 'Letter to the editor' to *Critical Care Medicine*.⁴ They advocated the use of TCD monitoring (and its derived indices) in management of severe TBI patients to optimize perfusion. We replied that TCD offers a useful estimator of CBF and the noninvasive nature of this technology makes it a readily available and desirable tool in ICU. However, with current TCD probe holders, monitoring over longer periods is not feasible,

even in sedated patients, allowing only intermittent assessments of CBFV. Therefore we believe that due to the intermittent nature it cannot, at present, replace continuous indices in establishing clear CPP thresholds in real time.⁵

GENERAL DISCUSSION

METHODOLOGICAL CONSIDERATIONS

Blood pressure measurements

After an acute stroke, autoregulation is impaired, which indicates that the brain becomes (to a certain extent) dependent on systemic BP.⁶ Accurate measurement of BP in the stroke unit is a vital component in the assessment and modification of cardiovascular risk factors and optimal perfusion management in the first hours to days after stroke. However, simply connecting patients to equipment that monitors BP, peripheral oxygen saturation, blood glucose and body temperature is only part of the process. It is critical that stroke physicians and nursing staff remain vigilant and act on any non-physiological variations.⁷ Factors able to affect readings by more than 5 mm Hg in high quality studies include talking, acute exposure to cold, incorrect arm position, and incorrect cuff size.⁸ Another factor that needs to be considered are the hydrostatic effects of changing arm cuff positions relative the right atrium. This especially concerns stroke or critically ill patients with frequent lateral turning to overcome immobilization complications. In the stroke unit frequent indirect (oscillometric) BP measurements are done without specific attention for hydrostatic forces. In chapter 5, we found large variations of on average 18 mmHg that occur with turning acute stroke patients from one lateral (anti-decubitus) position to the other one. The most likely explanation is the (unnoticed!) position change of the BP arm cuff from several cm above the right atrium to below this BP reference level (or vice versa) with turning.⁹ Intraarterial measurements with automatic hydrostatic (height) correction can improve reliable BP measurements with turning,¹⁰ although (stroke-specific) anatomical (vascular) factors accompanying lateral turning always have to be considered. The latter deserves further research, but at present we advise to measure indirect BP on the right arm in (stroke) patients with alternating lateral positions and to account for hydrostatic effects.⁹

Measurements of cerebral perfusion

Over the past years, there have been important advances in techniques to estimate cerebral perfusion.¹¹ These include, but are not limited to TCD, NIRS, (functional) magnetic resonance imaging (MRI), and positron emission tomography (PET). All techniques have advantages and limitations, which are summarized in chapter 2. Importantly, both MRI and PET scanning require that the subject is and remains as motionless as possible in the supine position. This makes it difficult to investigate the hemodynamic effects of postural changes and poses

important limitations to the evaluation of physiological challenges in affected or recovering patients.¹²

Continuous TCD, NIRS and BP measurements

Both transcranial Doppler (TCD) and near-infrared spectroscopy (NIRS) measurements provide an answer to these limitations and are easily combined with (non-invasive) continuous BP and peripheral oxygen saturation measurements. These instruments have low cost for acquisition and operation and are tolerated well by patients for intermittent recordings. Temporal resolution is excellent and as demonstrated in chapter 4 and 8, body position poses no important limitations for its use in healthy controls and acute stroke patients. NIRS measures changes in brain tissue hemoglobin oxygenation. The technique is limited to superficial areas of the brain, and it is impossible to know exactly the size and location of the tissue that is examined. This indicates that absolute NIRS values have limited value in awake subjects.^{3,13} However their relative changes correlate well with cortical brain changes measured with other techniques.¹⁴ NIRS can be regarded as an estimation of the 'end result' of complex hemodynamic changes at the brain tissue level. A reduction in rSO_2 suggests that the balance between oxygen supply and demand has shifted. TCD provides a measure of cerebral blood flow velocity, which is determined by flow and by vessel diameter. Intra-individual changes in flow velocity reliably reflect changes in flow, since vessel diameter (of the major basal arteries) does not change significantly during autoregulation or vasoreactivity (CO_2) tests.¹⁵ By contrast, inter-individual differences in CBFV can be determined by differences in MCA diameter, especially in patients with (transient) vessel abnormalities (thrombi and spasms). Therefore, in chapter 4 and 8 relative changes in flow velocity (i.e., % changes from baseline) were used, eliminating the effects of vessel diameter. In a simplified model, TCD changes reflect the dynamics of downstream smaller vessels (arterioles) by vasoconstriction and vasodilatation, in response to changes in BP (pressure autoregulation) or CO_2 (vasoreactivity). In the literature, the combination of the non-invasive techniques BP, TCD and NIRS (and CO_2) signals is advised.^{12,16} Because these techniques measure quite different aspects of cerebral hemodynamics, combining their results provides relevant complementary information. In chapter 8, we used the agreement in limited changes between TCD and NIRS to strengthen our statements concerning safety during early upright positioning in acute stroke patients.

Cerebral autoregulation and vasoregulation and confounding factors

Assessment of cerebral autoregulation seems an important adjunct to measurement of cerebral blood flow for diagnosis, monitoring or prognosis of cerebrovascular disease or traumatic brain injury. The most common approach evaluates the effects of changes in BP on cerebral blood flow, known as autoregulation. A 'gold standard' for this is not available and the literature shows considerable disparity of methods and criteria. Focusing on the stroke population with continuous TCD measurements, many different autoregulation study designs and

analyzing methods were found, which limited the synthesis of the data (chapter 3).⁶ This is understandable because cerebral autoregulation is more a *concept* rather than a physically measurable entity.¹⁷ Static methods utilize steady-state values to test for changes in cerebral blood flow (or velocity) when BP is changed significantly. This is usually achieved with the use of vasoactive drugs or shifts in blood volume (static autoregulation). With the inhalation of 5 - 8% CO₂ the static (metabolic) vasoreactivity can be tested in a similar way (chapter 2).

The long time interval between static measurements is a particular concern in many studies. Parallel changes in other critical variables, such as CO₂, venous drainage, hydrostatic forces, brain activation and sympathetic tone, are rarely reported or controlled for. Proposed indices of static autoregulation are based on changes in cerebrovascular resistance, on parameters of the linear regression of flow/velocity versus BP changes, or only on the absolute changes in flow. Static methods all have in common that they require large (controlled) changes in BP, volume or CO₂, making them less suitable for clinical research (chapter 2). However, as we point out in the discussion of chapter 8, in everyday challenges such as upright positioning, several critical variables will change (or balance each other out) making calculation of current static (BP) autoregulation indices difficult or unreliable. Newer methods of *dynamic* assessment are based on transient changes in cerebral blood flow (or velocity) induced by the deflation of thigh cuffs, Valsalva maneuvers, repeated tilting, breathing instructions and induced or spontaneous slow fluctuations in BP. Dynamic testing overcomes several limitations of static methods but it is not clear whether the two approaches are interchangeable.¹⁷ We also found no correlation between relative postural CBFV changes and impaired bilateral dynamic autoregulation estimates in acute stroke patients. Others also reported this discrepancy in stroke patients, but the exact meaning of it is not clear and requires further investigation.^{18,19} Classification of autoregulation performance using dynamic methods has been based on mathematical modeling, coherent averaging, transfer function analysis, cross-correlation function or impulse response analysis. Many papers urge the need for more research on reproducibility, variability and inter-method comparisons of autoregulation estimates (considering both 'snapshot' and 'monitoring' assessments).^{16,17} In chapter 4 we introduced a new bedside method in which passively and repeatedly the legs of a patient are raised to induce large BP fluctuations. Large BP fluctuations challenge the individual global autoregulatory capacity.²⁰ However, our results showed different effects on reproducibility and disappointing variability for 3 different autoregulation estimates in healthy cooperative volunteers. This is most probably explained by 1) the selective and disruptive influence of concurrent (leg raising induced) CO₂ fluctuations and 2) the limited size of the BP fluctuations induced with this maneuver (chapter 4). Different research groups also emphasize assessing autoregulation in individuals rather than patient groups.^{16,17,21} In collaboration with the brain monitoring group in Cambridge we improved a method that uses continuously monitored cerebrovascular pressure reactivity (as a component of the autoregulation process) to estimate a target perfusion pressure in individual TBI patients with continuous updating (chapter 11).

