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Cerebral Autoregulation

Control of Blood Flow in the Brain

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Stephen Payne
Department of Engineering Science
University of Oxford
Oxford
UK

ISSN 2193-097X ISSN 2193-0988 (electronic)
SpringerBriefs in Bioengineering
ISBN 978-3-319-31783-0 ISBN 978-3-319-31784-7 (eBook)
DOI 10.1007/978-3-319-31784-7

Library of Congress Control Number: 2016942528

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG Switzerland

Foreword

The publication of Cerebral Autoregulation by Stephen Payne is a landmark in the relatively brief, but rapidly evolving, history of cerebral blood flow regulation studies in humans. With this new book, newcomers to this field are privileged to have access to a thorough review of the background and techniques involved in studies of cerebral blood flow autoregulation. Although the concept and naming of this new area were proposed by Niels Lassen in 1959, textbooks that could be regarded as primers have been conspicuously absent, thus requiring anyone new to the field to study hundreds of journal papers to achieve the necessary expertise to become a research practitioner. Supported by nearly 550 selected references, the book provides a didactic and comprehensive introduction ranging from basic material to state-of-the-art methodology and clinical applications. For those who have been active in the field of cerebral autoregulation, this book will be of considerable utility, not only as a teaching guide, but also as an efficient way to access relevant information that has been condensed and organised in a systematic way.

One characteristic of the field of cerebral blood flow autoregulation studies in humans is the multi-disciplinarity it attracts due to the complexity of the cerebral circulation and the diversity of clinical applications involved. A research team working on research or clinical applications, typically involves different combinations of clinicians, surgeons, biomedical engineers, physiologists, medical physicists, mathematical modellers, statisticians, computing experts or even more unusual backgrounds. Any of these experts will also benefit from the book as a means to bridge the gap to those disciplines with which he or she is less familiar.

Of particular relevance are the quantitative methods required for cerebral autoregulation research, as well as clinical applications. To start with, the book covers the different measurement techniques that have been in use for obtaining the raw data required for assessment of cerebral autoregulation; not a simple task, given the access barrier imposed by the skull. Differently from other areas of physiological or clinical investigation though, first line measurements cannot in themselves provide the answers needed for assessment of cerebral autoregulation. Since autoregulation focuses on the CBF response to changes in ABP, some form of

quantitative modelling is always required to extract the information needed to assess the efficacy of autoregulatory mechanisms in health or disease. In other words, the information we are after is not to be found directly in the measurements per se, but in the model parameters that link ABP changes to the CBF response. This essential element of cerebral autoregulation assessment is covered in Chaps. 3 and 4 of the book and it will be particularly helpful to anyone who does not have a formal training in the mathematical tools of systems analysis. Chapter 5 also needs to be noted for the range of clinical contexts discussed; this provides an excellent overview of the relevance of cerebral autoregulation, and the potential, and indeed the need, for it to become engrained in many areas of medicine. As with the history of cerebral autoregulation studies in humans, this book is emblematic of the coming-of-age of this new frontier of investigation into the human circulation. It deserves a very wide audience.

R.B. Panerai
University of Leicester, UK

Preface

Every part of the human brain must be supplied with a sufficient and continuous supply of blood in order to maintain healthy function. Cerebral autoregulation, the means by which the brain achieves this, despite changes in other physiological variables such as blood pressure, is a highly complex mechanism. It has been widely implicated in a range of brain diseases, including stroke, stenosis and brain trauma and injury. With increasing clinical focus on brain disease, the importance of cerebral autoregulation has become more widely appreciated.

However, there is as yet no suitable overview of or introduction to the subject, despite the very substantial published literature; it is thus difficult to get a clear broad vision of this highly multidisciplinary field and to understand the key open questions. Studies are published in a very wide range of technical and clinical journals and the three most highly cited review papers were published in 1990, 1984 and 1998. No general book on cerebral autoregulation has yet been published, so there is no recent survey of the field that can be used by researchers working in this area or related fields.

The aim of this book is thus to provide an up-to-date review of the state of the art in cerebral autoregulation, providing the first such book in this field, covering all aspects of cerebral autoregulation, from the biological mechanisms to the clinical applications of advanced measurement and analysis techniques. This is particularly relevant as cerebral autoregulation starts to move from the laboratory to the bedside. The intention of this book is to provide an introduction to what is currently a very disparate field to the general scientific and clinical reader, whilst also giving a full coverage for the more specialist reader through the use of a comprehensive reference list. It is hoped that this will help to draw together the field and to assist researchers in setting out future directions with the current state of the art more clearly in mind, along the lines of the Cerebral Autoregulation Research Network (CARNet).[1]

Oxford, UK — Stephen Payne

[1] http://www.car-net.org.

Contents

Introduction

The human brain is one of the most complex organs in existence. Despite considerable advances, however, understanding of its structure and function remains poor. Despite the fact that it occupies only 2 % of body weight, it accounts for 20 % of body metabolism and 14 % of blood flow, Kety and Schmidt (1948). The tight coupling between flow and metabolism means that blood flow must be maintained within tight limits, despite many different disturbances; the mechanisms that perform this function are highly complex and collectively known as cerebral autoregulation. The brain is one of the most tightly regulated of all body organs and cerebral blood flow (CBF) is maintained almost constant over a range of approximately ±50 % change from baseline in arterial blood pressure (ABP).

Even a temporary interruption to this supply can lead to fainting (a phenomenon of significant importance to the elderly), whilst a more serious and prolonged shortage will lead to cerebral ischaemia. Periods of ischaemia are likely to result in transient ischemic attacks and are implicated in different types of dementia: long periods may result in ischemic stroke, with potentially devastating or fatal consequences. A failure of autoregulation has been implicated in all of these brain diseases as well as in brain injury and trauma.

Compared to heart disease, the options available to the clinician for cerebrovascular disease remain few and these can have equally devastating side effects. Given increases in life expectancy and the increased prevalence of cerebral disease, the importance of cerebral blood flow and its control in physiology and pathophysiology is likely to grow over time. This is compounded by the relative difficulties involved in assessing cerebral function and the multitude of different analysis techniques available to both the researcher and the clinician. An increased understanding of both cerebral autoregulation and its measurement will be vital in improving our diagnosis and treatment of cerebrovascular disease.

In the following chapters, all of these issues will be investigated, starting with the physiological basis for autoregulation. Then models and analysis techniques applied to cerebral autoregulation will be examined in detail, showing how the field has diversified and expanded. Finally, the role of cerebral autoregulation in a very large number of physiological and pathophysiological conditions will be examined

in detail, looking to set out the state of the art today and hence to suggest directions in which this field needs to move in order both to improve our understanding of cerebral autoregulation and to ensure its greater translation into the clinical environment.

Before starting, however, a very brief introduction of cerebral autoregulation will be given, to set out its historical background and to set the boundaries for what will and what will not be discussed in this book. The main restriction to note right at the start is that only studies on humans will be presented here: although animal models have indeed provided valuable data, the sheer number of studies that has now been performed on human subjects means that the additional benefit of animal models appears relatively meagre. The lack of translation from animal to human models has also been widely shown, for example Aaslid et al. (1991).

The term cerebral autoregulation was first used by Lassen in his 1959 review paper, Lassen (1959). It was originally thought that cerebral blood flow varied only passively with the perfusion pressure, because of the Monro-Kellie doctrine (which states that the intracranial volume is constant). It was only later, through measurements of pial vessel diameter, that vascular diameter was found to vary actively. Lassen first plotted the curve, shown in Fig. 1, which now bears his name. Lassen simply extracted measurements from 11 different published studies and plotted mean values of CBF against ABP. The resulting data points yielded a curve where CBF remained flat over a very wide range of mean ABP, only dropping off around 50 mmHg.

There have been a number of subsequent criticisms of Lassen's methods, but it remains widely accepted that steady-state CBF remains largely constant between two values of ABP, termed the lower limit of autoregulation (LLA) and upper limit of autoregulation (ULA) respectively (note that Lassen did not identify this upper limit). This is now known as static autoregulation and the subsequent history of cerebral autoregulation is largely an extension of this to dynamic behaviour and to the response to other stimuli.

CBF also responds to stimuli other than ABP and a recent study summarised these stimuli into five categories, as shown in adapted form in Fig. 2. The cerebral vasculature is most sensitive in fact to changes in arterial pCO_2, with very large changes in CBF occurring as pCO_2 is altered. The cerebral vasculature also responds globally to changes in cardiac output and locally to changes in neural activity (this latter behaviour being the foundation for many brain imaging techniques). In addition to autoregulation, there is also neurogenic control, although this is the least well understood.

Of course, CBF is not the only physiological parameter that changes in the brain. Cerebral blood volume is also maintained and the flows of cerebrospinal fluid (CSF) play a role in maintaining homeostasis within the confines of an incompressible fluid circulating inside a rigid skull. The role of intracranial pressure (ICP) is thus very important, particularly in the context of brain injury.

Figure 3 shows a very simplified schematic of the primary mechanisms and parameters involved in cerebral autoregulation. The three key mechanisms can be considered to be the neurogenic, myogenic and metabolic pathways. Again, these

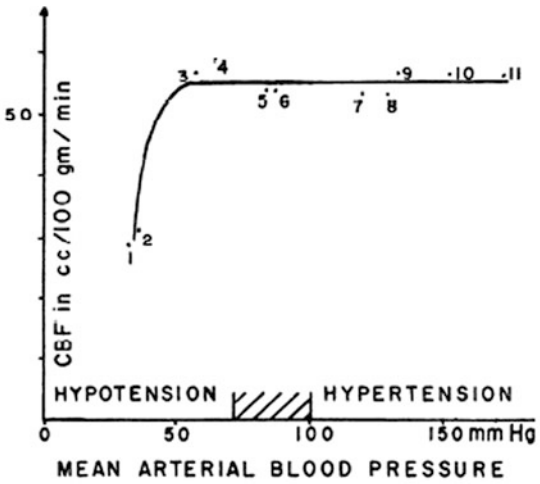

FIG. 1. Cerebral blood flow and blood pressure. Mean values of 11 groups of subjects reported in 7 studies have been plotted. Various acute and chronic conditions have been selected, characterized by a change in blood pressure. In all, this figure is based on 376 individual determinations.

1 and *2*, Drug-induced severe hypotension (81). *3* and *4*, Drug-induced moderate hypotension (206). *5* and *6*, Normal pregnant women and normal young men (206, 173). *7*, Drug-induced hypertension (230). *8*, Hypertensive toxemic pregnancy (206). *9*, *10*, *11*, Essential hypertension (229, 131, 228).

Fig. 1 Lassen curve, reproduced with permission from Lassen (1959)

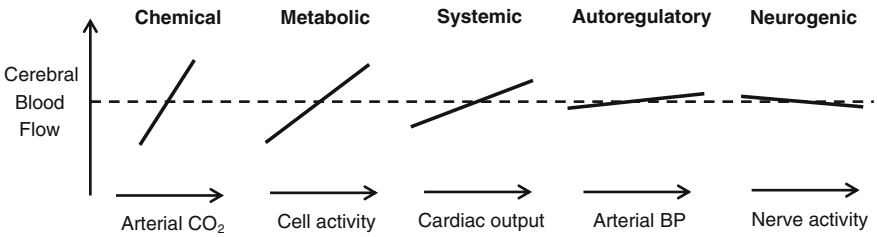

Fig. 2 Factors affecting cerebral blood flow, adapted from Ainslie and Duffin (2009)

are still only simplified terms for the complex regulation pathways that remain quite poorly understood. However, fundamentally the primary driver is taken to be cerebral perfusion pressure (CPP), which is the difference between ABP and the intracranial pressure (ICP) exerted by the skull on the brain. This acts on the cerebral vasculature, which is controlled to give a level of CBF. There is a strong correlation between CBF and cerebral blood volume (CBV). Through changes in intracranial compliance, which is variable, ICP is set through the level of blood volume and CSF fluid. This provides one feedback mechanism.

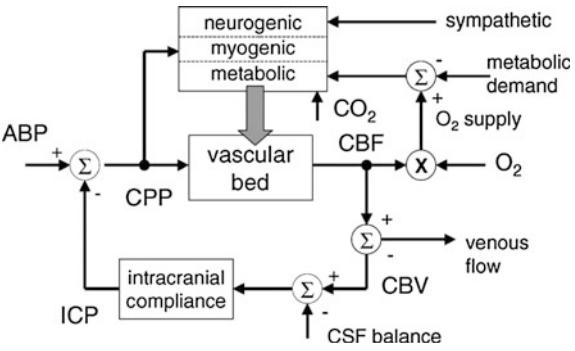

Fig. 3 Schematic of primary mechanisms involved in cerebral autoregulation, reproduced with permission from Panerai (2004)

In addition, the level of CBF sets the amount of oxygen (and other nutrients such as glucose) supplied to the brain. The demand for oxygen is equal to the cerebral metabolic rate of oxygen ($CMRO_2$): any local or global mismatch between supply and demand will feed back through the metabolic pathway to adjust local or global CBF. This gives a second feedback mechanism through complex signalling pathways in the cerebral vasculature.

The myogenic response refers to the active behaviour of the vasculature in response to changes in ABP: a decrease in ABP would be expected to yield a decrease in blood vessel radius, since the wall is a compliant material and this passive response is indeed found to comprise the first part of the response. However, there is also an active response that counterbalances the passive response and that acts to restore vessel diameter and hence to maintain CBF. Finally, in addition to the myogenic and metabolic mechanisms, there is a neurogenic response, but this is the least well understood, and sympathetic activity has proved to be the hardest both to interpret and to measure.

The field of cerebral autoregulation was transformed in the 1980s by the advent of Doppler ultrasound to measure cerebral blood flow velocity (CBFV) continuously, Aaslid et al. (1982). This opened up the possibility of assessing the dynamic response of cerebral blood flow to stimuli and has provided enormous insights into the mechanisms and their behaviour under a very wide range of conditions. The early reviews by Strandgaard and Paulson (1984) and Paulson et al. (1990) were able already to conclude that cerebrovascular disease could lead to impaired or even abolished autoregulation, for example in severe head injury or acute ischemic stroke, and that this could leave other brain tissue susceptible to injury caused by the loss of autoregulation.

The most popular metric to quantify cerebral autoregulation based on Doppler ultrasound measurements remains the autoregulation index (ARI) proposed by Tiecks et al. (1995). This quantifies autoregulation on a scale from 0 to 9, with 0 being no autoregulation and 9 maximal autoregulation. Although very crude, this does allow autoregulation status to be compared easily between subject groups through the use of a single metric.

Of course, if the brain can be considered as a system with a single input (normally ABP) and a single output (normally CBFV measured in the middle cerebral artery), then simultaneous measurements of time series for these two signals can be processed into a number of forms. The easy availability of data has opened up a wide field of analysis. Most early work assumed that the system is linear and stationary, although it is now generally agreed that the system is neither linear nor stationary and that multivariate analysis techniques should be used. The review by Panerai (1998) examined these in detail, although there has been considerable progress since then. Most recently, there has been a very large amount of work performed investigating cerebral autoregulation in the context of brain injury and disease.

In the following chapters, the current state of the art in cerebral autoregulation is now described. The book is divided into five chapters, covering physiological background, measurement techniques, models, analysis techniques and clinical applications. The aim is to provide sufficient detail in each chapter for the general reader to understand the key points, with further details being fully referenced for the more specialist reader or researcher in the field to gain more information.

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Chapter 1
Physiological Basis

In this chapter, the physiology that governs cerebral autoregulation is presented, beginning with the structure of the cerebral vasculature and how blood flows through it. How this flow is controlled in response to changes in pressure is then presented, before how cerebral blood flow responds to changes in blood gas levels and neurogenic control is examined. It should be noted that the metabolic response will not be examined here in any detail, likewise the role of CSF, since these are both considerable topics in their own right and outside the scope of this focus on cerebral autoregulation.

1.1 Cerebral Vasculature

The cerebral vasculature is a highly complex, structurally heterogeneous, interconnected network of blood vessels. Blood is supplied to the brain by four feeding vessels: the left and right internal carotid arteries (ICAs) and the left and right vertebral arteries (VAs). The former are found anteriorly, the latter posteriorly; the latter also join together to form the Basilar Artery (BA). The ICAs and BA are linked through the circle of Willis, which is made up of the left and right Anterior Cerebral Arteries (ACAs), the Anterior Communicating Artery (ACoA) and the Posterior Communicating Arteries (PCoA). The Middle Cerebral Arteries (MCAs) are also connected to the circle of Willis, as shown in the schematic of arterial blood vessels supplying the brain, Fig. 1.1. Branching off the circle of Willis can be found many other smaller arteries, each supplying a different region or territory of the brain.

It should be noted that there is very considerable variability in the structure of the circle of Willis between individuals. This has been recognised for many years:

S. Payne, *Cerebral Autoregulation*, SpringerBriefs in Bioengineering,
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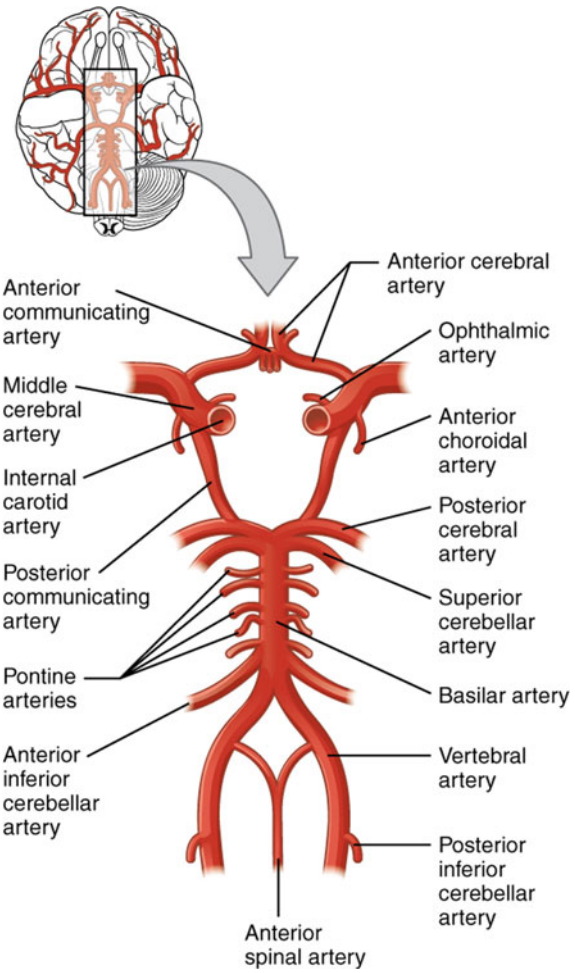

Fig. 1.1 Major arterial blood vessels in the brain (This figure is taken, without changes, from OpenStax College under license: http://creativecommons.org/licenses/by/3.0/)

for example, one 1959 study of 350 human brains with no evidence of vascular pathology, apart from atherosclerosis, showed that only 52 % of subjects had a complete structure, Alpers et al. (1959); a second 1963 study of 994 patients with signs of neural dysfunction showed that only 19 % of patients had a complete Circle of Willis, Riggs and Rupp (1963). These early studies, however, were able to draw few conclusions about the significance of these variations in terms of their impact on the function of the brain.

Papantchev et al. (2013) examined the circles of Willis in 500 subjects to quantify the variability; in total 58.6 % of these subjects had a variation in the circle of Willis. The most common feature (35.6 % of all subjects) was hypo- or aplasia of

the left PCoA; such a feature means that the territories supplied by the left MCA are at risk of hypoperfusion. The second most common feature (9.2 % of all subjects) was found to be hypo- or aplasia of the left P1 (the pre-communicating segment of the PCA) or right VA. A number of other variations were found, some of very low frequency. However, comparisons between different studies are frequently very challenging, due to the type of data reported, and there is little standardization in quantifying variations in the circle of Willis.

Despite these, the available comparisons are in pretty good agreement for the seven different types of anomaly and the total of 58.6 % of subjects having some variations is in good general agreement with other, earlier, studies by the same authors (48.2, 42.4 and 66.7 %) and the early study by Alpers et al. (1959). Of order half of all individuals thus have sufficiently significant variations in the circle of Willis that can be clearly seen when undergoing brain imaging.

These variations are likely to play a significant role in the variability of the response to changes in the blood flow supply. A key feature of the circle of Willis is the interconnectivity that this gives, enabling flow from any supply vessel in theory to reach any part of the cerebral vasculature. If a supply vessel is blocked, the degree to which tissue fed by this and downstream vessels will become ischaemic will depend upon both the level of occlusion and the ability of the collateral circulation still to provide sufficient CBF. This ability may of course vary over time, since flow pathways will change and the response of the circulation to this change may be time dependent.

A number of studies have investigated the effect of the collateral circulation on the response of the brain to disruptions in blood supply. Bang et al. (2011a), found that in a group of 22 patients with acute ischaemic stroke (AIS), revascularization was found to occur increasingly often as collateral grade improved, likewise haemorrhagic transformation was more frequently observed in those with poor collaterals and recanalization, Bang et al. (2011b). Collaterals were assessed using a collateral flow grading system ranging from 0 to 4 (with 0 indicating no collateral vessels and 4 complete collateral flow). One possibility for the finding is that ischaemic tissue damage was increased by the lack of collateral flow, making the tissue more vulnerable to haemorrhage. Collateral grade thus shows considerable potential in helping to guide treatment decision-making following AIS.

After blood has passed through the large arterial vessels, the remainder of the vasculature is sub-divided into different types of vessel in the same manner as the rest of the circulatory system. Blood passes into the arterioles, where thick vessel walls contain large amounts of smooth muscle cells and where vessel tone is strongly regulated to control blood flow. Blood then passes into the capillary bed, a complex inter-connected network, supplying nutrients to and carrying metabolic products away from tissue. Blood finally drains into venules and veins before being returned to the heart: the larger blood volumes and distensibilities of these vessels mean that the venous vessels play a key role in the maintenance of cerebral blood volume. The major venous vessels are shown in Fig. 1.2.

The flow of blood through the cerebral vasculature is thus highly complex, with a high level of spatial heterogeneity. Unsurprisingly, it requires very tight control to

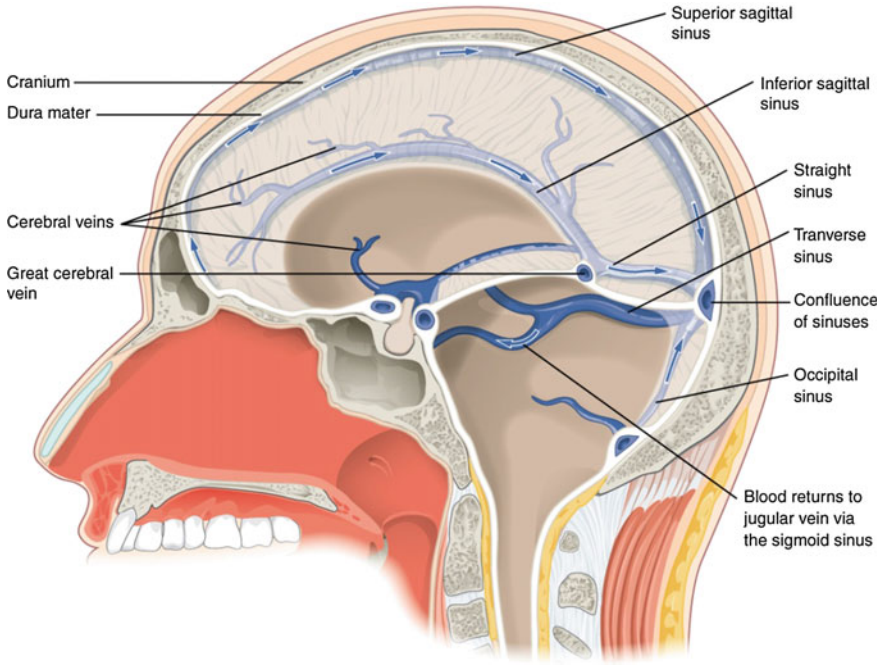

Fig. 1.2 Major venous blood vessels in the brain (This figure is taken, without changes, from OpenStax College under license: http://creativecommons.org/licenses/by/3.0/)

maintain adequate supply to every part of the brain, matching supply to demand. The processes that act to balance changes in demand at a local scale, rather than to balance demand and supply at a global level, are not considered here for reasons of space, although they are obviously strongly related.

1.2 Haemodynamics

Although the cerebral vasculature is highly complex, the flow of blood through the brain in the steady state can very simply be described by:

$$Q = \frac{\Delta P}{\mathcal{R}} \tag{1.1}$$

where Q refers to cerebral blood flow, ΔP to the pressure differential (arterial to venous) and $\mathcal{R}$ to the resistance to flow. Thus, as the pressure differential drops, CBF will drop unless there is an accompanying decrease in resistance to flow. The corresponding equation for a single vessel (the Poiseuille equation) states that the resistance of a vessel is given by:

$$R = \frac{8\mu L}{\pi R^4} \tag{1.2}$$

where the vessel has length L and radius R and the blood has viscosity μ. Although complicated by the fact that blood is a non-Newtonian fluid with viscosity that varies with both the diameter of the vessel and the haematocrit (the volume fraction of red blood cells) of blood, this relationship is very commonly used.

It should be noted that the Poiseuille equation is only strictly true for steady, laminar flow of a Newtonian fluid in an axisymmetric vessel; however in the brain most of these assumptions are reasonable, other than the requirement for Newtonian behaviour. This last is compensated for through the use of empirical relationships for viscosity. This is mostly only required in vessels of diameter less than approximately 100 μm. The relationship proposed by Pries et al. (1990) is commonly used, where viscosity, as a fraction of plasma viscosity, for a vessel of diameter D and discharge haematocrit H_D, is given by:

$$\eta_{rel} = 1 + \frac{e^{H_D\alpha} - 1}{e^{0.45\alpha} - 1}\left(110e^{-1.424D} + 3 - 3.45e^{-0.035D}\right) \tag{1.3}$$

where

$$\alpha = \frac{4}{1 + e^{-0.593(D-6.74)}} \tag{1.4}$$

This models the fact that relative viscosity increases exponentially with haematocrit for larger vessels ($D > 15$ μm), but that for small diameter vessels ($D < 5$ μm) relative viscosity is approximately linear with haematocrit.

Since pressure and flow can be linearly related, the resistance of blood vessels in series and in parallel can be combined in exactly the same manner as for electrical resistances. This makes the construction of lumped compartments relatively straightforward for branching vessel trees, although of course this averaging removes any spatial information.

Resistance can be used to model steady state flow; when the dynamics of blood flow are considered, it becomes necessary to include the effects of blood inertia and wall compliance. These are commonly modelled as inductance and capacitance respectively in electrical equivalent models, as will be examined in more detail in the context of lumped parameter models in Sect. 3.1.

1.3 Regulation of Flow

Since the resistance of a blood vessel is only dependent upon radius, length and haematocrit and the last two of these are largely invariant in time other than over extremely long time scales where adaptation can take place, blood flow is simply

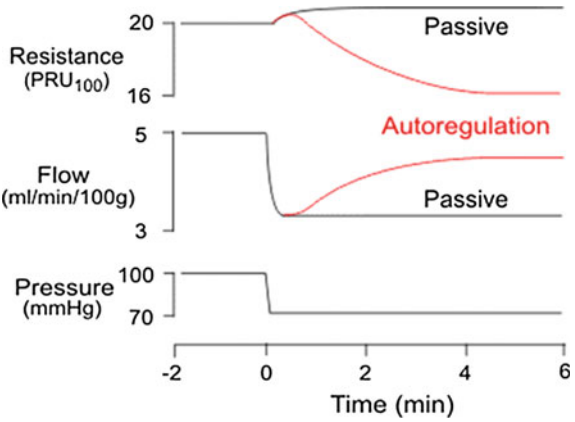

Fig. 1.3 Response of cerebral vasculature to step decrease in blood pressure, reproduced from cvphysiology.com with permission of Dr Richard E Klabunde

controlled through changes in vessel radius. The fact that vessel resistance is inversely proportional to vessel radius to the power four means that even small changes to radius cause large changes to the flow in individual vessels. This provides for a very fine degree of control, particularly since different generations of blood vessels react to changes in flow to different degrees. Of course, however, given the complexity of the cerebral vasculature, this control can be very complicated and the full mechanisms behind it are not yet well understood.

Since blood flow is linearly proportional to driving blood pressure if there are no changes in vessel radius, the maintenance of blood flow as blood pressure is reduced requires a seemingly paradoxical increase in vessel radius. This is directly opposite to the response that would be achieved with a purely passive vessel wall, which would constrict in response to a drop in driving blood pressure. This passive response produces the initial rapid drop in CBF found in response to a step decrease in blood pressure, Fig. 1.3.

The cerebral vasculature thus has to overcome this passive response through means of an active mechanism (the myogenic response). This balance between passive and active behaviour is what gives rise to the characteristic bi-phasic response of CBF in response to a change in ABP. The passive response is initiated immediately, before the active mechanism begins to operate, restoring CBF back to the desired level, as shown in Fig. 1.3.

This response has limits to its range, since there is a maximal dilation and a maximal constriction that can be achieved. Autoregulation thus exhibits both a lower limit (maximal dilation) and an upper limit (maximal constriction), as shown in Fig. 1.4. These upper and lower limits follow a power law relationship, as outlined in Chap. 3. The whole curve is known as the Lassen curve, after the original study by Lassen (1959).

There is thus a very strong active process that acts within this range to maintain CBF approximately constant. Given that the only parameter that can be adjusted to affect resistance is vessel radius and that this is set by the applied pressure and the wall stiffness (or its inverse, compliance), autoregulation is achieved entirely

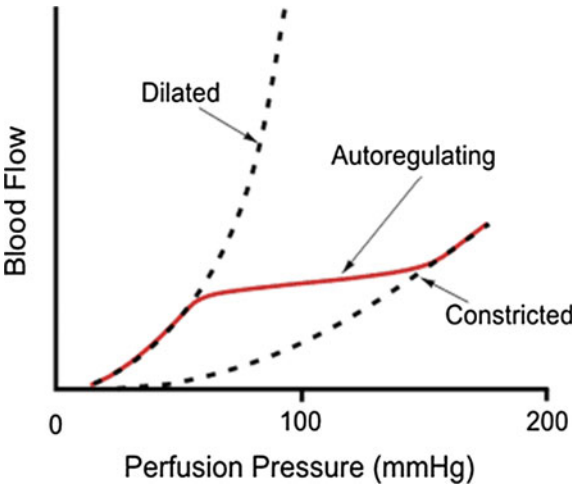

Fig. 1.4 Autoregulation curve, showing lower and upper limits, reproduced from cvphysiology.com with permission of Dr Richard E Klabunde

through the control of vessel compliance. This is why nearly all models of autoregulation are based on the concept of feedback via arterial compliance, as explained in Chap. 3.

The concept of vascular tone, the degree of constriction of a blood vessel relative to its maximally dilated state, is also used in this context. This gives an indication of the level of activation of the smooth muscle cells in the relevant blood vessels. Of course, in reality, not all vessels adjust to the same degree to changes in ABP; primarily it is the arterioles that control CBF, with the venous vessels acting largely to control CBV. This is because the arterioles are thick-walled vessels with their walls largely comprising smooth muscle cells. However, more recent evidence has pointed potentially to a greater role for pericytes than previously thought in controlling blood flow at a capillary scale.

Vascular smooth muscle cells are small fusiform cells about 5 μm by 50 μm in size, primarily made up of myosin and actin. These respectively thick and thin molecules make up chains that are attached to the cell walls: on contraction the two filaments slide over each other, the smooth muscle cell becomes shorter and hence the vessel wall contracts. The cross-bridge interaction between myosin and actin is predominantly set by the intracellular Ca^{2+} level. Intracellular Ca^{2+} forms a complex with the calcium binding protein calmodulin, which activates a phosphorylation enzyme called myosin light chain kinase (MLCK); this causes phosphorylation by ATP of the light chain protein that is one part of the cross-bridge head of myosin. The resulting phosphorylation allows for cross-bridge formation and cycling and hence contraction of the myosin and actin structures.

The fact that it is intracellular calcium that primarily governs this process means that the cellular membrane potential plays a key role in contraction. As a result K^+ dynamics, which are the main determinant of membrane potential, are important. There are many K^+ channels in the membrane that set this concentration, but the

key ones in this context are the inward-rectifying K^+ channel and the ATP-dependent K^+ channel.

An increase in intracellular Ca^{2+} can be caused by one of two different processes: electromechanical coupling, whereby membrane depolarization causes voltage-operated Ca^{2+} channels to open and intracellular Ca^{2+} to increase; or pharmacomechanical coupling. In the latter, neurotransmitters can cause an increase in intracellular Ca^{2+} through a vasoconstrictor agonist, such as norepinephrine, and a membrane-bound receptor, such as an α_1-adrenergic receptor, either opening a receptor-operated Ca^{2+} channel in the membrane or inducing the formation of an intracellular secondary messenger, inositol trisphosphate (IP3), that opens channels in the sarcoplasmic reticulum (SR), releasing stored Ca^{2+}. In both of these processes, the activated receptor stimulates specific guanosine triphosphate (GTP) binding proteins.

In addition to this, there are other specific receptors that link to other specific proteins to other enzymes to produce specific second messengers. One example is the β_2 receptor that is linked to adenylate cyclase, which catalyses the conversion of ATP to cyclic adenosine monophosphate (cAMP): increased levels of this cause the activation of protein kinase A and Ca^{2+} release. Cyclic guanosine monophosphate (cGMP) is one important intracellular second messenger that causes vascular smooth muscle relaxation; Nitric oxide, for example, operates via this pathway.

Although there is one simple mechanism for adjusting cerebral blood flow, precisely how this is achieved is highly complex, with many different influences playing a part in the control of arteriolar tone. A brief summary of these is given below, in the context of the arterial, capillary and venous vasculatures. Note that the local processes that adjust blood flow in response to changes in neural activity are not explicitly covered here, since this is outside the scope of this book. More detail can be found about both this and related topics in a number of physiology reference texts, for example Mohrman and Heller (2013).

1.3.1 Control of Arteriolar Tone

The response of arterioles can be divided into three types: local factors, neural factors and hormonal factors. Note that the local response is the most important, since it enables the response to be adapted to local needs, with the other factors acting to over-ride under certain circumstances and to provide a degree of coordination. Hormonal factors are thought to play only a minor role in autoregulation.

One response is that to hypoxia, where vasodilation is the response to a decrease in tissue oxygenation. This is indeed the origin of the functional MRI BOLD response, where this vasodilation increases CBV and deoxyhaemoglobin, leading to a measurable signal. How this happens is a complex process. Adenosine is an extremely powerful vasodilator that can be released with increased metabolic activity or hypoxia. It is thought likely that it is a combination of many of these

factors that results in changes in vascular tone and a number of mathematical models have been constructed to model the combined response, as explained in Chap. 3.

The metabolic response acts to control vessel tone through the use of vasodilating metabolites. These are released into the blood stream as the result of metabolic processes: in the steady state, they act to cause the levels of vasodilation necessary for adequate CBF, however, if the balance between supply and metabolism is affected by an increase in metabolism, more metabolites are released, resulting in an increase in flow. Likewise, if blood pressure drops and blood flow decreases, the resulting build-up of metabolites will result in increased vasodilation and hence a restoration of the balance between CBF and metabolism.

Nitric oxide, originally known as endothelial derived relaxing factor, EDRF, plays an important role in controlling vascular tone. NO is created from an amino acid, L-arginine, within the endothelial cells (the inner layer of blood vessel walls), through the action of a number of nitric oxide synthase (NOS) enzymes. It freely diffuses into the smooth muscle cells, where it stimulates the production of cGMP. Nitric oxide acts by activating the guanylyl cyclase enzyme that causes cGMP formation. cGMP activates protein kinase G, which results in the uptake of Ca^{2+} and the opening of calcium-activated K^+ channels. This fall in Ca^{2+} stops the myosin light-chain kinase (MLCK) from phosphorylating the myosin molecule, stopping the cross-bridge cycle and hence reducing vessel tone.

Nitric oxide is particularly important in this context as it is formed in response to shear stress on endothelial cells in some way. Any chemical agent that blocks the formation of NO through the inhibition of NOS enzymes will result in an increase in vascular resistance (hence why it is thought that there is a baseline level of NO production). The endothelium also produces several other vasodilators, including endothelial-derived hyperpolarizing factor (EDHF) and prostacyclin (PGI2), and the vasoconstrictor, endothelin.

In addition to the local control mechanisms, there are also neural influences. Sympathetic vasoconstrictor fibres play a key role in the maintenance of global ABP through the adjustment of total peripheral resistance. Norepinephrine is released from the terminal structures of sympathetic vasoconstrictor nerves; after joining with an α_1-adrenergic receptor on smooth muscle cells, this causes an increase in arteriolar tone. This is done through GTP-binding protein linkage of these receptors to phospholipase C and the second messenger IP3 activating the release of intracellular Ca^{2+}.

1.3.2 Control of Capillary Flow

Pericytes are isolated contractile cells on capillaries. They have been proposed to have a role in the stabilization of newly-formed capillaries, maintenance of the blood-brain barrier and the regulation of CBF, amongst other possibilities. There has been considerable recent interest in the potential role of pericytes in autoregulation. Having previously been thought to be driven by changes in arteriolar tone

with the capillary bed a passive recipient, there has been much discussion about whether capillary pericytes play an active role in this process.

Experiments by Hall et al. (2014) have shown that capillary dilation occurs faster than arteriolar dilation, with pericytes actively relaxing to induce this vasodilation, although it should be noted that this study was performed in rats. Neuronal activity resulted in a release of messengers that dilate capillaries prior to arterioles, with pericytes exhibiting a baseline tone that is relaxed; it remains uncertain whether arterioles and capillaries receive the same signals, but at different times, or whether arterioles receive a signal directly from the pericytes. Capillary dilation can play a significant role in increasing CBF at a local scale and thus would appear to be a significant component of the BOLD response, for example.

It is also worth noting that pericytes may play a role in the prolonged decrease in CBF after ischemia and reperfusion, since pericytes die quickly and may cause a lengthy decrease in capillary blood flow through increased capillary flow resistance. The potentially important role of pericytes in the regulation of CBF at a local level indicates that autoregulation of blood flow may be occurring over a broader range of length scales than has perhaps been previously appreciated.

1.3.3 Control of Venous Tone

It should be noted that, of course, the mechanisms that govern arteriolar tone also apply, in different ways, to the control of venous tone, although, since veins have much lower baseline tone, the degree of control is much less. For example, vasodilating metabolites have little influence. However, there is some smooth muscle in the vessel walls and so vasoconstriction can still be achieved through the innervation of sympathetic nerves in the same way, if not to the same degree. The main role of the veins in this context is the control of cerebral blood volume, particularly since they contribute some three-quarters of cerebral blood volume.

1.3.4 Neurogenic Control

A key part of the cerebral vasculature control is the spatial variation in methods of control. Different vessels are controlled by nerve fibres originating from different parts of the nervous system: peripheral nerve ganglia (extrinsic nerves) for surface vessels and intrinsic brain neurons (intrinsic nerves) for vessels within the brain, as shown in Hamel (2006). The sympathetic nervous system, as well as adjusting vascular tone, acts to shift the upper autoregulation limit, whereas the parasympathetic nervous system does not appear to play a significant role under normal conditions.

This division of controlling nerve fibres allows for a co-ordinated and precise degree of control. Considerable work has been performed in the context of the

neurovascular unit, primarily in investigating its response to stimulation rather than its role in autoregulation. How this changes in different states in humans is still only poorly understood, although it is known to be altered with ageing and in stroke, hypertension and Alzheimer's Disease, see for example Lecrux and Hamel (2011). This will not be described in any further detail here, since it is a very substantial topic in its own right.

In conclusion, it is worth noting that there are many different controlling mechanisms that operate at different levels of the vasculature, with different time and length scales over which they operate. The control of blood flow on both a global and local scale is thus the combination of many different processes that act together to maintain a continuous supply of blood and hence nutrients. Much work remains to be done to understand the interactions between these processes, both in health and disease.

1.4 Effects of Blood Gas Levels

CBF is also strongly influenced by changes in arterial blood gas levels. It is well known that increased levels of arterial CO_2 act to dilate blood vessels leading to a large increase in static CBF: Kety and Schmidt's second 1948 paper investigated the response to both arterial CO_2 and arterial O_2, Kety and Schmidt (1948). The dynamic response is also strongly influenced by CO_2: even relatively small changes in CO_2 levels will result in a substantial change in the dynamic response to changes in ABP. Indeed, a 5 % level of CO_2 is often taken as a marker of impaired autoregulation.