Testing versus monitoring of autoregulation

Classical testing of cerebral autoregulation requires the observer to apply a hemodynamic stimulus. With these methods the observer controls the exact time and grade of stimulation, and synchronously measures a change in CBF (or velocity) to quantify the reactive autoregulatory forces. Control over the hemodynamic input imparts precision to autoregulation testing techniques. Stimuli can be graded to create a favorable signal-to-noise ratio. The assumption that associated responses of CBF are causally related to the hemodynamic stimulus is less subject to confounding influences than a similar assumption made with spontaneous hemodynamic fluctuations.¹⁶ Despite these precision advantages, practical and clinical reasons limit frequent autoregulation testing. This point touches on an important practical question concerning autoregulation studies in several clinical conditions: how often does the state of autoregulation change over time and what to do with this information? Ideally, the rate of acquisition of autoregulation information would match the time course of changes in the state of autoregulation. Some autoregulation techniques are able to inform the observer about (subtle) local regulation disorders that might progress over time ('snapshot or risk factor assessment'). Other techniques are more suitable for long-term continuous monitoring of global vasoregulation ('monitoring assessment') where the continuously updated results can serve as feedback for treatment interventions and prognostification (chapter 2).

Continuous methods of autoregulation monitoring rely on the observation of spontaneous responses of CBF to spontaneous slow fluctuations in BP. The magnitude of such spontaneous 'slow vasocycling' in BP may be unpredictable and therefore, the signal-to-noise ratio, and subsequent precision is less favorable than in testing ('snapshot assessment'). In addition, the assumption that synchronously measured spontaneous slow waves of perfusion pressure and CBF are causally related is vulnerable to confounding influences, such as CO₂ changes, drugs, surgical interventions, etc. This loss of precision is compensated by the ability to repeat the measurements frequently and monitor changes in autoregulation continuously. Averaging the repeated measures over time reduces estimation error and renders the method clinically useful.¹⁶ This coupled to the clinical advantage of not requiring potentially harmful hemodynamic stimuli to patients with vulnerable brain. Several methods for continuous monitoring in critically ill patients (like severe traumatic brain injury patients) exist. One method (PRx) uses the invasive ICP signal to calculate cerebrovascular pressure reactivity (chapter 10 and 11). Cerebrovascular pressure-reactivity is defined as the ability of vascular smooth muscle to respond to changes in transmural pressure.²² This is one of the key mechanisms responsible for autoregulation of cerebral blood flow. However, the two expressions should not be used synonymously as vasodilatation reaches its maximum at BP below the lower threshold for constant cerebral blood flow.²³

In daily clinical practice, the pressure-reactivity indexes (PRx or PAx) can be displayed as a time trend alongside the primary modalities (like ICP, BP, CPP). The PRx has been extensively validated and shows significant agreement with the PET-CBF static rate of autoregulation

in TBI patients.²⁴ In patients with continuously monitored ICP (traumatic brain injury, subarachnoid hemorrhage, major ischemic or hemorrhagic stroke) the comparison of slow waves of ICP and BP can contain information about cerebrovascular pressure-reactivity. The method is explained (simplified) in Figure 3 in chapter 2. In theory, with good cerebrovascular reactivity, a change in BP should provoke inverse, reactive change in cerebral blood volume. With a steep pressure-volume curve, the change in CBV should produce correlated changes in mean ICP.^{25,26} Therefore, a negative correlation coefficient between changes in mean ICP and BP signifies good pressure-reactivity of cerebral arterioles, which is a condition necessary for intact autoregulation. Conversely, with disturbed reactivity, changes in BP produce passive, positively correlated changes in brain blood volume, therefore, correlation between BP and ICP slow waves is positive. However, at lower levels of ICP the linear relation between ICP and intracerebral volume may be abolished -due to high cerebral compliance- affecting reliable PRx calculation.^{27,28} This may be the case after medical or surgical interventions like decompressive craniectomy. However the compliance of the cerebral vessels is thought to be preserved. We assumed that even with low levels of ICP, changes in vascular tone brought about by slow waves in BP will be reflected by changes in the BP to ICP pulse transmission (chapter 10, Figure 7). Therefore we investigated the relationship between slow BP fluctuations and the ICP pulse amplitude (a new index called PAX) using a moving correlation technique to reflect the state of cerebrovascular reactivity (chapter 10). PAX was worse in patients who died compared to those who survived. In contrast to PRx, PAX was able to differentiate between fatal and nonfatal outcome in the group of 120 patients with ICP levels below 15 mmHg. We conclude that PAX is a new modified index of cerebrovascular reactivity which performs equally well as established PRx in long term monitoring in severe TBI patients, but importantly is potentially more robust at lower values of ICP.²⁹

The relationship between the pressure-reactivity indexes (or autoregulation (Mx) assessed using TCD) and CPP resembles a U-shape curve.^{16,30} The curve indicates that inadequate CPP and excessive CPP are both associated with pressure reactivity failure. Therefore, the hypothesis has been drawn that there is a CPP at which cerebral pressure reactivity is strongest, and that this 'optimal CPP' (CPP_{opt}) can be identified by plotting PRx against CPP in individual patients (from a moving time window of at least 4 hrs or more). Patients with greater deviation between their averaged CPP and post-hoc assessed overall CPP_{opt} had worse outcome after head trauma in a retrospective study.³⁰ The method which allows to obtain an individual CPP_{opt} based on monitoring of PRx has been improved in chapter 11 allowing for automated calculation of the CPP_{opt} from a clinically useful period of 4 hrs.³¹ Using retrospective data of more than 300 patients, we conclude that CPP should be not too low, not too high, but optimal, i.e., matched to an individually assessed value, which provides the best milieu for cerebrovascular reactivity and maximizes the ability of the brain to protect itself from both ischemia and hyperemic injury.^{32,33} The use of a moving window, updating at the bedside allows providers to track CPP_{opt} , a value which may change over time. It remains to be demonstrated whether such a strategy is able to improve outcome in neuro-critical care patients.³⁴

IMPLICATIONS

Having described these methodological issues, we will now turn to the implications of the findings in this thesis looking at the aims.

How does arterial blood pressure react to postural changes (decubitus, supine, sitting and standing position) in acute stroke and critically ill patients. Is there a correlation between postural BP responses and outcome after stroke.

In the upright position, the cerebral arteries are positioned ± 30 cm above the heart, and therefore their perfusion pressure seems to be reduced (but still within what is considered to be the autoregulatory range). Both the position of the cerebral circulation and the reduction on cardiac output (due to venous pooling) challenge cerebral blood flow. Although the postural reduction of flow velocity (TCD) and regional cerebral oxygenation (NIRS) is kept limited via systemic compensations and cerebral autoregulatory mechanisms, orthostatic intolerance is not uncommon in healthy subjects.^{35, 36}

Orthostatic changes are poorly investigated in acute stroke patients.³⁷ We found that BP (without height correction) increased when patients moved from the supine to sitting and from sitting to an active standing position. These changes were most pronounced within the first 24 hrs after a stroke. BP decreased significantly on standing in 13% of patients and increased significantly in 20% of the patients. The latter was independently associated with a favorable outcome. The rate of orthostatic hypotension was not different from the ones reported in healthy or hypertensive elderly.³⁸ Therefore we concluded that our results indicate no contraindication to early mobilisation in acute stroke patients.³⁹

In a way our findings are reassuring and would not support standard postural BP measurements to be included in stroke unit or early mobilisation protocol guidelines (covering the first 3 days post stroke). On the other hand, the association between postural orthostatic hypertension and good outcome suggests that the vulnerable penumbra may benefit from a 'hyperdynamic' cardiovascular system in the acute phase after stroke.^{37, 40} Which autonomic or physiological mechanisms are involved to accomplish these responses are not fully clarified.⁴¹⁻⁴³ Also the interaction between orthostatic hypertension and impaired cerebral autoregulation is unclear and deserves further research. All this might improve our knowledge in (sub) acute stroke physiology and guide difficult treatment decisions regarding early mobilisation, rehydration and medication adjustments, especially in hypertensive subjects.

What are the effects of in-bed-mobilization on estimates of cerebral perfusion and neurological status in the acute phase after stroke.

Little is known about the influence of different body positions on real time cerebral flow variables in the acute ischemic stroke phase. We assessed whether cerebral blood flow velocity (CBFV) changes significantly after (upright) positioning in bed and related this to changes in neurological status, functional outcome and dynamic autoregulatory status. We

investigated postural changes in neurological status and simultaneously recorded bilateral transcranial Doppler (TCD), near-infrared spectroscopy (NIRS), end-tidal CO_2 and non-invasive continuous BP data in 52 acute stroke patients. During the upright positioning, no neurological worsening or improvement (using motor NIHSS) was observed in any of the patients. The mean CBFV decrease upon sitting (70°) was not different between controls and stroke patients. No significant differences were found between affected and unaffected stroke hemispheres and between patients with unfavorable and favorable outcome. Dynamic cerebral autoregulation was bilaterally impaired in stroke patients. However, no correlation between bilateral impaired autoregulation status and positional mean CBFV changes was found. We conclude that upright positioning in bed of mildly to moderately affected stroke patients appears to be safe during the first 3 days on the stroke unit, despite a bilaterally impaired dynamic cerebral autoregulation. Supine or Trendelenburg positioning did not seem to augment real time flow variables or improve neurological status.

Our results indicate that sitting is well tolerated in mildly to moderately affected acute stroke patients. This may be due to the counterbalancing effects of BP elevation (hyperdynamic cardiovascular status), ICP reduction or increased cerebral venous return to stabilize cerebral perfusion pressure in the acute phase of stroke. Follow-up studies several days after stroke may be warranted because systemic compensatory mechanisms may become exhausted or cerebral autoregulation may deteriorate.⁴⁴ Our results do not hold for early sitting to the standing position (out of bed mobilisation), which may provoke different (probably larger) hemodynamic responses.⁴⁵ In the paucity of results from 'the early out of bed mobilisation stroke trials',⁴⁶ we have found no indications that upright positioning of mildly to moderately affected stroke patients is unsafe in the stroke unit. We propose that continuous CBF measurements in stroke patients during early activity out of bed could be the next investigation to reassure safe stroke unit (early) mobilisation.

How can the bedside monitoring of estimates of cerebral autoregulation/vasoregulation be improved in stroke and traumatic brain injury patients?

The near-infrared spectroscopy (NIRS)-derived rSO_2 is theoretically linked with multiple variables describing the ratio of delivery and utilization of local cerebral oxygen. NIRS-based autoregulation monitoring has several advantages. NIRS optodes are non-invasive and do not require precision focusing on small vessels or continuous correction for shifts. Experience in acute stroke patients is very limited.⁴⁷ In our pilot stroke study in 9 patients, 96% of systemic nocturnal peripheral desaturations were rapidly followed by local cerebral desaturations as measured by NIRS. Also, BP drops were more likely to be followed by NIRS drops in the affected than in the nonaffected hemisphere. Local nocturnal cerebral desaturations were more than twice as likely in the affected hemisphere.⁴⁸ This responsiveness to stroke-related changes makes NIRS an attractive technique when monitoring vulnerability of ischemic brain tissue to changes in the internal environment on the stroke unit.

Survival after TBI is dependent on the control of intracranial hypertension and the

provision of hemodynamic support to achieve an 'adequate' CPP and subsequent CBF ('optimal perfusion' concept). While methods of estimating CBF and CPP exist, there is still an ongoing debate with respect to which threshold of CPP should be adopted in TBI management and whether this threshold should be standardized or individual. While on the intensive care gross estimation of CBF (with for example TCD estimates) and ICP may be sufficient to initiate therapy, we believe that in the prolonged intensive care setting there is a need for a finer balance with the ability of continuous titration of hemodynamic parameters to minimize secondary brain damage.^{16,49} The method which allows obtaining an individual CPP_{opt} based on monitoring of the cerebrovascular pressure reactivity index PRx has been improved in chapter 11 allowing for automated calculation of the CPP_{opt} from a clinically useful period of 4 hrs.^{30,31} We conclude that in the management of severe TBI the threshold of CPP should be targeted to (continuously changing) physiology and not constitute a predefined number. We validated the new CPP_{opt} algorithm by determining the association between outcome and the deviation of actual CPP from CPP_{opt}.

The choice of the physiological parameter by which to guide treatment is difficult and so far has not been clearly established. In clinical practice, the use of cerebrovascular pressure regulation (PRx) is twofold. Firstly, unlike TCD indices, it is a continuous parameter which gives credible values as long as ICP monitoring is available. Unfortunately, with current TCD probe holders, TCD monitoring over longer periods is not feasible, even in sedated patients, allowing only intermittent assessments of CBF surrogates. Secondly, unlike other invasive intracranial parameters such as PbTO₂ microdialysis or thermal dilution regional CBF it is less susceptible to probe location.⁵ Further prospective studies are needed to support our hypothesis that aiming for CPP_{opt} will be beneficial in severe TBI patients.^{21,50} This can only be done with a randomized multicenter prospective trial, and can only be done with standardized interventions for PRx-monitoring results. Continuous calculation of CPP_{opt} with regular updating (i.e., hourly) might be a necessary step to perform such standardization.

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A black and white illustration of a giraffe and its calf. The adult giraffe is on the left, bending its long neck down towards the calf on the right. The calf is also bending its neck up towards the adult. Both animals have a distinctive spotted pattern. The background is plain white.