The classic study examining the effects of $PaCO_2$ on CBF was performed by Reivich (1964), although it should be noted that this was performed in (eight) rhesus monkeys (this is a rare exception to the use of animal models, based on the fact that there is, surprisingly, no equivalent experimental curve in humans). The relationship proposed by Reivich is:

$$CBF = 20.9 + \frac{92.8}{1 + 10570e^{-5.251 \log \mathrm{PaCO_2}}} \tag{1.5}$$

This is shown in Fig. 1.5, together with the resulting sensitivity of fractional changes in CBF to fractional changes in $PaCO_2$. CBF is very strongly dependent upon arterial CO_2, with the greatest sensitivity occurring at approximately 40 mmHg: at this value (a typical baseline value), CBF changes by 0.9 %_CBF/%_$PaCO_2$. This is considerably larger than the sensitivity to changes in ABP, Fig. 2 in the Introduction.

Given this high sensitivity, the influence of CO_2 levels on autoregulation has been widely studied, with numerous studies investigating the effects of hypocapnia and hypercapnia on both static and dynamic autoregulation under a range of different stimuli. Note that it is thought that arteriolar tone does not respond directly to

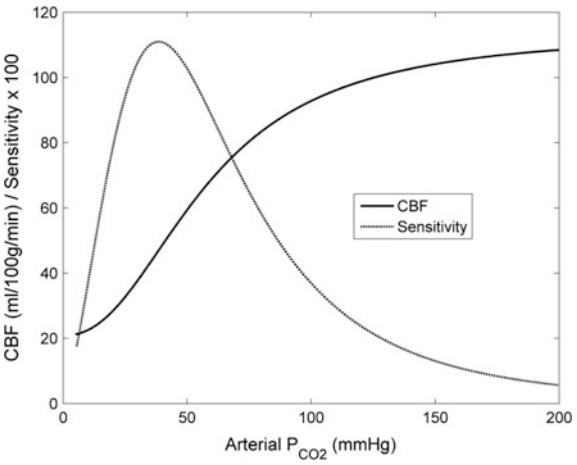

Fig. 1.5 Relationship between $PaCO_2$ and CBF and sensitivity of $PaCO_2$/CBF relationship (scaled), using relationship proposed by Reivich (1964)

changes in CO_2, but rather to changes in extracellular pH that are caused by changes in CO_2: the suggestion is that arterial CO_2 affects pH, which then affects NOS and hence vessel tone, Murkin (2007). Note also that mean CBFV is decreased in hyperoxia and hypercapnia, Nishimura et al. (2007), so the analysis will be affected by the fact that the system is operating about a different baseline. It has been concluded that in baseline conditions, there is no correlation between the response to arterial CO_2 and autoregulation, the two mechanisms being distinct, Carrera et al. (2009).

Hypocapnia has been shown to lower the autoregulation plateau, with little change in the LLA and no clear change in the ULA, Meng and Gelb (2015). Dynamic autoregulation (measured using RoR) has been found to be improved in hypocapnia, Ogoh et al. (2010a).

Hypercapnia moves the autoregulation plateau upwards, with the LLA moving to the right and the ULA moving to the left, Meng and Gelb (2015). Static autoregulation has been found to be impaired in hypercapnia, Perry et al. (2014); likewise dynamic autoregulation (measured using phase angle) has been found to be impaired after CO_2 inhalation, Carrera et al. (2009). Panerai et al. (1999) showed that coherence function and amplitude were significantly increased for frequencies below 0.05 Hz and that phase angle was significantly decreased in the frequency range 0.02–0.1 Hz, indicating that autoregulation is impaired in the presence of 5 % CO_2. This is in contrast to the results of Ainslie et al. (2008a), who found no changes in transfer function parameters or BRS, except for CBFV variability and phase which changed in the most extreme ranges of hypercapnia and hypocapnia. These changes were related to ventilation and so it was suggested that it is hyperventilation, not $PaCO_2$, that affects cerebral autoregulation.

CO_2 has been shown to affect dynamic autoregulation (measured using phase angle) more slowly than it affects CBFV, Liu et al. (2013). This is in agreement with the results of Dineen et al. (2010) who measured the temporal response of

autoregulation to transient hypocapnia and hypercapnia and found that there is a delayed dynamic response to changes in $PaCO_2$. Hypercapnia has also been shown significantly to affect the neurovascular coupling both at rest and during stimulation, with it being suggested that this acts through impairing the metabolic component of autoregulation, Maggio et al. (2013, 2014).

In addition to studies on the effects of changes in arterial CO_2 levels, there has been significant interest in the role of arterial O_2 levels, although of course it is not always straightforward to separate out the effects of arterial CO_2 and O_2 levels.

Mild **hypoxia** is known to impair dynamic cerebral autoregulation alongside a reduction in steady-state CBFV, measured using transfer function analysis, Katsukawa et al. (2012) and using both transfer function analysis and RoR, Bailey et al. (2009); this impairment has been shown to be persistent over the course of hours, Nishimura et al. (2010), again measured using transfer function analysis. Autoregulation is also impaired in acute hypoxia, measured both during resting and rapid cuff deflation with ARI, Subudhi et al. (2009). However, Ainslie et al. (2008b) found that in healthy subjects cerebral autoregulation was improved (as measured by low frequency gain increasing) during acute hypoxia.

The impairment found in isocapnic hypoxia is abolished in hypocapnic hypoxia, Querido et al. (2013), since hypocapnia improves the autoregulation response relative to isocapnic hypoxia, Ogoh et al. (2010a). Using RoR, Ogoh et al. (2010a) showed that autoregulation improves in hypocapnic hypoxia relative to normoxia, whereas in isocapnic hypoxia, autoregulation was impaired. Bailey et al. (2009) found no evidence of hyperperfusion, BBB disruption or neuronal-parenchymal damage in hypoxia, indicating that this is a healthy response.

In isocapnic **hyperoxia**, autoregulation was found to be unchanged, measured using RoR, Ogoh et al. (2010a), or by transfer function analysis, Ainslie et al. (2008b), Nishimura et al. (2007).

1.5 Neural Control

Although it is known that sympathetic activity plays a role in the control of CBF, this remains the least well understood aspect of autoregulation, particularly in humans. The primary reason for this is that measuring sympathetic activity is very challenging and sometimes it is simply assumed that any unexplained variability in experimental data is due to this effect. Since there are four main factors that act to control blood flow (the myogenic response, blood gas changes, neural activation and sympathetic activity), de-coupling these is very difficult, particularly in human subjects, when only a limited number of measurements can be made. A recent review suggested no fewer than eight reasons why the neural control of autoregulation is so poorly understood: redundancy; heterogeneous distribution of sympathetic innervation; BBB permeability; species divergence; duration and intensity of sympathetic stimulation; asymmetry and influence of perfusion pressure;

regional differences in cerebral autoregulation; and metabolic restraint, Ainslie and Brassard (2014).

A second recent review of autonomic neural control of the cerebral vasculature divided up this control into sympathetic and cholinergic control mechanisms, Tan and Taylor (2014). It was concluded that both played a role in autoregulation, although the evidence base is slim, particularly for the former. The use of trimetaphan for ganglionic autonomic blockade, which abolishes both forms of control, caused an increase in gain and a decrease in phase even when ABP was restored by infusion of phenylephrine in healthy subjects, Zhang et al. (2002). Alpha-adrenergic blockade with phentolamine was used for sympathetic blockage to show that autoregulation was affected, Hamner et al. (2010), indicating that sympathetic activity does play a role. The cholinergic control system has been shown to have an influence on autoregulation, Hamner et al. (2012), shown using glycopyrrolate to achieve cholinergic blockade.

The relative contributions of the sympathetic, cholinergic and myogenic mechanisms, using various pharmacological blockades, have been quantified in healthy volunteers. Although myogenic effects are the largest contribution to the ABP-CBFV relationship, these only influenced the relationship outside the autoregulation range, whereas the neurogenic control was dominant within this region, Hamner and Tan (2014). It is worth noting that nearly 40 % of the variability was still unexplained by these three mechanisms. Different time constants for the myogenic, metabolic and/or neurogenic mechanisms have been proposed in response to the handgrip manoeuvre, since time-varying ARI dropped at the beginning and end of the procedure, Nogueira et al. (2013).

The effects of nitric oxide on cerebral autoregulation have been investigated using the NOS inhibitor L-NMMA in comparison with both noradrenaline and phenylephrine (used to match the increase in ABP), White et al. (2000), Zhang et al. (2004). The latter study showed no difference between the two cases, whereas the former showed a significant difference between the two cases with the change in ARI larger with noradrenaline than with L-NMMA, indicating that NO mediates part of the dynamic autoregulation response.

Reactive oxygen species (ROS), many of which act as cellular signalling molecules, influencing mechanisms responsible for modulating pressure-induced myogenic tone and hence autoregulation, have been proposed as potential targets for therapeutic interventions in patients with hypoxic injury or altered cerebral metabolism, Terashvili et al. (2006).

Other earlier studies, using non-drug-induced changes, have come to varying conclusions. For example, the use of head-down-tilt in healthy volunteers has indicated a lack of sympathetic activation, Heckmann et al. (1999). Use of the thigh-cuff test and head-up-tilting found no impact of the sympathetic nervous system on autoregulation in healthy subjects, Gierthmühlen et al. (2011). Dynamic autoregulation, measured using RoR, is not affected by static handgrip exercise and its related increases in blood pressure, Ogoh et al. (2010b).

In healthy subjects in normocapnia, autoregulation is not affected by stimulation, Maggio et al. (2014), although brain activation has been shown elsewhere to result

in significant changes in dynamic cerebral autoregulation, with different tasks giving significant reductions in phase during activation on one or both hemispheres, Panerai et al. (2005). The use of a control system approach indicated that the responses to both a flicker light test and the thigh cuff test could be governed by the same control system, Rosengarten et al. (2001).

Sympathetic and parasympathetic activities have been investigated using midazolam, which causes sympathetic activity to dominate and has no effect on endothelium-dependent relaxation, and propofol, which causes parasympathetic dominance and suppresses endothelium-dependent relaxation, Ogawa et al. (2010). Only the former showed a change in autoregulation, despite lowering steady state CBFV by the same amount.

The interaction between baroreflex sensitivity and autoregulation has been investigated with an inverse relationship between ARI (and RoR) and baroreflex sensitivity, suggesting that the two counter-compensate to maintain cerebral blood flow, Tzeng et al. (2010).

Other factors potentially influencing autoregulation have been studied, which, for simplicity, are briefly considered here. Changes in cardiac output do not affect autoregulation, measured using ARI, in healthy control subjects, Deegan et al. (2010). Heat stress has been found to improve autoregulation, as evidenced by changes in the transfer function at very low frequencies, Brothers et al. (2009), Low et al. (2009). Hypovolaemia is known to play a role in autoregulation, Ogawa et al. (2013) and hypervolaemic haemodilution has been shown to cause impaired autoregulation, Ogawa et al. (2007).

1.6 Conclusions

Although the cerebral vasculature comprises a very complicated network of blood vessels, connected in such a way that brain tissue is or can be perfused by blood from multiple different sources arriving through multiple different pathways, fundamentally CBF is controlled simply by adjusting the diameter of individual blood vessels in response to changes in the supply. Vessel diameter, set through vessel tone, is controlled both locally, in response to surrounding conditions, and globally, through complicated signalling pathways and sympathetic activity. Blood gas levels also control blood flow and hypercapnia is often used as a means of simulating impaired autoregulation.

The balance between local and global control makes understanding autoregulation very challenging. Even in healthy subjects, the balance between these two is not well understood, and how this control is affected in pathological conditions or in response to insults is very poorly understood. One reason for this is the difficulty in making suitable measurements to disentangle the different effects, with every measurement modality having its own limitations and assumptions, as will now be seen in the next chapter.

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Chapter 2
Measurement Techniques

In this chapter, the ways in which cerebral autoregulation can be assessed through measurements of physiological parameters will be presented. The first work in this area dates from the 1940s and the following decades have seen very substantial progress made in the accuracy and repeatability of clinical measurement techniques in a variety of forms, leading towards very rich sources of data.

2.1 Development of CBF Measurements

The crucial parameter in assessing cerebral autoregulation is the need for accurate quantitative measurements of cerebral blood flow. The landmark study here was the method proposed by Kety and Schmidt (1948), termed the Nitrous Oxide method; this method relies on the well-known Fick principle. Inhalation of nitrous oxide was followed by measurements of nitrous oxide in both arterial and venous cerebral blood over time; the difference between the two is inversely proportional to CBF. Comparison between this method and a direct measurement of flow in monkeys was found to be very good and in normal young men CBF was estimated to be 54 ± 12 ml/100 g/min. CBF is normally quantified in these units, being defined as 100 ml of blood per 100 g of tissue per minute.

Nearly all imaging methods developed subsequently rely on the same principle to quantify CBF; that of tracking the passage of blood through the use of a tracer. Such tracers can be exogenous (where a tracer is injected into the bloodstream) or endogenous (where a property of the blood is tracked); the former requires the introduction of a tracer but has a high signal to noise ratio, whereas the latter is non-invasive but typically suffers from a poor signal to noise ratio. The Kety-Schmidt method incurs two additional disadvantages: there is a need for

S. Payne, *Cerebral Autoregulation*, SpringerBriefs in Bioengineering,
DOI 10.1007/978-3-319-31784-7_2

repeated blood sampling, which makes the measurement unpleasant to endure, and only one global measure of CBF can be obtained.

The review of methods for measuring CBF in 1965 by Ingvar and Lassen provides an interesting list of other possibilities, many of which have been discarded over the years (for example rheoencephalography, where changes in the electrical impedance of brain tissue were related to blood flow). The available methods can be divided into two groups, depending upon whether or not the inert indicator is non-diffusible (therefore staying within the bloodstream) or freely diffusible. The former category includes indicators such as a gamma-emitting radioactive bolus, a dye or radioactively labelled red blood cells. It should be noted that Ingvar and Lassen (1965) pointed out the difficulties of measuring CBF when the absolute value of CBV is not known; it was already known that CBV changed with CBF.

Ingvar and Lassen had previously proposed, Lassen and Ingvar (1961), the use of an intra-arterial isotope injection to measure quantitative regional values of CBF, as shown in Fig. 2.1a. This used either Krypton 85 or Xenon 133 and the same clearance model as Kety and Schmidt. The values obtained for perfusion were found to be in good agreement with those obtained by Kety and Schmidt (1948). Inhalation of Xenon 133 was also considered but it was acknowledged that there were difficulties with the accuracy of this technique. A camera was used to gain a cross-section of the flow, giving a photograph like the one shown in Fig. 2.1b.

One finding obtained using this method was that there is a fast and a slow component to the clearance of a tracer from the brain. It was suggested that the fast and slow flows correspond to the flows in the grey matter and white matter respectively. This was later confirmed, with the two compartments being found to have a fast half-time of 1.5 min and a slow half-time of 7–10 min, Torizuka et al. (1971).

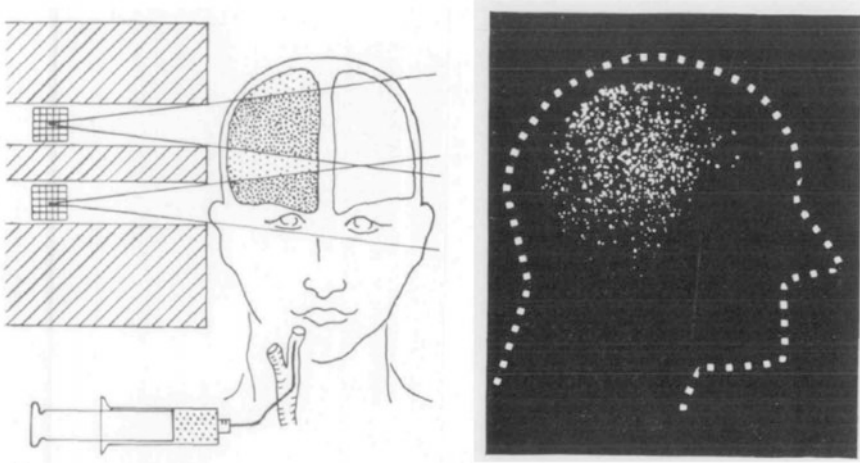

Fig. 2.1 Injection technique for measurement of CBF: **a** schematic of technique; **b** resulting photograph; reproduced with permission from Ingvar and Lassen (1965)

This latter half-time, together with the radioactive nature of the isotope, restricts the frequency of measurement very considerably.

The next stage in perfusion measurement was to convert the single viewpoint of perfusion (giving a 2-D representation) to a full tomographic 3-D image and to move towards improved exogenous agents. The advent in the 1970s of computed tomography (CT), which uses multiple images from different angles to reconstruct a three-dimensional image, enabled three-dimensional xenon-enhanced CT (Xe-CT) perfusion maps to be generated, built up of sequential slices through the brain. The review by Wintermark et al. (2005) gives a very thorough overview of all of the methods for CBF measurement: the information below is thus largely taken from this source, with minor modifications.

One of the difficulties with the use of Xe-CT is the low energy of the gamma rays emitted, which results in limited spatial resolution. The development of new tracers led to the introduction of single photon emission computed tomography (SPECT), based on the use of a gamma-emitting radioisotope being injected into the bloodstream of a subject. As with Xe-CT, multiple brain slices are reconstructed through a tomographic reconstruction. Regional CBF (rCBF) is then calculated using a model of the response, similar to the Kety-Schmidt model.

A similar methodology is positron emission tomography (PET), which can be used to measure a number of cerebral parameters, including regional CBF, regional CBV and regional oxygen extraction fraction. In order to measure CBF, a tracer such as $^{15}O_2$, $C^{15}O_2$ or $H_2{}^{15}O$ is used; this is injected and, when coupled with an arterial blood sample measurement, the Kety-Schmidt model can be used to estimate CBF. The tracers are normally occurring biological substances that have been labelled with positron emitting radioisotopes, hence the name. Dynamic perfusion CT (PCT) is based on a bolus infusion of iodinated contrast into a vein; images are reconstructed in the same way as the methods above.

MRI can be either invasive, using an exogenous contrast agent, or non-invasive, using an endogenous contrast agent. In the former, gadolinium chelates are used, injected into a peripheral vein. The indicator dilution model is then used to estimate CBF, alongside other parameters, through the use of deconvolution. Non-invasive CBF measurements are performed through the use of arterial spin labelling (ASL), where the magnetization of the water flowing into the brain is altered and then tracked at a downstream plane. A model is used to convert the resulting time series to perfusion values.

A brief summary of the characteristics of each of these perfusion measurements is given in Table 2.1, together with a comparison with TCD (described in the section below). The different techniques have different sampling times, accuracies, spatial resolutions and parameters that can be measured: as usual, the optimal technique is selected dependent upon the precise details of the application. However, it should be noted that few of the imaging-based techniques have enjoyed wide application in cerebral autoregulation studies, due to the advent of transcranial Doppler, which is described in the next section. Other modalities that have begun to gain in popularity more recently will be examined in more detail later.

Table 2.1 Summary of existing CBF measurement techniques, adapted from Wintermark et al. (2005) and Kazan (2009)

Technique	XeCT	SPECT	PET	PCT	MRI (DSC)	MRI (ASL)	TCD
Contrast agent	Diffusible exogenous	Diffusible exogenous	Diffusible exogenous		Non-diffusible exogenous	Diffusible endogenous	N/A
Half-life	Stable Xenon-gas ^{133}Xe 4 min	^{99m}Tc-HMPAO ^{99m}Tc-ECD ^{123}I-IMP 4 min	^{15}O—2 min ^{13}N—10 min ^{11}C—20 min ^{18}F—1.7 h		Gadolinium chelate (DTPA) 70–90 min	Hydrogen protons 1.35 s (1.5T) 1.65 s (3T)	N/A
Measured parameters	CBF	CBF	CBF, CBV, rOEF, CMRGl	CBF, CBV, permeability	CBF, CBV, permeability	CBF	CBFV
Spatial resolution	4 mm	4–6 mm	4–6 mm	1–2 mm	2 mm	2 mm (1.5T) 1 mm (3T)	N/A
Brain coverage	6 cm thickness	Whole brain	Whole brain	4–5 cm thickness	Whole brain	Whole brain	1 measurement/ hemisphere
Reproducibility	12 %	10 %	5 %	10-15 %	10-15 %	10 %	5 %
Quantitative accuracy	Yes	(Yes)	Yes	Yes	(No)	Yes	Yes
Time between measurements	20 min	10 min	10 min		25 min	2–3 min	0 min
Invasive	No	Yes	Yes	Yes	Yes	No	No
Radiation	3.5–10 msv	3.5–12 msv	0.5–2 msv		None	None	None
Drawbacks	Exposure to high doses of radiation; long acquisition times; uncomfortable for subject	Exposure to high doses of radiation; relative measurements only; inaccurate for low CBF	Exposure to high doses of radiation; very expensive		Limited number of measurements due to invasive nature; side effects on some patients	Low SNR; inaccurate when compared to PET; inaccurate for low and high CBF	No spatial resolution; not all subjects have an acoustic window

2.2 Transcranial Doppler

Transcranial Doppler ultrasound (TCD) has become the measurement option of choice for nearly all studies in recent years. This is for the simple reason that it offers excellent temporal resolution, allowing dynamic autoregulation to be quantified; although it must be noted that this is achieved at the cost of spatial resolution. Its ubiquity means that there is a degree of consistency across studies, although insonation windows are not found in every subject.