CHAPTER 13

NEDERLANDSE SAMENVATTING

INLEIDING

Vooruitgang in meettechnieken en rekenmethoden hebben het mogelijk gemaakt om stabiele en dynamische veranderingen in de bloeddruk, intracraniële druk en hersendoorbloeding te bestuderen. In dit proefschrift zijn deze technieken verder onderzocht, met specifieke aandacht voor hun inzet rondom de bewaking en verbetering van de zorg bij patiënten met een acuut herseninfarct of ernstig traumatisch schedelhersenletsel. Als eerste hebben we in dit proefschrift een overzicht opgenomen waarbij de waarde van het frequent meten van de bloeddruk, hersendoorbloeding, regionale hersenzuurstofvoorziening (rSO_2) en de intracraniële druk in deze patiëntengroepen wordt weergegeven. Tevens introduceren wij het concept achter de autoregulatie of vasoregulatie van de hersenen: het systeem waarbij hersenbloedvaten reageren op schommelingen in de bloeddruk om de hersendoorbloeding zo constant mogelijk te houden (hoofdstuk 2, 3 en 4). Vervolgens hebben we onderzocht of het innemen van de linker en rechter zijligging belangrijke bloeddruk meetfouten geeft (hoofdstuk 5 en 6) en of de posities zitten en staan gevaarlijk zijn voor het herstellende hersenweefsel na een acuut herseninfarct. Het innemen van een andere lichaamshouding kan de bloeddruk plots doen dalen waarbij de zelfregulatie (autoregulatie) van de hersenbloedvaten tekort kan schieten (hoofdstuk 7 en 8). De resultaten van de vasoregulatie of autoregulatiemetingen kunnen mogelijk dienen als terugkoppeling voor belangrijke behandelinterventies en zodoende de bewaking en uiteindelijke overleving en herstel verbeteren. In de laatste twee hoofdstukken onderzochten wij nieuwe methoden om een 'optimale' doorbloedingsdruk te berekenen bij patiënten met ernstig traumatisch schedelhersenletsel waarbij naast de bloeddruk ook de intracraniële druk gemeten werd op de intensive care (hoofdstuk 10 en 11).

In dit hoofdstuk bespreken wij de belangrijkste bevindingen van dit proefschrift, gevolgd door een algemene discussie van de resultaten.

SAMENVATTING

DEEL 2. KLINISCHE EN METHODOLOGISCHE ACHTERGROND

Hoofdstuk 2.

Vasoregulatie en autoregulatiemetingen van de hersenenvaten hebben als doel om perioden van verminderde hersendoorbloeding op te sporen en te voorkomen. Er zijn verschillende methoden om de autoregulatie, vasoregulatie en CO_2 vasoreactiviteit van de hersenenvaten te meten, te analyseren en te kwantificeren. Sommige technieken informeren de arts over lokale regulatiestoornissen ('snapshot evaluatie'). Andere technieken zijn meer geschikt voor langdurige globale metingen ('monitoring evaluatie') waar de bijgewerkte resultaten als terugkoppeling kunnen dienen voor behandelingen. We concluderen dat deze methoden in

een verscheidenheid van ziektebeelden kunnen worden ingezet en in de toekomst mogelijk behandelingen kunnen sturen. Referentiewaarden ontbreken momenteel echter nog, hetgeen de inzet in de klinische praktijk momenteel beperkt.

Hoofdstuk 3.

In dit hoofdstuk bespreken we de interactie tussen een (sub) acuut herseninfarct en de autoregulatie van de hersenen. Onderzoekers hebben hiervoor de transcraniële Doppler (TCD) techniek gebruikt omdat hiermee de hersendoorbloeding aan het bed van de patient voor een langere periode (niet-invasief) geschat kan worden. Deze methode is geschikt voor het bestuderen van de verschillende fysiologische regelmechanismen betrokken bij de autoregulatie (dynamische en statische autoregulatie). We hebben relevante studies uit de literatuur geselecteerd en beoordeeld. Deze studies tonen in het algemeen een belangrijke stoornis in de autoregulatie na een herseninfarct aan. De stoornis verslechtert mogelijk nog in de eerste vijf dagen na het herseninfarct en herstelt zich in de volgende drie maanden. Een gestoorde autoregulatie was geassocieerd met een verdere neurologische verslechtering, de noodzaak voor chirurgische ingrijpen en uiteindelijk slechter herstel. Ter verbetering van de synthese van gegevens uit de verschillende onderzoeksgroepen, is er dringend behoefte aan standaardisatie van de gebruikte methodologie in autoregulatiestudies.

Hoofdstuk 4.

Voor het correct berekenen van de dynamische autoregulatie van de hersenen vormt de aanwezigheid van grote, trage bloeddrukschommelingen een belangrijke voorwaarde. In dit hoofdstuk hebben we getracht de reproduceerbaarheid en variabiliteit van drie autoregulatieuitkomstmaten te verbeteren bij 16 gezonde vrijwilligers door het passief optillen van de benen van de onderlaag. De bloeddruk, de CO₂ spanning, en de doorbloedingssnelheid in de hersenen (transcraniële Doppler; TCD) werden continu tweemaal in rust en tweemaal tijdens het cyclisch optillen van de benen (5 sec omhoog, daarna 5 sec omlaag) gemeten. De bloeddrukschommelingen namen inderdaad toe rondom de opgelegde frequentie. De vrijwilligers gingen echter ook dieper en onregelmatiger ademen met veranderingen in het uitgeademde CO₂ gehalte. De variabiliteit van de dynamische autoregulatieuitkomstmaten namen niet af door de manoeuvre. De reproduceerbaarheid nam enkel toe voor één uitkomstmaat (de 'gain' parameter). Wij concluderen dat het nut van deze manoeuvre voor het correct berekenen van de dynamische autoregulatie beperkt is, waarschijnlijk door gelijktijdige CO₂ veranderingen. Het registreren van de CO₂ mag derhalve niet ontbreken bij autoregulatieberekeningen en voor de interpretatie hiervan.

DEEL 3. DE BLOEDDRUK, HERSENDOORBLOEDING EN VASOREGULATIE IN VERSCHILLENDE LICHAAMSHOUDINGEN BIJ PATIËNTEN MET EEN ACUUT HERSENINFARCT EN BIJ ERNSTIG ZIEKE PATIËNTEN

Hoofdstuk 5.

De bloeddruk wordt frequent gecontroleerd op de afdeling waar patiënten met een acuut herseninfarct worden opgenomen (stroke unit). Bedlegerige patiënten worden frequent in zijligging gelegd om complicaties van immobiliteit te voorkomen. Wij onderzochten het effect van deze wissellegging op de bloeddruk en keken of er een relatie is met de zijde van neurologische uitval. Bij 54 patiënten werd de (indirecte) bloeddruk gemeten aan de beide armen, allereerst liggend op de rug en vervolgens in beide zijliggingen (45°). De bloeddruk gemeten aan beide armen in rugligging was vergelijkbaar. In de zijligging was de bloeddruk significant lager (ongeveer 12 mmHg) indien de bloeddrukmanchet om de bovenliggende arm werd geplaatst. Significant hogere waarden (ongeveer 6 mmHg) werden gemeten in de onderliggende rechter arm. Dit effect leek minder uitgesproken wanneer de onderliggende linker arm werd gemeten. De zijde van uitval had hier geen invloed op. We concluderen dat bij het draaien van patiënten op de stroke unit grote verschillen in de bloeddrukwaarden gevonden worden (gemiddeld tot 18 mmHg). Dit kan grotendeels verklaard worden door hydrostatische factoren, mogelijk deels ook door anatomische veranderingen in de linker arm, maar niet door de zijde van neurologische uitval.

Hoofdstuk 6.

Op de intensive care worden patiënten frequent op de zij gedraaid om complicaties van immobiliteit te voorkomen. We onderzochten het effect van deze wissel zijligging (45°) op de intra-arteriële gemeten bloeddruk (met hoogte correctie), hartslag en perifere arteriële oxygenatie in 20 intensive care patiënten. De bloeddruk in de linker en rechter zijligging was gemiddeld 5 mmHg hoger dan in rugligging. Wij vonden geen significante verschillen tussen bloeddruk gemeten in de linker en rechter zijligging. Er werden geen belangrijke verschillen in oxygenatie en hartfrequentie waargenomen tussen de drie posities. Na correctie voor covariaten bleven de effecten bestaan. We concluderen dat er een kleine - maar klinisch niet relevante - toename is van de intra-arteriële bloeddruk in zijligging met continue hydrostatische hoogtecorrectie.

Hoofdstuk 7.

In dit hoofdstuk hebben we de effecten van liggen, zitten en staan op de bloeddruk bestudeerd bij patiënten met een acuut herseninfarct. De indirecte bloeddruk, hartfrequentie en perifere zuurstofsaturatie werden hiervoor in de liggende, zittende, en (indien haalbaar) actief staande positie gemeten op dag 1, 2 en 3 na het infarct bij 167 patiënten. Tevens werd gekeken of een forse bloeddrukstijging of daling bij staan gecorreleerd was met het uiteindelijke herstel na 3 maanden. Ongeveer 60% van de patiënten waren in staat om te staan. Gemiddeld nam de

bloeddruk toe bij de positieverandering van liggen naar zitten (Dag 1: \uparrow ongeveer 4 mmHg) en bij van zitten naar staan (Dag 1: \uparrow ongeveer 5 mmHg). Veranderingen waren het meest uitgesproken bij de metingen in de eerste 24 uur na het herseninfarct. Een significante bloeddrukdaling (orthostatische daling) trad op bij 13% van de patiënten, een significante stijging (orthostatische verhoging) werd gezien in 20%. De orthostatische verhoging was onafhankelijk geassocieerd met een gunstig herstel van het herseninfarct. We concluderen dat de bloeddrukveranderingen bij zitten en staan het meest uitgesproken zijn in de eerste 24 uur na een herseninfarct. Een significante bloeddrukstijging tijdens staan is onafhankelijk geassocieerd met een gunstig herstel na een acuut herseninfarct. De resultaten leveren geen argumenten tegen de vroege mobilisatie van patiënten op de stroke unit.

Hoofdstuk 8.

In deze studie onderzochten we of de doorbloedingssnelheid (TCD) van de grote hersenvaten significant verandert bij patiënten met een acuut herseninfarct die de zittende positie (in bed) innemen. Daarnaast hebben we het verband tussen deze fysiologische veranderingen en veranderingen in de neurologische status, het uiteindelijk herstel en de dynamische autoregulatie van de hersenen geëxploreerd. Naast de doorbloedingssnelheid (in aangedane en niet-aangedane hersenhelft) werden ook het 'near-infrared' spectroscopie signaal (NIRS), de CO₂ spanning en de niet-invasieve bloeddruk gemeten. In totaal werden 52 patiënten met een acuut herseninfarct en 20 gezonde controles gemeten. Na het innemen van de zittende positie werd geen verslechtering of verbetering van de neurologische uitval waargenomen. De gemiddelde doorbloedingssnelheid daalde niet meer in de zittende positie (70°) bij patiënten dan bij gezonde controles. Dit was het meest evident bij de meting op de eerste dag. Er werden geen significante verschillen gevonden tussen de aangedane en niet-aangedane hersenhelft en tussen patiënten met een ongunstige en gunstige uitkomst na 3 maanden. De dynamische autoregulatie was significant verminderd bij patiënten met een acuut herseninfarct, met name bij patiënten met afwijkingen in de grote toevoerende vaten. Deze verstoring werd aanvankelijk voor beide hersenhelften gevonden, en verbeterde enigszins bij de meting op dag 3 voor de niet-aangedane hersenhelft. Deze stoornissen hadden geen relatie met de veranderingen van de gemiddelde doorbloedingssnelheid tijdens de positiewisseling. Het innemen van de zittende positie in bed bij licht tot matig getroffen patiënten met een herseninfarct lijkt veilig tijdens de eerste 3 dagen op de stroke unit (ondanks een bilateraal aangetaste dynamische autoregulatie). De liggende of Trendelenburg positie verbetert de hersendoorbloeding niet en gaf geen verbetering van de neurologische uitval.

DEEL 4. TOEPASSINGEN IN KLINISCH ONDERZOEK

Hoofdstuk 9.

In dit hoofdstuk werd onderzocht of het meten van het bilaterale NIRS signaal kan worden gebruikt voor het bewaken van patiënten met een acuut herseninfarct. Het NIRS signaal

meet de veranderingen in de zuurstofconcentratie in de hersenen en kan mogelijk belangrijke effecten van forse schommelingen in de bloeddruk en dalingen van het zuurstofgehalte in het bloed opsporen. Negen patiënten met een acuut herseninfarct werden gedurende de nacht enkele uren op de stroke unit gemeten. We vonden significant meer NIRS dalingen in de aangedane vergeleken met de niet-aangedane hersenhelft (477 versus 184 dalingen). In de aangedane hemisfeer werden bijna alle zuurstof dalingen in het bloed ($n = 128$, 96%) gevolgd door een NIRS daling, in de niet- aangedane hersenhelft was dit slechts in 23% het geval ($n = 30$). Slechts een gedeelte van de forse bloeddrukdalingen werden gevolgd door een daling van het NIRS signaal. Dit was echter significant verschillend tussen de beide hersenhelften (32% versus 13%). Deze studie toont aan dat het NIRS signaal belangrijke fysiologische veranderingen in de aangedane hersenhelft weergeeft, maar vereist bevestiging in een grotere steekproef. Het lijkt aantrekkelijk om deze techniek in te zetten op de stroke unit om het kwetsbare hersenweefsel te bewaken.

Hoofdstuk 10.

Hoofdstuk 10 en 11 hebben betrekking op retrospectieve analyses met data van ernstig traumatisch hersenletselpatiënten met continue metingen van de bloeddruk en intracraniale druk op de intensive care. De metingen werden verricht om de hersendoorbloeding te optimaliseren. In hoofdstuk 10 onderzochten we de relatie tussen langzame spontane wisselingen in de bloeddruk en de amplitudo van het intracraniale druk signaal. Deze relatie kan worden uitgedrukt in een nieuwe index (P_{Ax}) en met een statistische bewerking als een trend over de tijd worden weergegeven. Deze trend weerspiegelt mogelijk de reactiviteit van de hersenvaten (vasculaire reactiviteit). In deze studie werd de nieuwe P_{Ax} index vergeleken met de gevestigde en gevalideerde PR_x index (de correlatiecoëfficiënt tussen gemiddelde waarden van bloeddruk en intracraniale druk signaal). De gegevens van 327 traumapatiënten werden gebruikt waarvan de uitkomst na zes maanden bekend was. De index P_{Ax} was minder negatief bij traumapatiënten die dood gingen in vergelijking met degenen die overleefden. In tegenstelling tot PR_x, kon P_{Ax} differentiëren tussen een dodelijke en niet-dodelijke afloop in een groep van 120 patiënten met intracraniale druk lager dan 15 mmHg. We concluderen dat P_{Ax} een nieuwe index van de reactiviteit van de hersenvaten vertegenwoordigt, die even goed presteert als de gevestigde PR_x index in langdurige bewaking van patiënten met ernstig schedelhersenletsel, maar ook bruikbaar is bij lagere waarden van de intracraniale druk. De definitieve waarde van deze nieuwe index moet verder worden onderzocht in prospectief gecontroleerd onderzoek.