The validation of Transcranial Doppler (TCD) ultrasound for measuring cerebral blood flow velocity in the Middle Cerebral Artery (MCA) in humans was first performed by Aaslid et al. (1982). TCD measures the red blood cell velocity within the vessel being insonated, Fig. 2.2, thus it is normally taken to be a direct measure of CBF Velocity (CBFV). TCD was shown to be the most commonly used method of measuring CBF in a review of 68 autoregulation studies, Panerai (1998) and Numan et al. (2014) in their meta-analysis of static autoregulation found that 41 of the 49 studies included in their investigation were based on the use of TCD.

However, apart from the difficulties in measurement in some subjects, the main difficulty with the use of TCD is that it does not measure CBF, but CBFV: to convert from one to the other requires knowledge of the dynamic cross-sectional area of the vessel. It is normally assumed that any changes are negligible and that CBFV is thus a direct marker for CBF, although there is relatively little direct evidence for this. This is most likely due to the fact that the measurement of what are relatively small changes in vessel diameter is technically challenging. The assumptions of constant vessel diameter (and of maximum velocity being a marker for mean velocity) have been challenged: see for example, Kontos (1989).

The first study to measure human cerebral arterial diameters directly was performed by Giller et al. (1993), who found that during craniotomy, there was only a small change in large arterial vessel diameter in response to changes in both ABP and end tidal CO_2 (the authors quoted an average of 4 % in response to changes of 30 and 14 mmHg respectively). It should be noted that the sample size used was

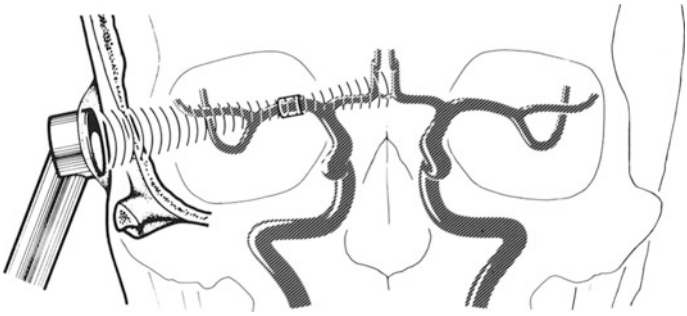

Fig. 2.2 Frontal view of Doppler probe insonation of middle cerebral artery, reproduced with permission from Aaslid et al. (1982)

very small, except for the CA and ACA, which have sensitivities in diameter of 0.3 and 0.78 %/mmHg $PaCO_2$ respectively (compared to sensitivities to changes in ABP of 0.28 and 0.46 %/mmHg respectively). Note that the authors measured outer diameter, not the more relevant inner diameter, but the value for the CA is very similar to that of Willie et al. (2012).

Poulin et al. (1996) concluded that there was little change in the cross-sectional area with CO_2, although they did not offer evidence directly to substantiate this statement, other than stating that the total power of the Doppler signal remained relatively constant (the signal power being taken to be a measure of cross-sectional area). It is worth noting that Numan et al. (2014) in their recent investigation of static autoregulation found no significant different between the results obtained using TCD and other CBF estimation methods.

The recent advent of high resolution imaging modalities, however, has enabled vessel diameters to be measured in vivo in response to a limited set of physiological challenges in the larger cerebral vessels. Results from these studies are summarised briefly in Table 2.2, although it should be noted that these are the sensitivities for small changes.

Willie et al. (2012) used ultrasound imaging to measure both CBFV and vessel diameter in the left ICA and the right VA simultaneously, as well as CBFV in the MCA and PCA; this was done for wide variations in both $PaCO_2$ (15–65 mmHg) and PaO_2 (36–434 mmHg). For changes in $PaCO_2$, the ICA diameter was found to change in a strongly non-linear manner (from −6.6 % at 15 mmHg to 11.5 % at 65 mmHg, with a regression slope of 0.36 %/mmHg), but the VA diameter showed no change. No change in either diameter was found for changes in PaO_2. The fractional change in CBF (ICA, VA) or CBFV (MCA, PCA) was found to be approximately 4 %/mmHg ($PaCO_2$), although this was higher in hypercapnia than in hypocapnia, and −1.5 %/% (SaO_2) in the ICA, MCA and PCA compared to −3 %/% in the VA. As the authors say, the cerebral vasculature is "exquisitely sensitive" to $PaCO_2$, being slightly less sensitive to PaO_2.

Serrador et al. (2000) also examined changes in MCA diameter and found no change in diameter either for changes in $PaCO_2$ (in the range 24–45 mmHg) or ABP (in the range baseline to baseline minus 40 mmHg). A later study measuring MCA diameter as a function of end-tidal CO_2 using MRI, Verbree et al. (2014), found that the relationship was non-linear and the authors used this to explain previous published results where the changes were found to be not significant. They quoted a study that gives a 3.8 %/mmHg increase in CBF, which would tally very closely with the ICA and give a diameter sensitivity of 0.4 %/mmHg, again very close to the ICA. There thus seems to be strong evidence that the sensitivity is non-zero at baseline conditions.

Liu et al. (2013b) examined the change in ICA diameter for changes in ABP; in this study the diameter was found to change by −0.11 %/%. CBFV was found to be linearly related to ABP with sensitivities of 0.24 %/% (MCA) and 0.22 %/% (ICA); however, when re-computed as CBF based on ICA diameter, CBF was found to be invariant with ABP over the range measured (−26 to 31 %).

Table 2.2 Sensitivity of individual vessels to changes in ABP and blood gas levels

	ICA	MCA	PCA	ACA	VA
CBF/ABP	NS [L]				
D/ABP (%/mmHg)	0.28 ± 0.17^{G} -0.11^{*L}	NS^{S}		0.46 ± 0.12^{G}	0.03 ± 0.01^{G}
CBFV/ABP (%/%)	0.22 ± 0.05^{L}	0.24 ± 0.07^{L}			
CBF/$PaCO_2$ (%/mmHg)	4.0 ± 0.38^{W}				4.4 ± 2.1^{W}
D/$PaCO_2$ (%/mmHg)	0.3 ± 0.09^{G} 0.36^{W}	NS^{S}		0.78 ± 0.18^{G}	0.2 ± 0.1^{G} NS^{W}
CBFV/$PaCO_2$ (%/mmHg)		2.9 ± 0.47^{W} 3.8^{V}	3.0 ± 0.62^{W}		
CBF/SaO_2 (%/%)	-1.71 ± 1.3^{W}				-3.3 ± 1.4^{W}
D/SaO_2	NS^{W}				NS^{W}
CBFV/SaO_2 (%/%)		-1.39 ± 0.5^{W}	-1.19 ± 0.3^{W}		

NS Not Significant; * %/%. *G* Giller et al. (1993a, b); *L* Liu et al. (2013b); *S* Serrador et al. (2000); *V* Verbree et al. (2014); *W* Willie et al. (2012)

Overall, the experimental results are found to be mostly consistent with each other. The sensitivity to SaO_2 appears to be most consistent: both CBF and CBFV exhibit a consistent increase of approximately 1.5 %/% decrease in SaO_2, with the vessel diameter remaining invariant; the VA shows approximately twice this sensitivity, which implies that the supply vessels in the neck are more sensitive than those in the brain.

The behaviour in response to changes in $PaCO_2$ is much more heterogeneous between vessels. The two studies for ICA diameter sensitivity are in very good agreement with each other, but other vessel diameters are both less and more sensitive; the results for CBFV sensitivity, however, are reasonably consistent at around 3 %/mmHg with the VA showing slightly greater sensitivity of 4.4 %/mmHg. Interestingly, CBFV appears to be more constant than CBF, although this is a somewhat tentative conclusion based on the current data.

Perhaps somewhat surprisingly, the results for sensitivity to ABP are most difficult to interpret, due to their sparse and contradictory nature. Little can be concluded from the existing data and this remains an area ready for further exploration.

The response of vessel diameter to pharmacological stimuli has also been examined. The study by Ogoh et al. (2011), which measured ICA diameter and ICA and MCA velocities in baseline conditions and in response to phenylephrine, found that MCA velocity increased but that ICA diameter and velocity (and hence flow) were unaltered. This increase in MCA diameter in response to phenylephrine was also noted by Stewart et al. (2013); they estimated the change in MCA diameter, but this should be treated with caution as being a somewhat indirect measurement. The authors did however conclude that using pharmacologically induced changes to quantify cerebral autoregulation should be done with other stimuli, if only TCD is being used. The response of individual vessels to such pharmacological stimuli thus remains relatively poorly explored and will need to be understood in greater detail if such stimuli are to be used reliably to assess autoregulation.

Finally, there has been some work on the effects of poor signal quality or interference on the estimates of cerebral autoregulation. Poor insonation conditions have been shown to reduce phase angle and hence to introduce a bias into this estimate of cerebral autoregulation, although Mx was not found to be significantly different, Lorenz et al. (2007). The continuous infusion of an ultrasound contrast agent during measurements has been shown to help to avoid potential bias and hence to improve reproducibility, Lorenz et al. (2008). Interference with the TCD signal, as might be caused by poor bone windows, can also yield a bias in the estimated cerebral autoregulation parameters, with a contrast agent again removing this bias, Lorenz et al. (2009).

In conclusion, TCD has been very widely used due to its very high temporal resolution and recent studies have begun to look at the most significant limiting factor in its operation, although no study has yet investigated the dynamic changes in vessel diameter. As this limitation becomes better quantified, this will allow TCD to be exploited with greater accuracy and reproducibility in the future. TCD has also been used with success in investigating the neurovascular coupling: for a recent review see Wolf (2015).

2.3 Near Infra-red Spectroscopy

More recently, there has been an increase in interest in the use of Near Infra-Red Spectroscopy (NIRS) to investigate autoregulation. The difficulty with this modality is the complexity of the signals that are recorded, since the signals are often only indirectly related to CBF, as discussed below. However, the ease and relative inexpense of measurement, the potential for high spatial and temporal resolution, and the multimodal nature of the data all mean that NIRS is potentially a very attractive modality. Before presenting the results of studies obtained using NIRS, the theory of NIRS will be briefly described and the different measurements that can be made explained.

NIRS relies on the modified form of the Beer-Lambert law, Delpy and Cope (1997), which relates the attenuation of light, A, entering a substance:

$$A = ln\left[\frac{I_0}{I}\right] = \alpha cdB + G \tag{2.1}$$

where I represents light intensity (I_0 the incident light intensity, I the transmitted light intensity), to α, the specific extinction coefficient of the absorbing compound, c, the concentration of the absorbing compound, and d, the distance between the measurement points. The dimensionless differential path length factor, B, accounts for the increase in path length due to scatter and G represents tissue absorption.

Since the level of absorption is unknown, only changes in attenuation can be used to detect changes in the concentrations of any given chromophore. For these changes to be in absolute units, all the other parameters in Eq. (2.1) need to be known. The path length is measured or estimated based on theoretical models or phantom studies. The extinction coefficient can be estimated experimentally for the chromophores of interest. The differential path length is more complicated, being dependent upon the scattering and absorption coefficients of the tissue being investigated. In humans an empirically-derived relationship is used to estimate this as a function of age, Duncan et al. (1995).

In order to measure the concentrations of oxyhaemoglobin (O2Hb) and deoxyhaemoglobin (HHb), their differences in light-absorption in the wavelength range 700–1000 nm are exploited by passing light through at a number of wavelengths within this range. Note that oxyhaemoglobin is simply the combination of haemoglobin with oxygen, whereas deoxyhaemoglobin is haemoglobin alone. The changes in chromophore concentrations are calculated from the attenuation measured at these wavelengths using a least-squares solution of the resulting linear simultaneous equations. Although near infra-red light was first used in vivo by Jöbsis (1977), the first studies in humans did not follow until some while after.

A NIRS probe thus consists of a laser diode that passes light in the near infra-red spectrum into the brain and a sensor that measures the (very much attenuated) returning light: both diode and sensor are mounted within the same probe, typically a distance of a couple of centimetres apart. The probe is normally placed on the

human forehead, away from the midline sinuses. As a result, it interrogates a wide variety of tissue types, including skin, subcutaneous fat, the skull, cerebrospinal fluid and brain tissue, inside which are found all the different types of blood vessel.

As a result, the signal is a mixture of the component signals arising from all of these sources and this has to be taken into consideration when interpreting the signals. This mixture is strongly dependent upon the spacing between the diode and the sensor, with the depth of penetration increasing for larger spacing and more photons passing into the brain. The spacing is thus a compromise between achieving a large component of the signal from the cerebrum, which requires a large spacing, and the need for a sufficient signal-to-noise ratio, which requires a small spacing.

NIRS was first used to measure CBF by Edwards et al. (1988), essentially using O2Hb as a tracer together with the Kety-Schmidt model. To induce a change in O2Hb, arterial saturation is perturbed (for example through breathing 100 % oxygen): an increase in this saturation will result in an increase in O2Hb and, through making a number of assumptions, an expression for absolute perfusion can be derived. Thus CBF can be measured non-invasively with only one additional measurement (that of arterial saturation). This method is of course very similar to other indicator methods, but can be repeated more regularly since there is no ingestion of a radioactive substance; although the temporal resolution is obviously still much poorer than for TCD and a stimulus is still required. CBV can also be measured in a similar manner, Wyatt et al. (1990). The use of phenylephrine has also been proposed to measure autoregulation, Wagner et al. (2011).

The extent to which NIRS measures cerebral, rather than extra-cranial, behaviour remains a substantial concern, see for example Germon et al. (1994), since the blood flowing in the intra-cranial and extra-cranial compartments exhibit very different types of behaviour. This could potentially bias any results obtained using NIRS to assess cerebral autoregulation unless the extracranial component is removed, see for example Kirkpatrick et al. (1998). Spatially resolved spectroscopy (SRS) attempts to overcome this through the use of multiple receiver probes, sited at different distances from the source. Since the closer measurements receive a larger signal proportion from the extra-cranial compartment and the further measurements a greater proportion from the intra-cranial compartment, a model can be used to separate out these two components.

Two additional parameters are then estimated: Tissue Oxygenation Index (TOI), which is a measure of cerebral tissue oxygenation, defined as:

$$TOI = \frac{O2Hb}{O2Hb + HHb} \tag{2.2}$$

and Tissue Haemoglobin Index (THI), defined as:

$$THI = k(O2Hb + HHb) \tag{2.3}$$

where k is an unknown coefficient. This latter measure can be taken as an indirect marker of CBV, if it is assumed that the haematocrit is constant. The TOI signal has been shown to be a measure of true cerebral tissue oxygenation with high sensitivity and specificity, Al-Rawi et al. (2001).

The influence of oxygen saturation has been investigated by Payne et al. (2011). A number of ways of removing its influence from NIRS signals have been proposed, using subspace projections, Caicedo et al. (2013b), and partial coherence, de Smet et al. (2010b). This latter method has been proposed as a new way of assessing impaired autoregulation, de Smet et al. (2010a).

One of the key advantages of NIRS is its ability to help to quantify the spatial variations in autoregulation, see for example Kainerstorfer et al. (2015), who used it in the prefrontal cortex. In this study, as in others, a model had to be be used to convert the signals into CBF before autoregulation could be quantified, and there is a need for studies to validate these conversions. However, the use of NIRS, which is sensitive to the microvasculature, does mean that localised, although indirect, measurements of autoregulation are possible, making this a very promising avenue for further exploration.

2.4 MRI

Although the details of MRI were briefly presented earlier, there has been some recent interest in trying to use MRI to assess cerebral autoregulation, which is now examined in more detail. It offers the potential advantages of actually measuring perfusion and doing so with a good spatial resolution. Recent work on vessel-encoded ASL has enabled the flows reaching individual voxels to be labelled by supply vessel, Okell et al. (2013). It is also widely used clinically in cerebrovascular disease and thus likely to be available for patient use. However, it should be noted that, as yet, no device has been shown to be able to record continuous blood pressure inside a MRI scanner accurately; this remains a considerable obstacle to the assessment of cerebral autoregulation. The most recent investigation, using the CareTaker^{TM} device, concluded that it was not yet a valid method for measuring ABP inside the scanner in the context of cerebral autoregulation, de Jong et al. (2015).

Wagner et al. (2012) measured both CBF and T2′ values and showed that there was a significant decrease in cortical CBF and T2′ values in the elderly compared to in the young. A hyperoxia challenge was shown to induce a reduction in CBF in the young but not in the elderly, suggesting “an age-appropriate cerebral autoregulation”: however, it is difficult to draw a conclusion about absolute cerebral autoregulation in this way.

Horsfield et al. (2013) measured the dynamic response to thigh cuff deflation at 1 Hz in 11 healthy subjects and found that there were significant regional differences within the brain; white matter showing a faster recovery than grey matter and the cerebral cortex showing a faster recovery than the cerebellum. No differences

were found between different cortical regions. The use of a global and repeatable challenge means that the spatial heterogeneity in autoregulation can indeed be quantified, although to achieve this temporal resolution, relatively poor spatial resolution was used.

MRI has also been used to measure arterial compliance in human cerebral arteries in healthy volunteers, Warnert et al. (2015). The values obtained were highly variable across different vessels, being largest for the RPCA and LPCA (1.1 %), smaller for the RMCA and LMCA (0.56 and 0.50 %) and smallest for the ACA (0.40 %). Finally, MRI has also been widely used to measure vasomotor reactivity, since the challenge is much more easily reproduced inside a scanner, see for example de Boorder et al. (2004).

2.5 Arterial Blood Pressure

Arterial blood pressure is the second measurement that must be recorded in order to assess autoregulation. The many ways in which this can be measured are most easily divided into two: invasive and non-invasive. Invasive methods are performed through the insertion of an arterial line, with a cannula needle being placed in an artery and connected to a pressure transducer. This technique is normally regarded as the 'gold standard', but can only be used under certain conditions. Non-invasive methods are thus much more widely used, although questions remain about their validity and the resulting accuracy.

The most common method is the use of a sphygmomanometer, based on inflation of a cuff around the upper arm. The cuff is inflated to a pressure well above the systolic pressure, preventing blood flow in the arm; this pressure is then allowed to drop and the intermittent onset of blood flow marks systolic blood pressure via the start of the Korotkoff sounds. The pressure at which the sounds disappear is then the diastolic blood pressure. This auscultatory method can be replaced by the oscillometric method, whereby the same inflation-deflation process is followed, but the cuff pressure is measured and oscillations recorded. The point of maximum oscillation corresponds to mean arterial blood pressure, with systolic and diastolic pressures being found at particular fractions of this maximum oscillation. Both of these methods have been validated in individual devices to a greater or lesser extent; they play only a small role in cerebral autoregulation studies, which are now almost uniformly based on continuous measurements.

These are made most commonly using the Finapres device, which has been in use now for over 30 years. This is based on the vascular unloading technique, where a pressure is applied to a peripheral artery (most commonly the finger) to maintain arterial blood volume constant by matching this applied pressure to the arterial blood pressure. The matching results in 'unloading' of the arterial wall, hence the name. The resulting ABP trace provides a continuous measurement with high temporal resolution; however, the measurement is made well away from the

brain, meaning that it must be assumed that peripheral ABP is the same in both locations.

A couple of studies have assessed the effect of using different measurements of ABP on the calculation of autoregulation parameters. Sammons et al. (2007) found that there is a good level of agreement when calculating autoregulation indices based on either the Finapres or invasive measurements of aortic blood pressure, although there are some biases, for example the Finapres giving higher values of ARI than invasive measurements. Petersen et al. (2014) then compared the values of cerebral autoregulation metrics (phase angle, gain, coherence and Mx) calculated using both invasive and non-invasive (Finapres) techniques. They found that both methods gave similar results, although there was a small difference when calculating both mean Mx and phase angle, which should be compensated for when using either method. Both studies thus show that the biases are relatively small over a wide range of autoregulation metrics, meaning that non-invasive blood pressure measurements can be used with confidence in the context of cerebral autoregulation, with obvious technical and clinical advantages.

As an aside, the phase angle between HR and CBFV has been proposed, Sommerlade et al. (2012), as an alternative method for showing differences between hemispheres, with this phase angle being significantly correlated with the ABP-CBFV phase angle. This opens up the possibility of assessing autoregulation using a single measurement device, although it has only been tested in patients with occlusive carotid artery disease and would need further validation.

2.6 Autoregulation Tests

Studies of autoregulation fall into two categories: those that rely on naturally occurring variability in the ABP and CBF(V) time series to assess the relationship between the two; and those that induce changes in ABP and assess the response in CBF(V). The former method is more pleasant for the subject, but can require long time series to get an accurate representation of cerebral autoregulation; the latter methods are quicker (and many are very simple) but they cannot be tolerated by all subjects, particularly those with serious conditions.

The most common of these manoeuvres, adapted from Panerai et al. (2001), are:

1. Thigh cuff: Blood pressure cuffs are inflated around a subject's thighs and subsequently deflated.
2. Lower body negative pressure: The lower part of the subject's body is placed in a box in which the pressure is reduced, typically by means of attachment to a vacuum cleaner. This has the advantage of being able to adjust the drop in ABP up to the subject's physiological limits.
3. Head-up/down-tilting: The subject lies on a bed and is then tilted up/down.
4. Cold pressor: One of the subject's hands is placed in a bowl of cold water, normally for one minute, and then removed.

5. Isometric hand grip: The subject grips an object with one hand and after a short while releases it.
6. Valsalva manoeuvre: The subject blows into a syringe to maintain an intrathoracic pressure and then releases the pressure.
7. Sit-stand: The subject stands from a sitting position.
8. Squat-stand: The subject stands from a squatting position.
9. Transient hyperaemia: The subject's carotid artery is compressed briefly.

The **thigh cuff** test is very commonly used and Mahony et al. (2000) showed that a distribution of ARI values was obtained that was not significantly different from normal in a group of normal subjects. They also showed that there is no accommodation to the test with repetition; they recommended that three iterations be performed to give accurate estimates of ARI in an individual subject. The choice of the cuff pressure has been investigated by Lorenz et al. (2006), who concluded that "the most reliable protocol is also the most inconvenient one for the patient", although there were no systematic biases in the results. This test has been used to show that the recovery in CBFV is faster in the posterior CA compared to in the MCA by about 1 s, Rosengarten and Kaps (2002).

The **lower body negative pressure** test has also been very widely used. For example Brown et al. (2003) showed that cerebral autoregulation is maintained even under high levels of orthostatic stress. Birch et al. (2002) showed that the repeatability of sinusoidal LBNP testing, measuring phase angle at 1/12 Hz, was greater at high vacuums, although these were too uncomfortable for patient use.

The use of the **head-up-tilt** test has been widespread and combined with the thigh cuff test, Lefthériotis et al. (1998), where it was shown that in healthy volunteers, the thigh cuff test resulted in a larger drop in ABP during 40° head-up-tilt than when supine; however, there was no significant change in RoR in both conditions, indicating that cerebral autoregulation was unaffected.

The **sit-stand** test has been shown to give an increase in coherence due to increased power spectral density in both blood pressure and blood flow, when used repeatedly, van Beek et al. (2010). It has been compared to the thigh cuff technique, showing that there is greater tolerance for the sit-stand test with small intra-subject variability in ARI, although the inter-subject variability in ARI was larger than for the thigh cuff test, Sorond et al. (2009).

The **squat-stand** test has also been shown to improve estimates of transfer function analysis (as measured by greater coherence and lower variability in phase angle estimates), Claassen et al. (2009).

The **transient hyperaemia** test has been shown to give results that are strongly correlated with clinical status in patients with neurosurgical disorders, Giller (1991). In healthy volunteers, it has been found to be highly reliable when used repetitively to detect changes in autoregulation at different CO_2 levels, Mahajan et al. (1998). It has been shown that factors such as the length of carotid artery compression and magnitude of the decrease in CBFV can significantly affect the transient hyperaemic response, although the effects on estimates of cerebral autoregulation have not been quantified, Cavill et al. (1998). Smielewski et al. (1996) compared results obtained

with the transient hyperaemia and thigh cuff tests at different levels of CO_2. The responses were both significantly associated with CO_2 and there was a linear correlation between THRR results and ARI, although the THRR results were found to be more reproducible than ARI from single tests.

Passive cyclic leg raising has been proposed as a test by Elting et al. (2014), who examined whether fluctuations in the ABP could be increased and hence whether estimates of cerebral autoregulation would be more reproducible and less variable. Although they found that there was a correlation between phase and gain reproducibility and MABP variability in the rest condition, the manoeuvre only increased the reproducibility of the gain; it was found that during the leg raising end-tidal CO_2 increased in variability, reducing its utility. This is a common difficulty with this and similar manoeuvres that needs to be carefully considered.

There have been a few studies investigating sinusoidal tests, both head-up-tilt in the frequency range 0.07–0.25 Hz, Gisolf et al. (2002), and LBNP at both 0.1 and 0.2 Hz, Brown et al. (2004). The former study confirmed the high-pass filter model of autoregulation, but the latter study found that autoregulation is compromised during oscillatory stress, compared to constant stress, particularly at higher frequencies.

The most comprehensive study comparing the results obtained by different methods was performed by Panerai et al. (2001). The authors compared the resting state with the thigh cuff test, LBNP, cold pressor test, hand grip and the Valsalva manoeuvre and found that ARI measurements were independent of the type of manoeuvre, although the amplitudes of the impulse and step responses were significantly affected by the type of manoeuvre. They also concluded that there was no evidence of different levels of sympathetic activity in the different tests being reflected in the autoregulatory responses.

The accuracy and repeatability of methods based on spontaneous fluctuations are thought to be less than those based on a physiological stimulus, Aaslid (2006). Additionally, Liu et al. (2005) found that in recordings with relatively high spontaneous variability in ABP, lower variability in the autoregulation parameters was found. This has led to the use of pseudo random perturbations in thigh cuff pressure to increase the variability in both the ABP and CBFV time series, Katsogridakis et al. (2012). This has been shown also to increase the sensitivity and specificity of detection of impaired autoregulation (as simulated via hypercapnia), without affecting the estimates of the step response, Katsogridakis et al. (2013). This technique has the advantage that it is well tolerated, although it is relatively complicated to set up; the authors also found that no significant sympathetic response was generated.

The relationship between different metrics as measured both in spontaneous oscillations and in thigh-cuff deflation tests and squat-to-stand manoeuvres has been investigated by Tzeng et al. (2012). They found that “metrics were generally unrelated or showed only weak to moderate correlations”: although some metrics were found to be correlated, these were few, indicating that the system cannot simply be characterised by a single parameter.

Interestingly, it has also been shown that the impulse-like disturbances to ABP caused by ectopic heart beats are enough to quantify cerebral autoregulation, giving results that are in agreement with other methods, Eames et al. (2005). The authors also showed that it is not necessary to remove ectopic heart beats before quantifying cerebral autoregulation, even up to eight ectopic heart beats per minute. Finally, it is worth noting that differences in the response to LBNP testing in the different hemispheres in left and right handed volunteers have been found, Müller et al. (1992).

In conclusion, it can be seen that essentially the greater or more variable the stimulus, the more reliable the estimate of autoregulation. There remains no gold standard test, but there is no evidence that there are significant differences in the estimates derived from different tests; however, more detailed comparisons would be required to conclude either that the choice of test (when performed suitably and for the necessary length of time) was entirely irrelevant, or conversely that there is an optimal test.

2.7 Conclusions

Measurements of both ABP and CBF have made substantial progress over the last few decades. However, despite the clinical importance of accurate measurements of blood pressure, there are many different devices available using many different techniques and algorithms to measure blood pressure. There is no non-invasive gold standard and the errors involved in using each device are often poorly understood. Since invasive measures of ABP are likely to remain restricted to a small proportion of patients and cannot be used for routine procedures, there remains a need to improve measurements of ABP and to determine a single method with the greatest accuracy and reliability.

Measures of CBF, although possessing good temporal resolution and accuracy, remain confined to a single vessel or at most one per hemisphere, due to the need to be able to insonate the vessel (with the limitation of the assumption of constant vessel cross-sectional area). This is a major limitation to assessing cerebral autoregulation, since it provides no spatial information and is thus of limited value in clinical contexts where there is any significant heterogeneity within the brain. As this is often the case, there remains a need to improve measurements of CBF. Although MRI has showed promise, this remains heavily limited by temporal resolution and the difficulty of measuring ABP within the scanner.

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Chapter 3
Mathematical Models

As has been shown, cerebral autoregulation is a highly complex phenomenon with many different physiological variables being involved in the maintenance of cerebral perfusion. This complexity has led to a number of different approaches to model the system relating ABP to CBF(V), from very simple, high-level, models to highly detailed descriptions of the mechanical and biochemical processes involved. In this chapter, the models used to describe autoregulation are presented briefly. First, the simpler high-level compartmental models are presented, before more detailed models are presented, expanding both the vascular detail and the biochemical descriptions.

3.1 Compartmental Models

Almost the simplest description of the cerebral vasculature is as two compartments, arterial and venous, with the arterial compartment driven by ABP and the flow passing from arterial to venous and exiting at venous pressure. The flow of blood through the brain, q, is then governed in the steady state by the Poiseuille equation (Eq. 1.1):

$$P_a - P_v = q(R_a + R_v) \tag{3.1}$$

where the subscripts a and v refer to arterial and venous conditions respectively. The expression for resistance is then given by Eq. (1.2) for each compartment, based on 'typical' values of radius, length and viscosity. Note that resistance will be denoted by R in this chapter.

The simplest case is one where both resistances are fixed (i.e. all vessels are rigid): thus flow and pressure are linearly related with a 1 % decrease in driving pressure difference giving rise to a 1 % decrease in cerebral blood flow. This can be termed the **rigid** response of the cerebral vasculature, with a 1 %/% sensitivity.

S. Payne, *Cerebral Autoregulation*, SpringerBriefs in Bioengineering,
DOI 10.1007/978-3-319-31784-7_3

However, as described in Chap. 1, there is both a passive and an active response to changes in ABP. Considering first just the passive response, since arterial resistance is proportional to blood volume to the inverse second power:

$$R_a = R_{ao}\left(\frac{V_{ao}}{V_a}\right)^2 \tag{3.2}$$

where we denote baseline conditions by the subscript o. If arterial compliance is assumed constant and ICP is assumed negligible, arterial blood volume becomes:

$$V_a = C_a P_a \tag{3.3}$$

Hence (and assuming that venous pressure is also negligible):

$$\frac{q}{q_o} = \frac{P_a}{P_{ao}} \frac{1}{\left(1 - r + r\left(\frac{P_{ao}}{P_a}\right)^2\right)} \tag{3.4}$$

where

$$r = \frac{R_{ao}}{R_{ao} + R_v} \tag{3.5}$$

i.e. the baseline arterial resistance fraction. This can be termed the **passive** response. At baseline conditions this has a sensitivity of $1 + 2r$ %/%, which is considerably higher than the rigid response.

The **active** response thus has to compensate for this passive response to reduce the sensitivity down to a fraction of 1 %/% in order to achieve autoregulation, as shown in Chap. 1. As outlined earlier, it is predominantly achieved through changes in arterial compliance. Therefore, any model of autoregulation needs to include this and this is nearly always done through the use of an equivalent electrical circuit, which is now examined in more detail. This also allows for the (numerous) assumptions made above to be relaxed.

3.1.1 Equivalent Electrical Circuits

Equivalent electrical circuits have a very long history in cardiovascular modelling, with the first studies being performed (and models physically constructed) in the 1960s, see for example Noordergraaf et al. (1963), Westerhof et al. (1969). This built upon the concept of the windkessel model, which has a much longer history.

Equivalent electrical circuits are constructed simply by lumping together sections of the vasculature into compartments and then modelling them using a combination of resistance, inductance and capacitance. The first of these simulates the pressure drop along a vessel due to viscous forces, using a resistor as equivalent. The second mimics the inertia of blood using an inductor. The third simulates the compliance of the vasculature that enables it to store blood, using a capacitor. A combination of these three components can be used to model a section of the vasculature relatively simply.

It should be noted straight away that the analogy between fluid flow and electrical current is not exact and that these models are only approximations to the actual behaviour, particularly since the compartments often contain very large numbers of generations of vessels. It is most common to divide the brain into only two or three compartments, since this reduces the complexity of the model and the parameters (such as arterial compliance) can be thought to have some physiological meaning (and to be capable of being estimated from data); however, they are very substantial approximations as a result. The construction of equivalent electrical circuit models for the brain requires a balance between simplicity and accuracy, just as for any physiological model.

3.1.2 Whole Brain Models

In this section, only those models that use a lumped compartment approach will be considered, as models that explicitly consider individual vessels will be described below. The model by Sorek et al. (1989) is one of the first attempts to develop a multi-compartmental model of the cerebral vasculature; the authors proposed seven compartments, as shown in Fig. 3.1.

Note the feature common to many whole brain models: that of the skull. The idea that the total volume of the skull is constant is based on the Monro-Kellie doctrine. This means that the total change in blood, CSF and brain tissue volumes is zero and that an expansion in one must be matched by a contraction in another. Since blood and CSF are basically incompressible, their volume can only be changed through changes in inlet and outlet flows; brain tissue is compressible, however, this will result in changes in ICP. Sorek et al. (1989) were able to estimate a number of different parameter values from available experimental data. It is notable though that the seven compartments include only one arterial compartment and that the authors did not attempt to model autoregulation.

The first model that attempts to model the whole brain circulation is that by Ursino (1988a); this is based on the equivalent electrical circuit concept, as shown in Fig. 3.2. This is also the first model to include autoregulation, where it is

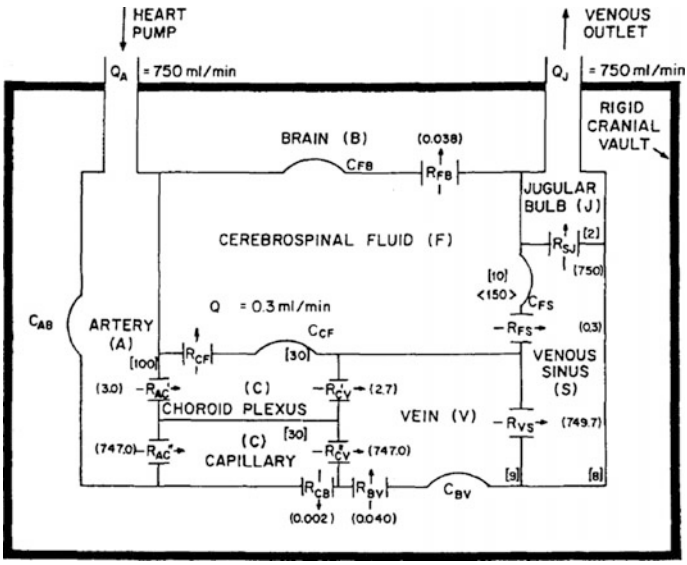

Fig. 3.1 Lumped parameter compartmental model of cerebral blood flow, reproduced with permission from Sorek et al. (1989)

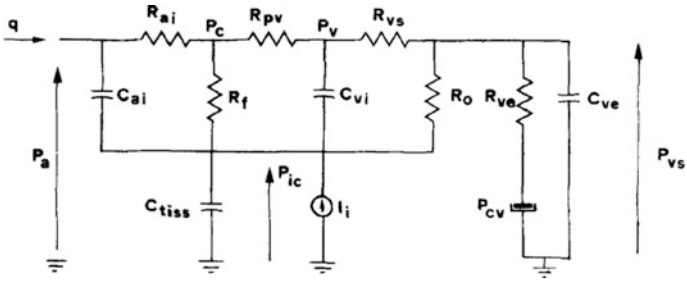

Fig. 3.2 Electrical equivalent circuit model of the cerebral circulation, reproduced with permission from Ursino (1988a)

assumed that arterial conductance ($G_{ai} = 1/R_{ai}$) is adjusted in response to changes in driving pressure through a low-pass filter with gain and time constant:

$$G_{ai} = G_{ain}\left(1 - \frac{1}{\pi}\tan^{-1}(\pi x)\right) \tag{3.6}$$

$$\frac{dx}{dt} = -\frac{1}{\tau}x + \frac{1}{\tau}\left(\frac{P_a - P_v - P_{an} + P_{vn}}{P_{an} - P_{vn}}\right) \tag{3.7}$$

where the symbols correspond to the variables in Fig. 3.2. Arterial compliance is assumed to be non-linearly related to pressure as:

$$C_{ai} = \frac{1}{K_a(P_a - P_{ic})} \tag{3.8}$$

where K_a is a constant determining baseline arterial compliance.

CSF production and reabsorption are governed by two resistances, R_f and R_o respectively. The venous compartment is modelled through two resistors, the first of which, R_{pv}, is the proximal venous resistance, and the second of which, R_{vs}, is the extra-cranial venous resistance. The latter is not a constant resistance, since it includes the potential for collapse, hence:

$$R_{vs} = \frac{P_v - P_{vs}}{P_v - P_{ic}} R'_{vs} \tag{3.9}$$

where R'_{vs} is a constant. Venous compliance is again related to pressure, with a constant offset, P_{v1}:

$$C_{vi} = \frac{1}{K_v(P_v - P_{ic} - P_{v1})} \tag{3.10}$$

The Monro-Kellie doctrine is adopted to conserve total volume, with an injection term included in the model, I_i, in order to simulate specific neurological tests. Finally, ICP is set through the tissue compliance, which is assumed to be inversely proportional to a quadratic function of ICP (hence tissue compliance decreases rapidly with increased ICP). The final three components in the model relate the venous sinus pressure to the central venous pressure via the extra-cranial resistance and compliance. This model was compared to a number of experimental simulations, Ursino (1988b), showing good agreement.

This model forms the fundamental basis for all subsequent models of autoregulation proposed by Ursino and colleagues, as well as strongly influencing many other authors. The main changes that have been made are those in the autoregulation pathway and the number of arterial compartments. In this section only those autoregulation pathway models that are high-level will be considered: more detailed pathway models will be considered in the following section.

The model was used to model ICP dynamics in patients with acute brain damage, Ursino et al. (1995); it was shown that ICP is governed by both CSF dynamics and blood flow and blood volume changes. A similar study into ICP dynamics was performed by Giulioni and Ursino (1996). A much simplified version of the model was then proposed by Ursino and Lodi (1997), in particular merging the proposed two feedback compartments (see the next section) back into one, and returning to a simple flow-based feedback mechanism described by a single gain and time constant. Very similar behaviour was found to be exhibited by the reduced model, which has only approximately 12 parameters.

The two arterial compartment model was extended to include CO_2 reactivity, Ursino and Lodi (1998), before being simplified back into one arterial compartment again, Ursino et al. (2000), with feedback based on flow and arterial CO_2. It is worth noting in passing that the resulting plots of CBF as a function of both ABP and $PaCO_2$ are validated only against experimental data gained from animal models: Harper et al. (1984), MacKenzie et al. (1979), Reivich (1964) and Harper and Glass (1965). The flow feedback parameter has been proposed as a measure of autoregulation strength, Ursino and Giulioni (2003).

Similar models have subsequently been proposed by a number of authors, with different levels of complexity. The model proposed by Olufsen et al. (2002) contains just three equivalent electrical components with values that vary with time and that are matched to the sit-stand manoeuvre. The model by Kirkham et al. (2001) is based on a simple flow-feedback mechanism with gain and delay: if these are too large, the model is found to transition from stable to oscillatory and then unstable behaviour, in a similar manner to the oscillatory behaviour shown by Ursino and Lodi (1997). The model by Czosnyka et al. (1997) is very similar to that of Ursino and Lodi (1997), but somewhat simplified.

The model by Payne (2006) is of substantially the same form as the Ursino et al. (2000) model, but also includes the contribution from neural activation and is thus able to draw upon validation data from three physiological challenges. The ABP-CBFV behaviour of this model has been shown to be equivalent to a second order system with five degrees of freedom, four of which can be estimated from the experimental impulse response alone, Payne and Tarassenko (2006). This model was extended to consider haemoglobin transport and hence to model NIRS signals, Payne et al. (2009).

Another model that is very similar in style to the single arterial compartment model of Ursino and colleagues, which also includes neural activation is that by Spronck et al. (2012): this includes four feedback terms, based on myogenic, shear stress, neurogenic and metabolic regulation. In eleven subjects, five of the feedback gains and time constants are fitted to data and the parameter values show consistency across the subject group. This model has the advantage that the different feedback mechanisms are more explicitly included. The venous outflow has been modelled in detail by Gadda et al. (2015), particularly in response to changes between supine and upright positions.