Hoofdstuk 11.

In dit hoofdstuk hebben we geprobeerd een methode te ontwikkelen waarbij door het weergeven van de reactiviteit van de hersenvaten (PR_x) over een periode van 4 uur een 'optimale' doorbloedingsdruk (of 'cerebral perfusion pressure'; CPP) gevonden kan worden voor patiënten met ernstig traumatisch schedelhersenletsel. De methode hebben we gevalideerd door de associatie tussen de uitkomst na zes maanden en het verschil tussen de

berekende waarde en de werkelijke doorbloedingsdruk te analyseren. Met een wiskundige methode werd de 'optimale' doorbloedingsdruk in de hersenen automatisch in een grafiek aangegeven als de waarde waarbij de hersenvaten de beste reactiviteit vertoonden. Door een statistische bewerking kan deze 'optimale' waarde als een trend worden weergegeven. Identificatie van een 'optimale' doorbloedingsdruk was gemiddeld mogelijk gedurende 55% van de gehele registratieperiode op de intensive care. De uitkomst na zes maanden correleerde met het verschil tussen de berekende (optimale) en werkelijke waarde, waarbij de uitkomst gedichotomiseerd werd in dodelijke en niet-dodelijke afloop. Dodelijke afloop was geassocieerd met relatieve 'verminderde doorbloeding' (werkelijke waarde < 'optimale' waarde), ernstige invaliditeit met 'toegenomen doorbloeding' (werkelijke waarde > 'optimale' waarde), en een gunstige uitkomst was geassocieerd met kleine verschillen tussen de werkelijke en de individuele 'optimale' doorbloedingsdruk van de hersenen. Wij concluderen dat een 'optimale' doorbloedingsdruk kan worden geïdentificeerd in de meerderheid van de opnameperiode op de intensive care bij ernstig traumatisch schedelhersenletsel patiënten met continue intracranieële drukmetingen. Patiënten met een doorbloedingsdruk dicht bij berekende 'optimale' waarde hadden meer kans op een gunstige uitkomst dan degenen bij wie doorbloedingsdruk afwijkt van de individueel berekende 'optimale' waarde. Behandeling van ernstig schedelhersenletsel met het meewegen van de individuele reactiviteit van de hersenvaten verdient verder (prospectief) onderzoek om de uitkomst te verbeteren.

IMPLICATIES

Na de beschrijving van de samenvatting van de verschillende hoofdstukken, zullen we nu ingaan op de implicaties van de bevindingen in dit proefschrift aan de hand van de doelstellingen en vragen.

Hoe reageert de bloeddruk op verschillende houdingsveranderingen in patiënten met een acuut herseninfarct (zijligging, liggende, zittende en staande positie) en patiënten opgenomen op de IC (zijligging)? Is er een verband tussen deze bloeddruk-veranderingen en de uitkomst na een acuut herseninfarct?

In de zittende en staande positie bevinden de hersenvaten zich ± 30 cm boven het hart, met directe gevolgen voor de doorbloedingsdruk in de hersenen (maar nog steeds binnen wat wordt beschouwd als het bereik van de autoregulatie). Zowel de positie van de hersencirculatie als de verlaging van het hartminuutvolume (door veneuze pooling) vormen een uitdaging voor een constante bloedstroom in de hersenen in deze posities. Hoewel de gemeten vermindering van de bloedstroomsnelheid (TCD) en lokale zuurstofvoorziening (gemeten met NIRS) in de hersenen beperkt worden gehouden via systemische fysiologische aanpassingen en via de autoregulatie, is houdingsgebonden intolerantie (orthostase) en flauwvallen niet ongewoon bij gezonde mensen.

Houdingsgerelateerde fysiologische veranderingen zijn beperkt onderzocht bij patiënten met een acuut herseninfarct. Wij vonden dat de bloeddruk (zonder hoogtecorrectie) toeneemt wanneer patiënten gaan zitten en vanuit de zittende positie actief gaat staan. Deze veranderingen zijn het meest uitgesproken in de eerste 24 uur na een acuut herseninfarct. De bloeddruk neemt aanzienlijk af bij 13% en aanzienlijk toe bij 20% van de patiënten. Deze orthostatische bloeddruk toename (hypertensie) was onafhankelijk geassocieerd met een gunstig herstel van het herseninfarct. Het percentage patiënten met orthostatische afname (hypotensie) was niet anders dan gemeten bij gezonde en hypertensieve ouderen. Daarom concluderen wij dat onze resultaten geen contra-indicatie vormen voor het opstarten van vroege mobilisatie bij patiënten met een acuut herseninfarct. De wisselgigging op de stroke unit gaf verrassende bloeddrukvariëaties, die grotendeels op hydrostatische veranderingen terug te voeren zijn. Met intra-arteriële metingen met hoogtecorrectie bij ernstig zieke patiënten op de intensive care werden deze verschillen inderdaad fors teruggebracht. De lagere bloeddruk in de onderliggende linker arm bij patiënten met een acuut herseninfarct verdient verdere aandacht. Mogelijk dat er een anatomische verklaring bij deze patiënten gevonden kan worden.

In zekere zin zijn onze bevindingen geruststellend en vormen zij geen ondersteuning voor het standaard invoeren van houdingsgerelateerde bloeddrukmetingen op de stroke unit of voorwaarden alvorens met vroege mobilisatie te starten. Anderzijds is de associatie tussen orthostatische hypertensie en een goed herstel na een herseninfarct mogelijk een indicatie dat het kwetsbare herstellende hersenweefsel (penumbra) voordeel heeft bij een 'hyperdynamisch' cardiovasculair systeem in de acute fase. De hierbij betrokken autonome of fysiologische mechanismen zijn nog niet opgehelderd. Ook de interactie tussen orthostatische hypertensie en een gestoorde autoregulatie van de hersenen is onduidelijk en verdient verder onderzoek. Dergelijke onderzoeken vergroten niet alleen onze kennis over de fysiologische veranderingen en aanpassingen in de (sub)acute fase na een herseninfarct, maar kunnen ook moeilijke beslissingen sturen met betrekking tot vroege mobilisatie, rehydratie en aanpassingen van de medicatie (met name van antihypertensiva).

Wat zijn de effecten van in-bed-mobilisatie op de doorbloeding van de hersenen en de neurologische status in de acute fase na een herseninfarct?