The interaction between cerebral autoregulation and the wider systemic circulation has been investigated by a number of authors, for example by Neidlin et al. (2014), who coupled a numerical model of blood flow in the aortic arch with a lumped parameter model of autoregulation in cardiopulmonary bypass patients, and Panunzi et al. (2015) who proposed a stochastic delay differential model of cerebral autoregulation based on four differential equations for central venous pressure, arterial blood pressure, heart rate and CBFV, with two other state variables for brain arterial pressure and peripheral vascular resistance.

3.2 Biochemical Feedback Models

Within lumped compartment models, there have been a number of attempts to include more detailed models of the autoregulation pathways. The first of these was described by Ursino et al. (1989a), based on chemical oxygen-dependent processes and including oxygen diffusion from capillary to tissue, production of the metabolites adenosine and H^+ and their diffusion to the vasculature. The main assumption was that regulation is achieved by the release of two vasodilating metabolites, adenosine and H^+.

This approach was then extended by Ursino et al. (1989b) to a five compartment resistor network. They assumed that the metabolic regulation acted only on the medium and small pial arteries and the intracerebral arterioles. Laplace's law was used to relate intravascular pressure and ICP to wall tension, T, which was assumed to comprise both passive elastic and active terms (the latter relating to smooth muscle):

$$p_i r - p_e(r+h) = T_e + T_m \tag{3.11}$$

where the wall tensions were assumed of the form:

$$T_e = \frac{Eh}{\left(r_o + \frac{h_o}{2}\right)}\left(r + \frac{h}{2} - r_o + \frac{h_o}{2}\right) \tag{3.12}$$

$$T_m = T_o\left[-4\left(\frac{r}{r_p}\right)^2 + 4\left(\frac{r}{r_p}\right)\right]\left[1 + G_1(pH - pH_n) - G\log_{10}\frac{c_{ad}}{c_{adn}}\right] \tag{3.12}$$

i.e. elastic tension is set by Young's modulus, E, which decreases as the inner vessel radius, r, expands and the wall thickness, h, decreases according to conservation of wall volume. Active tension has a maximum at a particular value of radius and is linearly proportional to pH and logarithmically proportional to adenosine concentration. The three different types of regulating vessel have different values of gain, as well as different geometries.

This model was then adapted to investigate the plateau waves found in ICP under certain conditions, Ursino and Di Giammarco (1991). A revised electrical equivalent circuit was proposed, Fig. 3.3, where the arterial resistance/conductance was split into two separate compartments, with the first (up to and including the largest pial arteries) and second (from the medium pial arteries to the capillary bed) responding to changes in perfusion pressure and CBF respectively.

Wall tension was assumed to have three components: elastic, viscous and active:

$$p_i r - p_e(r+h) = T_e + T_v + T_m \tag{3.13}$$

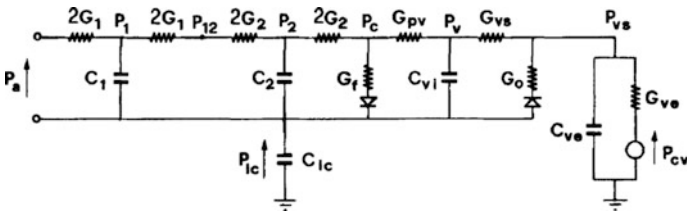

Fig. 3.3 Electrical equivalent circuit of cerebral circulation, reproduced with permission from Ursino and Di Giammarco (1991)

Elastic tension was assumed to be exponentially related to radius:

$$T_e = h\left[\sigma_o\left(e^{k_e\frac{r-r_o}{r_o}} - 1\right) - \sigma_{coll}\right] \tag{3.14}$$

where the wall thickness was calculated from the incompressibility condition:

$$h = -r + \sqrt{r^2 + 2r_o h_o + h_o^2} \tag{3.15}$$

The viscous term was a simple damper:

$$T_v = h\frac{\eta}{r_o}\frac{dr}{dt} \tag{3.16}$$

and the active term was here taken to be of the form:

$$T_m = T_{mo}(1+M)exp\left(-\left|\frac{r-r_m}{r_t-r_m}\right|^{n_m}\right) \tag{3.17}$$

i.e. dependent upon an activation factor, M, which is the mechanism through which feedback occurs. This is different between the two arterial compartments, with the first compartment exhibiting feedback based on changes in pressure:

$$\frac{dM_1}{dt} = -\frac{1}{\tau_1}M_1 + \frac{1}{\tau_1}\frac{2}{\pi}\tan^{-1}\left(\frac{P_a - P_v - P_{an} + P_{vn}}{P_{ref}}\right) \tag{3.18}$$

and the second compartment feedback based on changes in flow.

$$\frac{dM_2}{dt} = -\frac{1}{\tau_2}M_2 + \frac{1}{\tau_2}\frac{2}{\pi}\tan^{-1}\left(\frac{q-q_n}{q_n}\frac{1}{q_{ref}}\right) \tag{3.19}$$

Values for all of the (40) parameters are given by the authors, based on a number of experimental studies. This is the first study to investigate the stability of the system based on the values of the eigenvalues. This was related to the generation of plateau waves in ICP, through the restriction of CSF outflow and the build-up of ICP.

The effects of CO_2 reactivity were then included by Ursino and Lodi (1998) through a second contribution to activation factor. Equations (3.18) and (3.19) were altered to make activation factor exhibit a sigmoidal dependence on the sum of two state variables, which responded to flow and the logarithm of $PaCO_2$ separately with first order dynamics. Each pathway could thus be characterised in terms of a gain and time constant in each compartment.

The work of Ursino and colleagues has been presented in detail partly because it forms the basis for a number of other models. In particular, the model by Banaji et al. (2005), which has been used extensively, assumes the model form above, but replaces the two feedback equations with a detailed model of the biochemical pathways, such that the activation factors are set by the MLC phosphorylation in each compartment. Vascular tone is then set by the balance between phosphorylation (controlled by intracellular calcium) and dephosphorylation (controlled by nitric oxide) of myosin light chains. NO production is controlled by pressure and pH in each compartment, whereas intracellular calcium is controlled by a detailed model of flow and metabolism, Fig. 3.4.

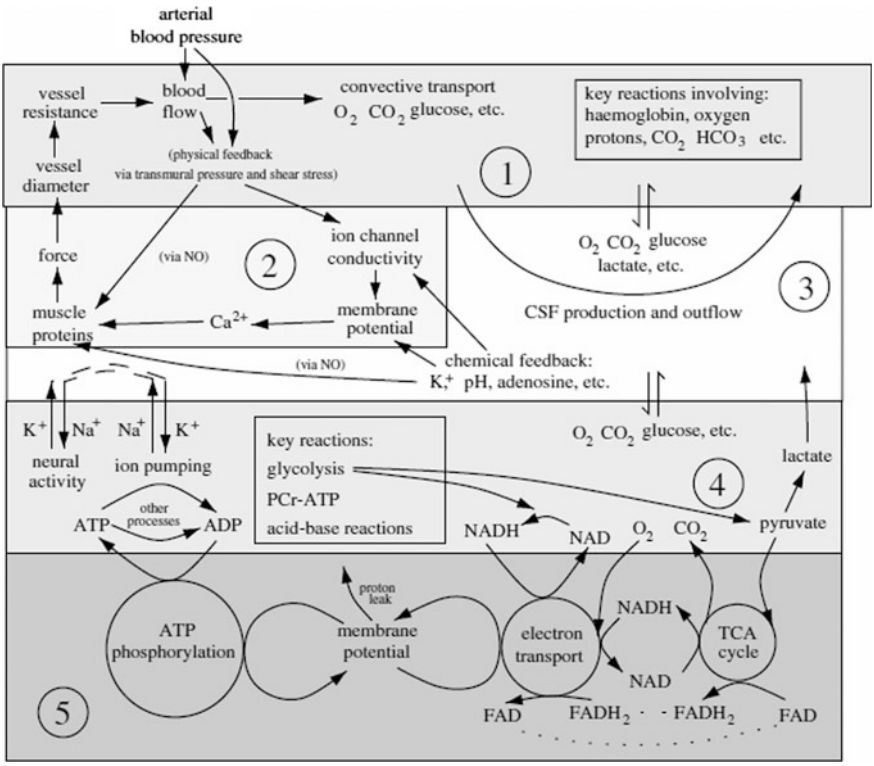

Fig. 3.4 Schematic of Banaji model, reproduced with permission from Banaji et al. (2005)

This model, with further adaptions, has been used in a number of studies, although these are mainly animal studies, apart from the work of Moroz et al. (2012) in healthy adults. Different parameters in the model have been optimised to fit time series, as discussed below. A similar, but much simplified, version of a calcium-NO phosphorylation model of smooth muscle cells was independently proposed by Payne et al. (2005), based on the study by Yang et al. (2003). This formed the basis of the model of Catherall (2014), which incorporated a coupled intracellular calcium-NO phosphorylation model within the model of Payne (2006).

A few studies have coupled a model of cerebral autoregulation with a gas exchange model, Diamond et al. (2009), Lu et al. (2004). The vascular models in both are based on those by Ursino and colleagues. The former study was used to help to remove physiological 'noise' in NIRS data in preference to simple regression or transfer function approaches, whilst the latter study was used to explore the interaction between the different mechanisms during a number of test protocols. It should be noted that both models inevitably contain a very large number of parameter values.

3.3 Network Models

Thus far, all of the models considered here have been based on the lumped compartment approach. Even those models with highly detailed feedback pathways are still based on models of the vasculature that are no more than a handful of equivalent electrical components. However, there has been some progress made in the construction of more detailed vascular models, based on the actual anatomy and connectivity of the cerebrovasculature. This has been driven by the desire to understand the spatial heterogeneity of the brain and the potentially different behaviour of particular regions of the brain. Unsurprisingly, these models are less well developed, since validation is challenging, particularly since it is not possible to image individual vessels with dimensions under a couple of millimetres. Since few of these vascular network models explicitly include autoregulation, this section will only provide a brief overview of the available models with a focus on those models that attempt to mimic autoregulation.

One of the earliest detailed models of the human cerebral circulation was developed by Zagzoule and Marc-Vergnes (1986); this model contained 34 segments based on physiological data, and solved the continuity, momentum and tube law equations, however they did not attempt to include autoregulation. In the context of autoregulation, one of the first models that attempted to move towards spatial resolution was that by Piechnik et al. (2001), who extended the equivalent electrical circuit model to include both hemispheres separately, Fig. 3.5. This also illustrates how different anatomical regions can be modelled through smaller division of the anatomical structures into different components. The model was used to investigate the results of different hemispheric reactivity on the flow and pressure, with a global "steal effect" being shown to be unlikely.

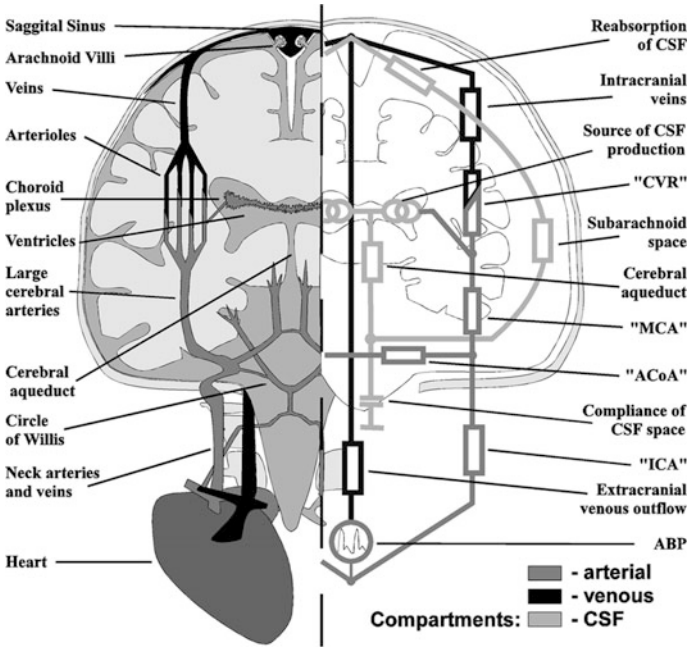

Fig. 3.5 Schematic representation of two hemisphere model, illustrating equivalence between physiology and equivalent electrical circuit, reproduced with permission from Piechnik et al. (2001)

The model by Ursino and Giannessi (2010) takes the lumped parameter model of Ursino and colleagues and extends it to individual large arterial vessels, including the circle of Willis, approximately 40 in total.

Although the model structure is still relatively simple, it does clearly illustrate the rapid increase in complexity through the introduction of more compartments. This is particularly seen to be the case when considering the feedback mechanisms that act to control flow and the interaction between vessels in different generations. Essentially, such approaches can be divided into two: those that start with the large vessels and model the smaller vessels as lumped compartments, and those that build up from the capillary bed, with the larger vessels being primarily treated as a fixed pressure supply. Given the considerable complexity of both types of models and the very large numbers of model parameters and computation time, it is not surprising that little work has been performed on modelling the whole cerebral vasculature as an active network.

One of the first studies to attempt to model autoregulation across different generations of arterial and arteriolar vessels, Gao et al. (1998), used four generations, each with different characteristics. Diameters (in the range 50–300 μm) and lengths (in the range 1.2–20 mm) were selected from experimental data and the number of vessels in each generation was calculated using Murray's law. Static

autoregulation was included through the use of empirical pressure-diameter relationships in each generation. The resulting network showed good agreement with experimental data, although it is clear from the vessel geometries that these are not intended as direct representations of individual vessels.

The vascular model proposed by Boas et al. (2008) contains 6 arterial, 1 capillary and 6 venous vessel generations. The primary focus of this study is the fMRI BOLD response and how changes in activation affect not just the vessels upstream and downstream but also parallel paths. The number of vessels included and the size of the vessels, however, make this network considerably smaller than a typical imaging voxel; activation is assumed to act directly on arteriolar resistance, so the mechanisms that drive this change are not explicitly included.

The vascular model proposed by Piechnik et al. (2008) contains 9 arterial, 1 capillary and 9 venous vessel generations. The primary focus of the study is on vascular reactivity and the resulting CBF-CBV relationship (since the focus is on MRI), so autoregulation is not explicitly included (and the calculation of the vessel geometry and numbers of vessels is not clearly stated). It is worth noting though that the reactivity varies very considerably across different generations of vessels. It can also be noted that the relationship between vessel pressure and diameter across the vessel generations, which is shown in normocapnia, hypocapnia and hypercapnia, is compared to the (cat and rabbit) data of Zweifach and Lipowsky (1977), which is also the dataset used by Lucas (2012). This model was later extended by Lampe et al. (2014) to include a dependence of radius on pressure and hence to model autoregulation; the authors also compared their results to those of Ursino and Lodi (1997), but no validation was performed.

The model by Lucas (2012) generates a bifurcating network, explicitly fitting the data of Zweifach and Lipowsky (1977), with 6 arterial, 1 capillary and 6 venous vessel generations. This is a much smaller model than that of Piechnik et al. (2008) and much more similar to Boas et al. (2008). However, its primary focus is on the feedback mechanisms that control blood flow, which are adapted from those models of adaptation of the microvasculature proposed by Secomb and colleagues.

These models of adaptation essentially state that there is an adaptation in vessel diameter in response to different stimuli, which include direct and shear stress, and metabolic state, see for example Secomb and Pries (2011). It is still not fully understood, however, how information is transferred between vessels, both upstream and downstream in order to maintain homeostatis, Pries and Secomb (2014), and so the precise nature of the stimuli and the vascular response to them remains unclear.

One feature of all of these detailed models is the single generation for the capillary vessels; however, it is well known that the capillary network is a highly complex interconnected distribution of vessels with a vessel density of approximately 8000 vessels/mm^3. Little work has been done to model this, although see for example Reichold et al. (2009), Su et al. (2012), Linninger et al. (2013). Many of these studies draw heavily on experimentally measured vascular information derived from microscopy, see for example Gagnon et al. (2015).

It is clear, even from the very brief overview given above, that models of the cerebral vasculature that incorporate spatial and generational information are still very much at a very basic stage. The primary challenge is that a model that simulated every vessel would be computationally intractable; thus new mathematical approaches will be needed to include behaviour at every length scale. Recent work on homogenisation has shown that this could play an important role in further development, El-Bouri and Payne (2015).

3.4 fMRI BOLD Response Models

It is interesting to note that models of cerebral autoregulation, which are built on global control of blood flow, are in many ways very similar to models of the BOLD response, which are built on the local control of blood flow. This is particularly the case in the spatially-varying models examined in the previous section. However, despite the close relationship between the two, there has been little effort made to link them or to use results from one set of models to inform the other.

The BOLD response is driven by the fact that local CBF increases by a greater fraction than does local metabolic rate following activation; this leads to a 'wash-out' effect where the amount of deoxyhaemoglobin actually decreases. Since deoxyhaemoglobin is paramagnetic, changes in its concentration result in a signal that can be detected using MRI, Ogawa et al. (1990). Functional MRI has proven a very powerful tool to investigate the brain noninvasively in both normal and pathological conditions, see for example Faro and Mohamed (2010).

The earliest models to simulate the fMRI response include those by Buxton et al. (1998), Friston et al. (2000), Zheng et al. (2002), Buxton et al. (2004). A more detailed model, based on multiple compartments, was then proposed by Griffeth and Buxton (2011). The review of the field by Buxton (2012) emphasised that whilst the physics of the BOLD response is now well understood, the underlying physiology is less well understood. It should be noted that this review, which summarises the current view of the BOLD response shown in Fig. 3.6, also provides a much more comprehensive overview of the field than is contained here.

It is clear that cerebral blood flow and volume play a key role in this response and hence autoregulation plays a role in the BOLD response, although this is not often commented upon. Models of the BOLD response are very similar to those proposed in the context of cerebral autoregulation, usually being based on the concept of a 'balloon', whereby a venous compartment expands and contracts. The BOLD response also relies on the transport of deoxyhaemoglobin, which has only briefly been considered in the context of autoregulation, Payne et al. (2009), where it was analysed in the context of NIRS.

The fact that both fMRI and NIRS rely on the transport of haemoglobin means that there is considerable overlap in the underlying mechanisms that determine the measurements. It is somewhat surprising that there has not been more cross-fertilisation between the models, particularly given that there has also been

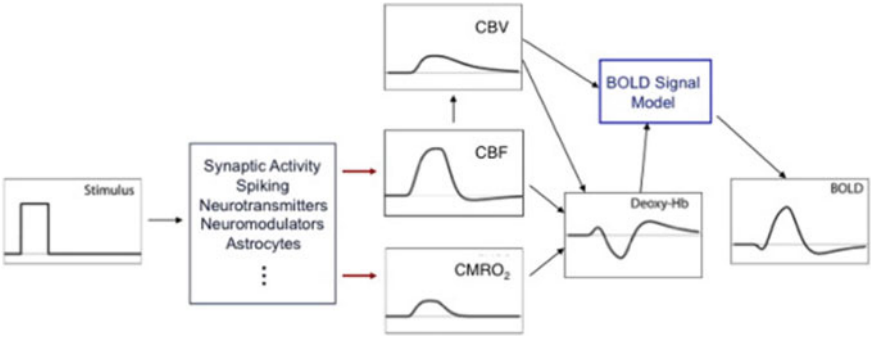

Fig. 3.6 Schematic of physiological basis of BOLD response, reproduced with permission from Buxton (2012)

extensive work in the field of autoregulation modelling. This is an area where drawing together insights from models from different modalities would repay detailed study.

3.5 Parameter Fitting and Sensitivity Analysis

Despite the fact that there have been several models proposed to simulate the relationship between ABP and CBFV, there have been relatively few attempts to estimate the parameters in these models in a rigorous way from experimental data. There have been even fewer attempts to estimate model parameters from individual subjects and to use these to understand changes in autoregulation both within healthy groups and between different patient groups.

One primary reason for this is that the models tend to have relatively large numbers of parameters and the estimation of large numbers of parameters from what are normally relatively small data sets is challenging. The published approaches have thus focussed on estimating a very small number of parameters, with some studies performing a preliminary analysis to identify which parameters to fit.

One of the earliest studies was performed by Ursino et al. (1997), based on fitting four parameters: CSF outflow resistance, intracranial coefficient, autoregulation gain and autoregulation time constant, to ICP time series in 20 patients with severe acute brain damage. Lodi et al. (1998) then used a weighted least squares cost function, based on fitting both ICP and CBFV simultaneously, in recordings from six patients with severe head injuries. A good fit was achieved and the numerical values obtained were in reasonable ranges.

Ursino et al. (2000) performed a similar analysis in 13 patients with severe head injuries and fitted six of the model parameters: CSF outflow resistance, intracranial coefficient, autoregulation gain, CO_2 gain, CO_2 time constant and baseline CO_2. No

further analysis has been made in any of these three studies and there appear to be no significant relationships between the estimated parameter values and other clinical metrics from the published results.

There has been some more recent interest in parameter fitting using the expanded model from Banaji et al. (2005). A measure of autoregulation was estimated from NIRS measurements in three critically brain-injured patients, Highton et al. (2013); however, a larger sample would be needed to relate this to clinical status.

A second topic closely related to parameter estimation is sensitivity analysis. This is the method by which the influence of the model parameters on the model outputs are quantified such that the most important parameters can be identified. Precisely how this is calculated is a complicated subject, see for example Saltelli et al. (2004). In the context of cerebral autoregulation, the only studies that have been rigorously performed are those by Catherall (2014) and Moroz (2014), both of which used the Morris method. However, this has not yet been combined with patient data to perform stratification of patient groups. Such an approach would provide a clear role for models in this context, helping to reduce clinical time series to estimated values of physiological parameters in a rigorous way that has not yet been performed in this context.

3.6 Conclusions

There have been a substantial number of models proposed to simulate cerebral autoregulation and many of these provide accurate representations of the relationship between ABP and CBFV. However, these models have not yet reached their full potential, being limited by a number of factors. The first is that the variety of models makes them unappealing for others to use, since it is not clear which is the 'best' model. Indeed, the fact that there are no obvious criteria for 'best' makes this a very difficult question to answer. The second limitation is one shared by nearly all physiological models: the balance between simplicity and realism. A very simple model may be easy to relate to data, but will provide only limited insight into the actual processes; a very realistic model will provide great detail about the underlying processes, but will be very difficult to validate and to relate to data.

Models do have an important role to play in interpreting cerebral autoregulation data, particularly since there are many factors at work in controlling CBF, but they have yet to reach maturity. As will be seen in the section below, the proposal of a very simple one parameter analysis metric (ARI) has enabled cerebral autoregulation to be quantified and changes in autoregulation to be compared when analysing data. Although ARI has many limitations (as will be discussed below), it has enabled autoregulation to be quantified and translated into a clinical setting: and other more complex metrics can then be used in parallel.

A similar approach may need to be taken with models of cerebral autoregulation, reducing them to a very small number of parameters that can be estimated from clinical data and used to distinguish autoregulation status. Mathematical tools do

exist that would help to do this and although it should be stressed that physiological models have other roles to play in addition to this, without this direct link to clinical practice, there remains the danger that models of cerebral autoregulation will fail to reach their potential in interpreting data and aiding clinical practice.

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Chapter 4
Analysis Techniques

The introduction of TCD probes, together with the vascular unloading ABP technique, meant that since the 1980s it has been possible to obtain continuous and simultaneous measurements of both ABP and CBFV at high temporal resolution and at relatively low cost. This has resulted in a rich literature of analysis methods that attempt to understand the relationship between these two variables. The first studies mostly assumed that the relationship is univariate, linear and stationary; however, all of these assumptions have been challenged by later investigations. In particular, the role of blood gas levels is now known to be of considerable importance.

In this chapter, analysis methods will be presented, starting with the earliest, simplest methods, before exploring how later techniques have extended the analysis to non-linear, non-stationary and multivariate methods. For ease of presentation, analysis techniques are divided into those that are based in the time domain and those that are based in the frequency domain, although there is no fundamental theoretical difference between them.

4.1 Time Domain Analysis

The first methods developed attempted to characterise the temporal response of CBFV to changes in ABP, firstly using a single parameter and then using a complete time history. In this section, these methods are presented, approximately in order of increasing complexity.

S. Payne, *Cerebral Autoregulation*, SpringerBriefs in Bioengineering,
DOI 10.1007/978-3-319-31784-7_4

4.1.1 Rate of Regulation (RoR) and Autoregulation Index (ARI)

The earliest metric to quantify autoregulation was termed Rate of Regulation (RoR), Aaslid et al. (1989). Deflation of thigh cuffs was used in normal volunteers to induce a step change in ABP under normocapnia, hypocapnia and hypercapnia and the speed of return of CBFV to baseline was quantified. Cerebrovascular resistance (CVR) was calculated by dividing relative ABP by relative CBFV. When averaged over 10 subjects, characteristic response curves were obtained, as shown in Fig. 4.1. RoR was then calculated from the slope of the regression line for changes in both CVR and ABP:

$$RoR = \frac{1}{\Delta ABP}\frac{\Delta CVR}{\Delta t} \tag{4.1}$$

The resulting values of RoR were found to be 0.38, 0.20 and 0.11 /s in hypocapnia, normocapnia and hypercapnia respectively; this gave a highly significant inverse relationship between RoR and $PaCO_2$.

Although RoR can be calculated very straightforwardly and gives a simple metric, it suffers from the difficulties involved in the division of any two noisy time series making it potentially non-robust under certain conditions; likewise it is entirely dependent upon the precise nature of the test being performed. This makes it prone to non-repeatability across centres. Finally, it relies on being able to perform the thigh cuff test, which is not tolerated by all subjects. As an aside, it is

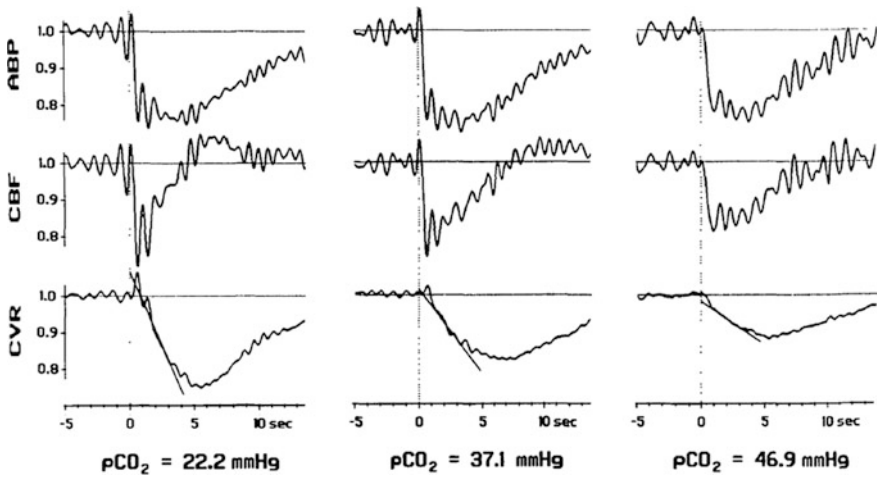

Fig. 4.1 Group-averaged responses to thigh cuff test in hypocapnia, normocapnia and hypercapnia, reproduced with permission from Aaslid et al. (1989)

worth noting that this is the most highly cited paper in cerebral autoregulation, possibly because it is the first paper to quantify dynamic autoregulation.

The third most cited paper is that by Tiecks et al. (1995), where the authors introduced a second order difference equation to relate the changes in CBFV recorded in response to changes in ABP induced by the thigh cuff test. The equations are based on three parameters: gain, K; damping factor, D; and time constant, T, and are set out in the form:

$$dP = \frac{(MABP - cABP)}{(cABP - CCP)} \tag{4.2}$$

$$x_2[n] = x_2[n-1] + \frac{x_1[n] - 2Dx_2[n-1]}{fT} \tag{4.3}$$

$$x_1[n] = x_1[n-1] + \frac{dP[n] - x_2[n-1]}{fT} \tag{4.4}$$

$$mV[n] = 1 + dP[n] - Kx_2[n] \tag{4.5}$$

where mean velocity is denoted by mV, dP is the normalized change in mean arterial blood pressure, $MABP$, relative to its control value, $cABP$, calculated with reference to the critical closing pressure, CCP. f represents the sampling frequency and the state variables are assumed to be equal to zero in the control phase.

Ten sets of parameter values were proposed, each set corresponding to a different value of autoregulation index (ARI), which varied from 0 (indicating no autoregulation) to 9 (maximal autoregulation), as shown in Table 4.1. The value of ARI for a given subject is usually taken to be the value that gives the minimum RMS error between the actual and predicted CBFV time series, based on the input ABP time series. The authors also calculated the equivalent value of RoR.

Table 4.1 Parameter values for Tiecks' model of ARI

T (s)	D	K	ARI	dROR (%/s)
	0.00	0	0	0 (No autoregulation)
2.00	1.60	0.20	1	2.5
2.00	1.50	0.40	2	5.0
2.00	1.15	0.60	3	10.0
2.00	0.90	0.80	4	15.0
1.90	0.75	0.90	5	20.0 ("Normal autoregulation")
1.60	0.65	0.94	6	30.0
1.20	0.55	0.96	7	40.0
0.87	0.52	0.97	8	60.0
0.65	0.50	0.98	9	80.0 (Fastest autoregulation)

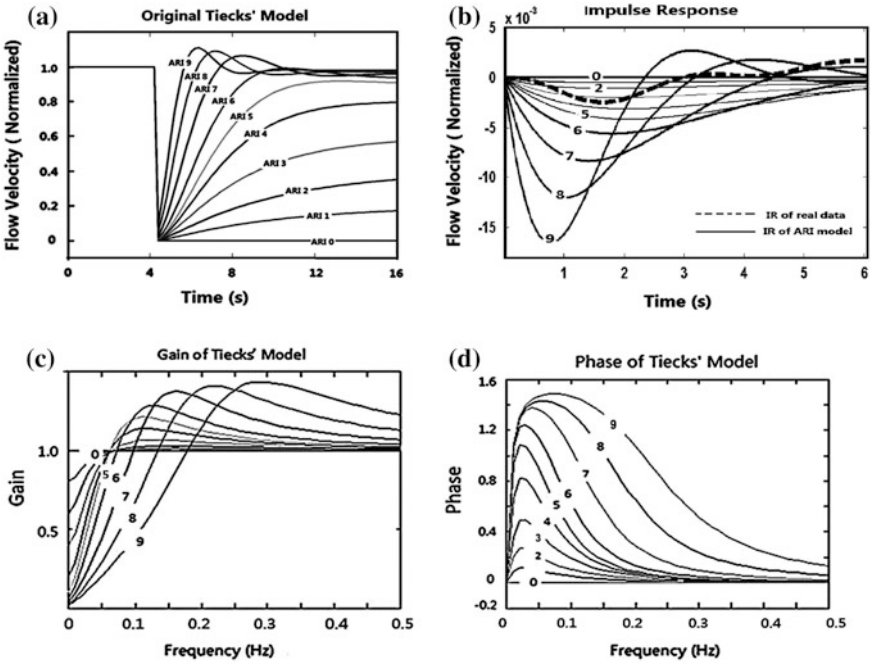

Fig. 4.2 Response of ARI model of Tiecks et al. (1995): **a** step response; **b** impulse response; **c** gain; **d** phase. Reproduced with permission from Liu et al. (2015)

No details or justification are given for the particular choice of parameters, which result in the step responses given in Fig. 4.2a as well as the corresponding impulse response (b), gain (c) and phase (d) responses. It should be noted that despite its seeming arbitrariness, ARI has proven extremely popular and is still extensively used to quantify dynamic autoregulation and hence to differentiate between different subject groups.

Tiecks et al. (1995) used ARI to compare static and dynamic autoregulation in 10 normal subjects undergoing elective orthopaedic surgery. Static autoregulation was assessed using the response to phenylephrine and measurements were performed during propofol and isoflurane administration to mimic intact and impaired autoregulation. The correlation between static and dynamic autoregulation was found to be highly significant. It is worth noting here that Tiecks et al. (1995) claimed that impairment of autoregulation first affects the latency and then the efficiency of the response (based on unpublished results).

A number of improvements to ARI have been proposed and it has been used to estimate autoregulation as a non-stationary process, using a sliding window, although time-varying estimates of ARI have been shown to be very sensitive to artefact, with ARI dropping to zero at times, Panerai et al. (2008). Such non-stationary estimates of ARI are not significantly different when estimated using a Finapres as compared to

those values obtained using an aortic catheter, Panerai et al. (2008). It has been shown, from analysis of intra-subject variability in healthy volunteers, that 45 subjects are needed to distinguish ARI changes less than 1, whereas only 11 subjects are needed to distinguish a change less than 2, Brodie et al. (2009).

Autoregressive moving average (ARMA) models have been used to estimate ARI (hence termed ARMA-ARI). Considerable differences between ARMA-ARI and ARI have been found in terms of stability, variability and sensitivity to discrimination between subjects. ARMA-ARI exhibited much greater stability and reduced variability compared to ARI, Panerai et al. (2003). An ARX model was also proposed by Liu and Allen (2002), based on time series from 11 healthy subjects using the thigh cuff technique, where it was found that the R5% response (the 5 s recovery percentage) could be used to assess cerebral autoregulation, even when there was considerable measurement noise. Liu et al. (2003) then used the ARX model to calculate both step response and phase shift at 1/12 Hz. It has been shown that just 1.5 min of ABP and CBFV time series is sufficient to estimate a linear model of cerebral autoregulation based on an ARX models, Gehalot et al. (2005).

Finally, an investigation into whether an unconstrained version of the Tiecks model, where K, D and T were allowed to vary independently, rather than as constrained as in Table 4.1, showed that the unconstrained value of K could provide a more stable and reliable metric than ARI, although it would be necessary to validate its use in multiple scenarios, Chacon et al. (2008).

4.1.2 Impulse Response and Step Response

Both RoR and ARI attempt to characterise autoregulation in a single parameter: this has the merit of simplicity, but does potentially miss considerable information about the ABP-CBFV response. There has thus been interest in deriving the complete response of the system, both in terms of the impulse response (IR) and the step response (SR).[1]

The response of a linear stationary system can be represented in the time domain as a convolution integral:

$$y(t) = \int_{-\infty}^{\infty} x(\tau)h(t-\tau)\,d\tau \tag{4.6}$$

where $h(t)$ is the impulse response relating the input $x(t)$ to the output $y(t)$. The step response is then found from integration of the impulse response:

[1]The impulse response and step response are the modelled responses of the system to an impulse and a step respectively; they can each be derived from the other and provide a simple representation of the response of a linear time-invariant system.

$$s(t) = \int_0^t h(\tau)\, d\tau \tag{4.7}$$

Precise details of how the IR and SR are derived from time series differ from study to study. The procedure set out by Panerai et al. (1999a) is presented briefly here as an illustration.

Following pre-processing of the two time series (removal of artifacts, low-pass filtering, re-sampling and normalization), the time series are divided into segments and multiplied by a cosine-tapered window before being transformed using the FFT with superposition. The average of the result is then calculated and smoothed before being low-pass filtered and having the inverse FFT applied to generate the IR. Care has to be taken to remove artifacts and noise in order to obtain an accurate representation of the response.

The IR and SR have been derived by a number of authors, for example Panerai et al. (1999a), who derived the responses shown in Fig. 4.3, in normocapnia, hypercapnia and on return to normocapnia. These results are typical of all studies into normal subjects: the IR shows undershoot, occurring just before 1 s, returning to baseline quickly with possible occasional slight overshoot. The equivalent step

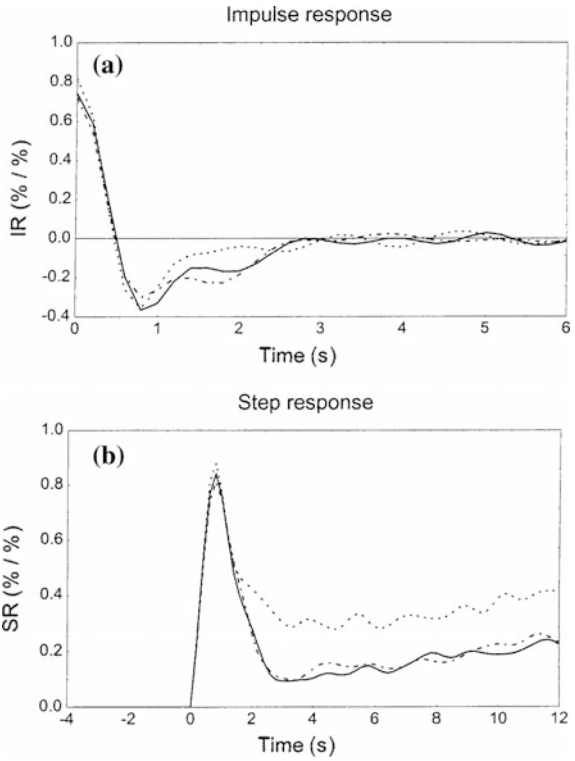

Fig. 4.3 **a** Impulse and **b** step responses for 15 subjects in normocapnia (*solid line*), 5 % CO_2 breathing (*dotted line*) and return to normocapnia (*dash-dotted line*), reproduced with permission from Panerai et al. (1999a) (© Institute of Physics and Engineering in Medicine. Reproduced by permission of IOP Publishing. All rights reserved.)

response then shows slight overshoot before settling down to a baseline value of less than 1 (when calculated as %/%). The step response clearly shows the bi-phasic nature of the response as governed by the initial passive and delayed active mechanisms. It should be noted that these responses were derived from spontaneous fluctuations in ABP and CBFV.

The amplitudes of the IR and SR have been found to be significantly influenced by the type of autoregulation test used to derive them. The initial value of the step response (and hence also of the impulse response) has then been shown to be highly correlated with the resistance-area product, Panerai et al. (2001).

Although the use of step and impulse responses has largely been superseded by other, mainly frequency domain, methods, it is worth noting that a recent study that compared 13 different metrics (both time and frequency domain, linear and non-linear), the parameter that was found to give the smallest intra-subject variability with good inter-subject variability was the parameter termed H1, which is the second coefficient of a first-order (i.e. two coefficient) FIR filter, Angarita-Jaimes et al. (2014).

4.1.3 Correlation Coefficient (Mx)

Another very simple, but effective, metric that has been widely used is correlation coefficient. First proposed by Czosnyka et al. (1996), in the context of head injury, this simply takes a sequence of consecutive samples of two time series and calculates Pearson's correlation coefficient over this period. This correlation coefficient, which is simply the ratio of the covariance of the two time series to the product of the individual standard deviations, varies between −1 (perfect negative correlation), 0 (no correlation) and 1 (perfect positive correlation).

The rationale for using this as a metric of autoregulation is that a positive value indicates impaired autoregulation due to a passive relationship being shown between ABP and CBFV, whereas a zero value indicates that CBFV is not directly driven by ABP and hence autoregulation is intact. Steinmeier et al. (2002b) found that correlation coefficient was a valid means to monitor autoregulation status continuously, although it still needed improvements to its sensitivity and specificity to play a role in clinical decision making.

Steinmeier et al. (2002a) found a time delay between ABP and CBFV in cross-correlation analysis, with impaired autoregulation being exhibited by lack of this delay and by a positive correlation coefficient. However, this was only tested in healthy volunteers and remains to be tested in pathological conditions.

There have been a couple of studies that have looked at correlation coefficient in different frequency bands. Chiu and Yeh (2001) used cross-correlation analysis in three frequency bands (0.015–0.07, 0.07–0.15 and 0.15–0.4 Hz), finding that in normal subjects the time lag at peak cross-correlation increased significantly from LF to HF ranges. Christ et al. (2007) then calculated correlation coefficient using only the frequency band below 0.1 Hz and found a delay in slow oscillations of

2.0 s in healthy subjects, which was abolished in patients (comprising a mixture of severe head injury and SAH).

Before moving to consider frequency domain methods, it is worth noting that Rosengarten and Kaps (2002) used peak systolic velocity-pressure curves as an alternative measure of autoregulation in comparison with ARI in healthy subjects undergoing the thigh cuff test. They found that this was the most accurate representation of autoregulation, since all the values calculated lay above the passive velocity-pressure non-autoregulating curve. They also found no difference between autoregulation in the territories of the MCA and posterior CA.

4.2 Frequency Domain Analysis

Since the 1990s, transfer function analysis has proven a valuable method of quantifying cerebral autoregulation and has become one of the default ways in which autoregulation is described. One of its advantages is that it provides considerable information about the response across different frequencies and the coherence function gives a measure of certainty about the accuracy of the results. It can also be extended easily to multivariate analysis.