Er is weinig bekend over de invloed van de verschillende lichaamshoudingen op de doorbloeding van de hersenen in de acute fase na een herseninfarct. Wij onderzochten of de doorbloedingssnelheid significant afneemt bij rechtop zitten in bed en relateerden dit aan eventuele veranderingen in de neurologische status tijdens de meting, de uitkomst na drie maanden en de dynamische autoregulatie status. Tijdens rechtop zitten werd geen neurologische verslechtering of verbetering vastgesteld en daalde de doorbloedingssnelheid gemiddeld bij patiënten met een acuut herseninfarct niet meer dan bij gezonde controles. De dynamische autoregulatie was voor beide hersenhelften gestoord bij de patiënten in de acute fase. We concluderen dat de zittende positie bij licht tot matig aangedane

patiënten met een herseninfarct veilig is tijdens de eerste drie dagen op de stroke unit, ondanks een gestoorde autoregulatie. Onze resultaten geven aan dat de zittende positie goed verdragen wordt bij patiënten die gezien hun neurologische beperking en algemene conditie momenteel al redelijk snel in deze positie gebracht worden door de verpleging. De hydrostatische verandering wordt bij zitten blijkbaar voldoende gecompenseerd door een (tijdelijke) 'hyperdynamische' cardiovasculair systeem, een adequate intracraniele druk reductie, een toegenomen veneuze afvloed of een combinatie van deze factoren.

Het herhalen van deze metingen tot meerdere dagen na het herseninfarct kan interessant zijn, aangezien de genoemde fysiologische compensatiemechanismen uitgeput kunnen raken en er aanwijzingen zijn dat de autoregulatie nog verder kan verslechteren na de subacute fase. Onze resultaten gelden niet voor het mobiliseren van patiënten van de zittende naar de staande positie omdat dit andere (waarschijnlijk grotere) hemodynamische veranderingen geeft. Bij gebrek aan resultaten uit lopend (gerandomiseerd) onderzoek aangaande de voor- en nadelen van vroege mobilisatie bij patiënten met een acuut herseninfarct, stellen wij voor bij milde tot matig aangedane patiënten het rechtop zitten niet te beperken in de (sub) acute fase. Verder stellen wij voor om met continue doorbloedingssnelheidsmetingen (TCD) de veiligheid van de staande positie te testen in de nabije toekomst.

Kan de bewaking van patiënten met een acuut herseninfarct of traumatisch schedelhersenletsel verbeterd worden door inzet van autoregulatie/vasoregulatie monitoring?

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De NIRS-afgeleide regionale zuurstofvoorziening (rSO_2) in de hersenen is theoretisch verbonden met meerdere variabelen die de verhouding tussen levering en verbruik van zuurstof in de hersenen aangeven. De op NIRS gebaseerde autoregulatie bewaking heeft verschillende voordelen. De techniek is niet-invasief en vereist geen precieze focus op hersenvaten of continue correctie door verschuiving van het meetinstrument. De techniek is vooralsnog zeer beperkt onderzocht bij patiënten met een acuut herseninfarct. In onze studie bij 9 patiënten met een herseninfarct werden bijna alle (96%) nachtelijke perifere zuurstof desaturaties gevolgd door een significante afname van het rSO_2 signaal. Ook grote bloeddrukdalingen werden significant vaker opgepikt door de NIRS in de aangedane hersenhelft dan in de niet-aangedane hersenhelft. Nachtelijke rSO_2 dalingen kwamen tweemaal zo vaak voor in de door het herseninfarct getroffen hersenhelft. Deze bevindingen maken NIRS een aantrekkelijke techniek voor de (nachtelijke) bewaking van kwetsbaar hersenweefsel op de stroke unit.

De overleving na een ernstig schedelhersenletsel is mede afhankelijk van de beheersing van de oplopende intracraniele druk en het waarborgen van een adequate doorbloedingsdruk in de hersenen. Therapieën zijn erop gericht om voldoende doorbloeding in het gezwollen en gekneusde hersenweefsel te bereiken. Er bestaan diverse methoden om de doorbloeding (druk) te bepalen maar momenteel ontbreken individuele grenswaarden bij patiënten met ernstig schedelhersenletsel. Met TCD kan een goede schatting van de hersendoorbloeding en

de daaraan gekoppelde intracranieële druk gemaakt worden, maar voor langdurige bewaking is er behoefte aan een meer continue en derhalve gevoeliger methode om aanvullende schade door zwelling en zuurstoftekort van het omgevende weefsel te voorkomen. In hoofdstuk 11 hebben wij een methode doorontwikkeld die het mogelijk maakt om automatisch een 'optimale' doorbloedingsdruk te berekenen door het vervolgen (4 uur) van de vasoreactiviteit van de hersenvaten. We concluderen dat bij de behandeling geen vaste grenzen voor de doorbloedingsdruk moeten worden aangehouden maar dat het niveau op basis van fysiologische veranderingen in de hersenen moet worden aangepast. Onze nieuwe methode werd gevalideerd aan de hand van de gevonden relatie tussen de uitkomst na 6 maanden en het verschil tussen de berekende 'optimale' en werkelijke doorbloedingsdrukwaarde.

Aan de hand van welke fysiologische parameter het beleid bij ernstig schedelhersenletsel patiënten moet worden aangepast is onderwerp van veel (wetenschappelijke) discussie. De voordelen van het gebruik van de vasoreactiviteitsmethode PRx (met bloeddruk en intracranieële druk als variabelen) is tweeledig. In tegenstelling tot de niet-invasieve TCD methode zijn de bloeddruk en intracranieële druk robuuste signalen die over lange tijd betrouwbare berekeningen geven. Met het huidige TCD bevestigingssysteem is bewaking van de doorbloeding (snelheid) gedurende een langere periode niet betrouwbaar. Zelfs in gesedeerde patiënten is een intermitterende meting van het TCD signaal het hoogst haalbare. In tegenstelling tot andere invasieve parameters zoals de lokale zuurstofspanning ('partial pressure of oxygen in brain tissue'; $PbTO_2$) metingen en analyse van metaboliëten in het hersenvocht (microdialyse), is de intracranieële druk parameter minder gevoelig voor de locatie van de meting. Dit alles neemt niet weg dat verdere (prospectieve) studies nodig zijn om onze hypothese te ondersteunen dat een behandeling met een individueel berekende 'optimale' doorbloedingsdruk gunstig is voor herstel van een ernstig hersentrauma. Definitief bewijs zal mogelijk volgen uit een goed opgezette prospectieve studie met gebruik van de reactiviteit van de hersenvaten (PRx). De door ons ontwikkelde automatische methode vormt een belangrijke voorwaarde voor de opzet van een dergelijke studie.



CHAPTER 14

DANKWOORD/ACKNOWLEDGMENTS

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Door de jaren heen heb ik op verschillende andere afdelingen in het ziekenhuis kleinere of grotere (lopende) onderzoeksprojecten mogen doen. Ik wil graag de afdeling Intensive Care (dr De Smet, professor Zijlstra en dr Regtien), de afdeling Klinische Neurofysiologie (dr Van der Hoeven), de afdeling Neurochirurgie (professor Groen, dr Van Dijk) en the department of Clinical Neurosciences Cambridge (Professor Pickard en Professor Menon) hiervoor bedanken. With preparing manuscripts or letters, I received many valuable comments of experienced researchers whom I would like to thank: Ken Brady, Peter Hutchinson, Angelos Kolias, Luzius Steiner, Andrea Lavinio, David Menon, John Pickard and Danila Radolovich.

Het onderhouden van vriendschappen is niet gemakkelijk. Zeker niet als je dichter bij de Noordpool woont dan anderen. Maar ondanks fijne neurologie collegae, meegereide huisdieren (Joris), (oud) UMCG fietsvrienden en fijne burens zijn bijeenkomsten met oud studiegenoten uit Boxtel en Nijmegen, Ferus Ebrius reünies, bezoeken aan mijn H.H.D. huisgenoten, het jaarlijkse Meerssen fietsevenement (familie Saris en spinning docters), vrienden

uit België (Dirk Bosmans en Jan Versijpt) en vrienden op leeftijd (Harry en Mariette Wegdam, Albert Lemmens) altijd weer een feest. Speciale gelegenheden zijn de weekenden met het culinair genootschap (Jack, Uriel, Chris, Stefan en Martijn) en het weerzien met de mannen van S.E.M.E.N (Teun, Edwin, Chris, Robert Jan en Daan).

Mijn pa en ma wil ik hartelijk danken voor de eeuwige steun op vele vlakken. Voor deze promotie beperkte zich dit niet enkel tot interesse, bezoeken of complimenten, maar ook tot serieuze bemoeienis met het invliegen van het Brabants kerkkoor als de ideale controlegroep voor één van de studies met collectief 'informed consent'.

Ook de schoonfamilie Joosten vormt al jaren een belangrijke rots in de branding. Ook jullie deuren staan altijd wagenwijd open, en daarachter schuilt immer gezelligheid! Ook familie op afstand ben ik dankbaar. De familie McCulloch (Stephen, Paul en Edna) konden mijn geklungel met figuren, Excel en Engels vocabulaire niet lang konden aanzien en grepen in. Many thanks!

Myriam, het is fijn om mijn oudere en wijze zus als paranimf naast me te hebben staan. Door de jaren heen zijn al heel wat hulplijnen vanuit Brabant gebruikt! De intrigerende vraag wie van ons nu de échte Aries is (...of produceert) blijft er een voor de toekomst.... Ik heb wel zo een vermoeden.

Lieve kleine Sarah, ook jij bent fan van Giraffes. Hopelijk wil ook jij papa's boekje bekijken, beknagen en later hopelijk lezen. Daarom speciaal voor jou nog een beetje aangepaste 'literatuur':

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*Dikkertje Dap klom van de trap,
met een griezelig grote stap,
Op de nek van de Giraf,
zette Dikkertje Dap zich af,
Roetsj daar gleed hij met een vaart,
Tot aan 't kwastje van de staart, Boem! Au!!
Dag Giraf, zei Dikkertje Dap,
Morgen kom ik weer hier met de trap.*

(Dikkertje Dap, Annie M.G. Schmidt)

Lieve Hanneke, al jaren zijn wij heel gelukkig bij elkaar! Stef vat 'ons' heel mooi samen:

*En jouw armen zijn een haven
En jouw handen zijn een zegen
En al sta ik hier alleen
Ik draag jou altijd met mij mee*

(Wie mij liefheeft laat mij los, Stef Bos)



CHAPTER 15

CURRICULUM VITAE

CURRICULUM VITAE

Marinus Johannes Hermanus Aries was born on March 9th 1979 in Boxtel, The Netherlands. He completed his secondary education at Jacob Roelandscollege, Boxtel in 1997. After one year of veterinarian medicine in Gent, Belgium, he went on to medical school at the Radboud University Nijmegen in 1998. At the Institute of Pathology in Nijmegen (Professor Ruiter), Marcel performed a scientific research on 'cMET expression in different stages of prostate cancer'. He conducted this research in combination with the function of editor in chief of the Dutch Medical Journal student-edition (Amsterdam) and associate editor of studentBMJ (London). At the same time he was involved in writing a textbook on radiology. He obtained his doctoral degree in 2003. After clinical elective in Kazan, Republic of Tatarstan (Russia), he continued regular residencies in the Netherlands and Nottingham (United Kingdom). He completed his final residency in Techiman, Ghana (dr Wegdam). After graduating in 2005, Marcel started his training as a neurological resident at the department of Neurology of the University Medical Center Groningen (Professor Kremer), having spent six months of that time in Antwerp, Belgium (Professor De Deyn). In 2007, he obtained a 'AGIKO' research grant of the Netherlands Organization for Health Research and Development (ZonMw) to study the effect of body positions on physiological parameters and cerebral blood flow in acute stroke patients (promoters: Professor De Keyser; Professor Kremer). In 2010, he received a travel research grant from the European Federation of Neurological Societies to study cerebrovascular reactivity in severe traumatic brain injury patients at the Department of Clinical Neurosciences, Addenbrooke's hospital in Cambridge, UK (Professor Pickard). After completing his neurological training, he started in November 2012 as a clinical fellow at the Critical Care Department in Groningen. Marcel is married to Hanneke and the father of Sarah.

CURRICULUM VITAE

Marinus Johannes Hermanus Aries werd geboren op 9 maart 1979 in Boxtel. Hij voltooide zijn gymnasium schoolopleiding in 1997 aan het Jacob Roelandscollege in Boxtel. Na één jaar diergeneeskundestudie in Gent, België, begon hij in 1998 met de studie geneeskunde aan de Radboud Universiteit Nijmegen. Marcel verrichtte wetenschappelijk onderzoek bij de afdeling Pathologie in Nijmegen (Professor Ruiter) op het onderwerp 'cMET expressie bij verschillende stadia van prostaatkanker'. Dit onderzoek combineerde hij met de functie van hoofdredacteur van het Nederlands Tijdschrift voor Geneeskunde studenteneditie (Amsterdam) en redacteur van de studentBMJ (Londen). Hij was betrokken als redacteur bij een radiologie leerboek. Marcel behaalde zijn doctoraalexamen in 2003. Na een klinische keuzestage in Kazan, Republiek Tatarstan (Rusland), volgde hij zijn reguliere coschappen in Nederland en Nottingham (Verenigd Koninkrijk). Zijn laatste coschap deed hij in Techiman, Ghana (dr Wegdam). In 2005 kreeg Marcel zijn artsenbul, waarna hij begon met zijn opleiding tot neuroloog aan de afdeling Neurologie van het Universitair Medisch Centrum Groningen (UMCG) (Professor Kremer). Hij volgde 6 maanden van zijn opleiding in Antwerpen, België (Professor De Deyn). In 2007 kreeg hij een 'AGIKO' subsidie van de Nederland Organisatie voor gezondheidsonderzoek en zorginnovatie (ZonMw) toegewezen om het effect van lichaamspositie op fysiologische parameters en cerebrale bloedddoorstroming bij patiënten met een acuut herseninfarct te bestuderen (promotors: Professor De Keyser; Professor Kremer). In 2010 ontving hij een reis onderzoekssubsidie van de 'Europese Federatie van Neurologische Verenigingen' om de cerebrovasculaire reactiviteit in patiënten met ernstig traumatisch schedelhersenletsel op de afdeling Klinische Neurowetenschappen, Addenbrooke's ziekenhuis in Cambridge, UK (Professor Pickard) te bestuderen. Na zijn neurologische training, begon hij in november 2012 als klinische fellow op de afdeling Intensive Care in Groningen. Marcel is getrouwd met Hanneke en de vader van Sarah.

A detailed illustration of a giraffe and its calf. The adult giraffe is on the left, bending its long neck down towards the calf. The calf is on the right, standing on its hind legs and reaching up with its mouth open, appearing to nuzzle or kiss the adult's neck. Both animals have a distinctive pattern of large, irregular brown spots on a lighter background. The background is a plain, light gray.

CHAPTER 16

PUBLICATIONS/PUBLICATIES

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