4.2.1 Univariate Analysis

For a univariate, linear and stationary system, the two time series can be converted into a transfer function very simply, based upon the two power spectra. These are usually calculated based on:

$$S_{xx}(f) = E[X(f)X^*(f)] \tag{4.8}$$

$$S_{yy}(f) = E[Y(f)Y^*(f)] \tag{4.9}$$

where X and Y are the power spectra of ABP and CBFV respectively as functions of frequency, f; E represents expectation; and * represents the complex conjugate. The power spectra are calculated from the individual time series, following the same approach described earlier for the impulse and step responses. The expectation represents the fact that the time series are divided into a number of segments before the FFT and the resulting spectra are calculated. The cross-spectrum is also calculated:

$$S_{xy}(f) = E[X(f)Y^*(f)] \tag{4.10}$$

From these, the transfer function relating the time series can be calculated:

$$H(f) = \frac{S_{xy}(f)}{S_{xx}(f)} \tag{4.11}$$

This is normally converted into gain and phase based on the real and imaginary parts; likewise the magnitude-squared coherence function can be calculated:

$$\gamma^2(f) = \frac{\left|S_{xy}(f)\right|^2}{S_{xx}(f)S_{yy}(f)} \tag{4.12}$$

This is the ratio of the power contained in the predicted output signal, based on the estimated frequency response at that frequency, as a fraction of the actual power in the output signal and lies in the range 0–1. The frequency response can only be taken to be a valid measure of the system dynamics at frequencies where coherence is higher than a threshold, normally taken to be 0.5. It should be noted that this has not been rigorously justified and will in fact vary dependent upon the number of data segments, as shown by Wang and Tang (2004).

The frequency response is thus characterised by three parameters: gain, phase and coherence. Note that since most time series are converted to beat-to-beat values and then re-sampled at 1 Hz before being Fourier transformed, the resulting range of frequencies is 0–0.5 Hz.

The first estimation of the transfer function between ABP and CBFV was carried out by Giller (1990), who calculated gain and coherence (described by the authors as correlations) in both normal subjects and patients with subarachnoid haemorrhage. Coherence was found to be lower in the normal subjects, indicating intact autoregulation. Giller and Iacopino (1997) also used coherence to identify consistent correlations in time series. Zhang et al. (1998) then plotted gain, phase and coherence over the whole frequency range in both normocapnia and hypercapnia, as shown in Fig. 4.4. These results are typical of other studies.

To assist in quantifying the transfer function, the frequency spectrum is often divided into three bands. Those used by Zhang et al. (1998) are given below and are marked by the following characteristics, which are consistent with those of a high pass filter (to which autoregulation is regularly compared):

Very low frequency (<0.07 Hz): Low coherence (<0.5), low gain and large phase lead.

Low frequency (0.07–0.20 Hz): High coherence (>0.5), increasing gain and decreasing phase.

High frequency (>0.20 Hz): High coherence (>0.5), relatively large gain and minimal phase lead.

The results presented by Panerai et al. (1999a) in normocapnia are very similar, although the gain at high frequencies is slightly different. Hypercapnia is found to increase gain and coherence and to decrease phase in the low frequency band: these changes are normally quoted as evidence in other studies that autoregulation is

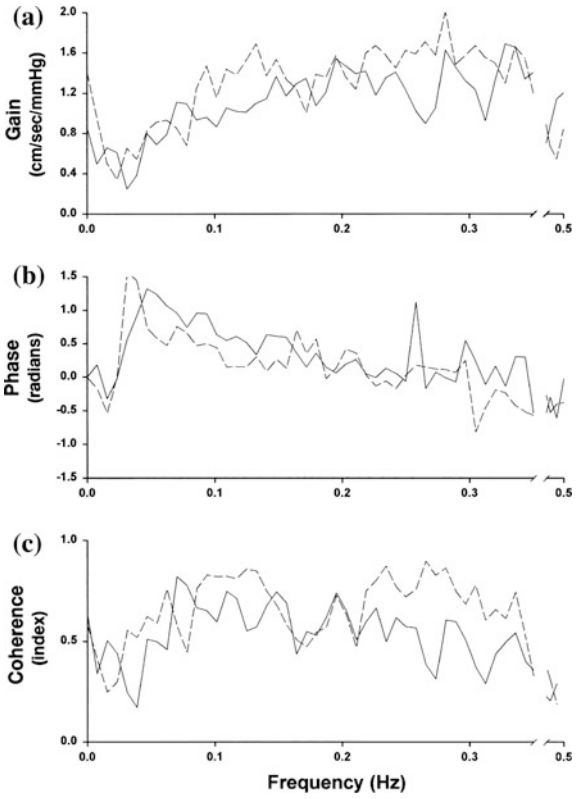

Fig. 4.4 **a** Gain, **b** phase and **c** coherence as functions of frequency in normal subjects at baseline (*solid line*) and during 5 % CO_2 breathing (*dashed lines*), reproduced with permission from Zhang et al. (1998)

impaired. It should be noted that the frequency bands used here and elsewhere do not necessarily correlate to underlying physiological processes, rather being used simply for convenience. As an example of a different approach, Diehl et al. (1998) characterised the gain, phase and coherence in two tightly defined frequency bands, termed M-waves (3–9 cycles/min) and R-waves (9–20 cycles/min).

Since these early studies, there have been very many studies in a wide range of subject groups, quantifying autoregulation in terms of gain, phase and coherence. These will be presented in the relevant sections below, but as an illustration, the review by Meel-van den Abeelen et al. (2014a) found 113 publications that used transfer function analysis. They concluded that there is no gold standard for using transfer function analysis and that even in the studies that report the settings used there is a great deal of diversity, making it very difficult to compare results between different studies. It is worth noting, however, that Jachan et al. (2009) compared the results obtained from spontaneous oscillations using three estimates of transfer function (both parametric and non-parametric) and found that there was no significant difference between any of the methods.

The effects of data loss (for example, those caused by blood pressure calibrations or TCD signal loss) have been shown still to yield accurate estimates of transfer

function. At most frequencies of interest (0.07–0.5 Hz), up to 5 s of data loss per 50 s can be tolerated. Accurate estimates can be made from time series as short as 1 min, although care has to be taken at higher frequencies, Deegan et al. (2011).

More recently, there has been interest in the sub-very low frequency band, Müller and Osterreich (2014). Phase angles were found to be significantly lower in the sVLF (0.005–0.02 Hz) band, compared to the VLF (0.02–0.07 Hz) band (gain and coherence were unaltered), with hypocapnia resulting in significant phase increases and gain and coherence decreases in all frequency ranges.

The most commonly cited measure calculated from transfer function analysis is the phase shift at 0.1 Hz. This is for two main reasons: firstly, that there is normally a high power in both time series at this frequency, making the estimate robust; and secondly, that this is where the phase angle is large, thus making impaired autoregulation easier to detect. This phase angle has been shown significantly to increase in hypocapnia and significantly to decrease in hypercapnia, see for example Birch et al. (1995).

4.2.2 Multivariate Analysis

It was shown in the early transfer function analysis studies that the gain, phase and coherence were all affected by blood gas levels, particularly changes in CO_2. As an alternative to simply quantifying the effects of blood gas levels on the transfer function, some studies have attempted explicitly to model the multivariate nature of the relationship.

The multivariate transfer function relationship between ABP, end-tidal CO_2 and O_2, and CBFV was calculated by Peng et al. (2008) amongst others. The resulting multivariate coherence was found to be significantly higher in the frequency range below 0.04 Hz; likewise the multivariate gain was found to be significantly higher in this range, showing how the low univariate coherence at low frequencies is due to the effects of variability in blood gas levels.

It should also be noted that one study has included cerebrovascular resistance (defined as ABP/CBFV) as a second variable, Panerai et al. (2006). The resulting multiple-coherence was found to be significantly higher, although the threshold for significance is also higher; the validity of using this derived measure as an independent measure does also need careful consideration.

4.3 Non-stationary Analysis

All of the analysis above has considered autoregulation to be a linear and stationary mechanism. More recently, there has been interest in investigating the time-varying nature of autoregulation, both to understand better the nature of autoregulation and to be able to track improvement or deterioration over time. This is most often done

by assessing the relationship between the time series over short periods and using a sliding window to quantify changes in this relationship. The length of the window is set by a compromise between time and frequency resolution, since the Gabor limit sets the maximum localization that can be achieved.

The review by Panerai (2014) set out the techniques that have been proposed for non-stationary analysis; these include ARMA models with sliding windows, recursive least-squares, Laguerre-Volterra networks, wavelet phase synchronization and multimodal analysis. It was concluded that "one key priority for future work is the development and validation of multivariate time-varying techniques to minimise the influence to the many co-variates which contribute to … non-stationarity."

Time-varying filters have been used by Liu et al. (2010), who used an adaptive filter to measure the non-stationary ABP/CBFV phase, noting that the changes in autoregulation during transient increases in CO_2 were not symmetrical, and by Aoi et al. (2011), who used an ensemble Kalman filter to estimate the parameters of a non-linear mathematical model of cerebral autoregulation. The Wigner-Ville distribution was used by Noack et al. (2007) to calculate an instantaneous transfer function in the low frequency band.

A **least squares** technique was used by Panerai et al. (2000) to determine the coefficients of Finite Impulse Response (FIR) filters between both end-tidal CO_2 and ABP and CBFV. The fluctuations in end-tidal CO_2 were found to explain a proportion of the CBFV variability; however, determination of the FIR filters required long sections of data and the recovered dynamics were the time-averaged values for the whole data section, thus averaging out any temporal changes in their behaviour. Liu et al. (2014) then proposed a new method that provides a time-varying multivariate model to quantify the phase difference between ABP and CBFV continuously, compensating for dynamic changes in $PaCO_2$.

Wavelet phase synchronization was proposed by Latka et al. (2005) as a measure of temporal variability in phase angle. Wavelets are used to calculate the instantaneous phase angle and then synchronization index is calculated as:

$$\gamma(a) = \langle \sin \Delta\phi \rangle^2 + \langle \cos \Delta\phi \rangle^2 \tag{4.13}$$

where the phase angle is transformed before being averaged (denoted by $\langle\rangle$). This lies in the range 0–1, with 0 denoting a uniform phase distribution and 1 time-invariant phase angle. The use of wavelets at different scales, a, means that synchronization index is a function of scale (or frequency). The resulting distribution in healthy normal subjects, Fig. 4.5, exhibits two distinct peaks, one at 0.11 Hz and one at 0.33 Hz, when using the complex Morlet wavelet. In the very low frequency range, variability is shown to be an inherent property of intact autoregulation. It was noted, however, that synchronization index is only valid when coherence is high. A recent review of wavelet methods in the context of NIRS monitoring of autoregulation, Addison (2015), has highlighted the importance of monitoring phase dynamics in real time.

Multimodal analysis is based on the use of empirical mode decomposition, which breaks down the signal into intrinsic mode functions, Huang et al. (1998).

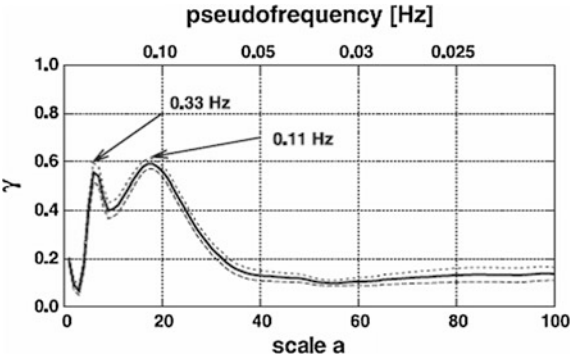

Fig. 4.5 Synchronization index as a function of scale, reproduced with permission from Latka et al. (2005)

These modes are simple oscillatory modes but can exhibit time-varying amplitude and frequency, hence providing a more flexible basis set. The Hilbert transformation can then be used to calculate time-varying phase in each mode. This has been shown to give significantly different phase angles between normotensive, hypertensive, and minor stroke subjects, being significantly smaller in the hypertensive and minor stroke groups than in the normotensive group, Novak et al. (2004).

Multi-modal analysis was then later used by Hu et al. (2008) in a number of subject groups, showing that phase shifts were reduced in hypertensive and stroke patients when using the Valsalva manoeuvre; also the phase shifts measured during baseline and the VM were highly correlated. In TBI patients, the results obtained using ABP and CPP were highly correlated. They found that MMPF had better repeatability than ARI, although it has been shown by Gommer et al. (2010) that both multi-modal and transfer function analysis techniques exhibited poor reproducibility in the context of whether the pre-processing, spectral estimation technique, time of day or nature of breathing affected the results.

It is clear that there is interesting behaviour that can be revealed by the use of non-stationary methods, particularly when used in a multivariate technique; however, the intrinsic non-stationarity of cerebral autoregulation remains still to be quantified in a rigorous manner and the likely physiological meaning of this is still to be resolved.

4.4 Non-linear Analysis

In a similar manner to non-stationary models of autoregulation, there has also been interest in assessing the non-linear behaviour of autoregulation. Evidence for this has been cited by Giller and Müller (2003), Bellapart and Fraser (2009). This interest has been partly driven by the low values of coherence found at very low frequencies. The greatest difficulty in this analysis, however, is the difficulty of interpreting the results (since there is no unique representation of a non-linear system) and in understanding the physiological significance. It should be noted that non-linear time series analysis

is a very considerable subject and only those studies that have been performed that are directly relevant to cerebral autoregulation will be considered here. For a much more comprehensive overview, the book by Kantz and Schreiber (2004) is recommended.

The first study into the non-linear relationship between ABP and CBFV was carried out by Panerai et al. (1999b), where the authors first compared transfer function analysis, ARI and the linear Volterra-Wiener kernel, all of which were found to give equivalent results. They then added in the quadratic kernel in the Wiener-Laguerre representation and found that this substantially improved the model accuracy on the training data set; however, there was little change when evaluating the step response and the fitting to the test data set was worse than all of the linear methods. This last result was found to be the case for both spontaneous fluctuations and the thigh cuff test.

Mitsis et al. (2002) used Laguerre-Volterra networks with both fast and slow dynamics to model cerebral autoregulation. The fast component is considerably larger than the slow component and the resulting IR shows undershoot with a return to baseline, in good agreement with Panerai et al. (1999b) although with slight differences in the timing and magnitude of this undershoot. Autoregulation was found to be both non-linear and non-stationary, with considerable variability in specific frequency bands below 0.1 Hz. The nonlinearity was prominent in the low and middle frequency ranges, where there was also reduced gain.

The effects of end-tidal CO_2 were then included by Mitsis et al. (2004), Panerai et al. (2004). The former found that above 0.04 Hz, ABP explains most of the variability, but that below this, end-tidal CO_2 fluctuations and non-linear interactions between ABP and end-tidal CO_2 have a considerable influence. Non-linear behaviour is mostly present in the very low frequency range and in the end-tidal CO_2-CBFV coupling, with this latter coupling also showing significant non-stationarity. The latter study compared transfer function analysis, ARI, the Wiener-Laguerre representation and a time lagged recurrent neural network; they were found to produce similar results. The authors also estimated both the positive and the negative impulse responses, concluding that the differences between the two were indicative of non-linear behaviour. A later study by Kostoglou et al. (2014) showed a decrease in phase lead during hypercapnia and found that the use of a multivariate input reduced the non-stationarity of the estimate of autoregulation.

The effects of changes in ABP were assessed, using LBNP testing, by Mitsis et al. (2006), including end-tidal CO_2 dynamics. The magnitude of both the linear and the non-linear ABP-CBFV kernels increased significantly at high LBNP levels, whilst the magnitude of the end-tidal CO_2-CBFV kernels decreased during LBNP testing. End-tidal CO_2 contributed a large proportion of the variability in CBFV at lower frequencies, particularly at high LBNP levels.

Alternative non-linear techniques have also been proposed in the context of cerebral autoregulation. Projection pursuit regression (PPR) was used by Taylor et al. (2014) in conjunction with oscillatory LBNP testing to quantify the non-linear

relationship between ABP and CBFV. Oscillatory LBNP was found to produce larger fluctuations in ABP, but smaller fluctuations in CBFV, as the frequency of oscillations decreased. The relationship between ABP and CBFV was found to be more non-linear at lower frequencies, with the plateau region disappearing at frequencies above 0.05 Hz. It should be noted that the plateau region, even at the smallest frequency studied here, was found to be very small, of order 10 mmHg.

The study by Katura et al. (2006) was based on the use of transfer entropy, which is a time series measure that calculates non-linear coupling. It also provides a quantification of the direction of the coupling, using conditional probability density functions. The authors quantified (although the methodology is not clearly explained) the different two-way couplings between ABP, HR and O2Hb, and concluded that the contribution of low frequency oscillations in HR and ABP to low frequency oscillations in O2Hb is approximately 10 %. This suggests that low frequency variability can primarily be attributed to regulatory mechanisms within the brain, rather than global systemic regulation processes.

There are many other techniques, such as entrainment, whereby phase locking is observed between two oscillations at frequencies that are harmonics of each other, Zernikow et al. (1994), and bivariate autoregressive spectral coherence, Riera et al. (2014). The primary difficulty with many of these methods, however, is the need for very considerable amounts of data, which is challenging in a clinical context.

The non-linearity of cerebral autoregulation has thus been demonstrated at low frequencies by a number of studies; however, the requirement for large data sets and the difficulties involved in interpreting and presenting the results have meant that these techniques have yet to make a substantive impact on the field.

4.5 Conclusions

It can be seen from the review above that there is a very wide choice of analysis techniques available to quantify cerebral autoregulation. This rich variety has the potential to provide very detailed understanding of autoregulation, but it also means that the field is highly disparate with different groups pursuing different techniques and even groups supposedly using the same tools implementing them in different ways, Meel-van den Abeelen et al. (2014b). The review by Panerai (2009) showed that in some pathologies there is good agreement between results (for example head injury and carotid artery disease), but that this is not the case in all pathological conditions (for example syncopal patients). The difficulties in coming to conclusions about a particular pathophysiology are clear and this remains an open challenge to the field, particularly given the need to have clear, repeatable and reproducible techniques for clinical applications, as will now be examined.

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Chapter 5
Clinical Conditions

A key driver for research in cerebral autoregulation is the desire to understand how it is involved in pathophysiological conditions. There is the important question of whether measuring cerebral autoregulation, either at the bedside or during surgery, has clinical value and, if so, how such measurements can be potentially incorporated within decisions about therapy for particular patient groups. It is noticeable how recent studies have investigated a very wide range of clinical pathologies and how much more is known about these in the context of cerebral autoregulation than even just a few years ago. In this chapter, a wide range of clinical contexts will be examined, both 'normal' physiological conditions and pathophysiological conditions.

Before beginning, it is worth noting that the clinical context in which autoregulation is considered is still uniformly only one of measurement, rather than treatment, i.e. autoregulation is tested for impairment in different conditions, but it is not directly treated. Autoregulation remains essentially a potential symptom of disease or altered physiology, but it is not one that can directly be adjusted, rather other therapies aim to improve the condition with the potential side benefit being that of improved autoregulation. This will be considered in more detail in the final chapter.

5.1 Static Autoregulation

The earliest studies into cerebral autoregulation were all performed on a static basis, examining the relationship between steady state ABP and CBF. The paper by Lassen (1959) was the first to propose a plateau-style relationship, as shown in Fig. 1 in the Introduction, where CBF remains constant for changes in ABP in the range approximately 60–150 mmHg. With the minor modification that the slope is not absolutely flat, this has long been accepted as the fundamental basis for autoregulation, although it has been widely pointed out that this curve was based on a very selective set of data points from only 7 different studies, Numan et al. (2014). It is also worth noting that no upper limit for autoregulation was seen by Lassen,

S. Payne, *Cerebral Autoregulation*, SpringerBriefs in Bioengineering,
DOI 10.1007/978-3-319-31784-7_5

despite the very high upper range for ABP, and that studies 3–11 were astonishingly consistent in estimates of CBF, even though CBF was highly challenging to measure at the time. Finally, it should be noted, Numan et al. (2014) that this curve attempts to represent a population average autoregulation curve, which is likely to prove difficult given the differences between subjects in mean ABP and the resultant re-setting of baseline conditions.

The sources used in Lassen's study were re-analysed by Heistad and Kontos (1983), who excluded those subjects with pre-medication that is now known directly to affect autoregulation. The results then showed a sensitivity of CBF to changes in ABP of 0.2–0.7 %/mmHg for decreases in ABP and a sensitivity of 0.7 %/mmHg for increases in ABP, which is a substantial difference from a flat plateau. Even these gradient values are smaller than those reported by Lucas et al. (2010), recorded using TCD rather than Xe133, who found that the gradient was of order 0.82 %/mmHg for both increases and decreases in ABP, when induced using pharmacological agents. This was also found to be highly variable even amongst healthy subjects, within a range of 0.50–1.74 %/mmHg, and no deviation from this linear behaviour was observed, even when ABP was changed by nearly ±60 %.

The need to control for changes in $PaCO_2$ was emphasised by Numan et al. (2014) who performed a meta-analysis of static autoregulation studies. Despite the importance of autoregulation, only 40 studies were found in the literature and the resulting plot for CBF as a function of mean ABP is shown in Fig. 5.1. The resulting gradients were found to be 0.82 ± 0.77 and 0.21 ± 0.47 %/% for decreases and increases in ABP respectively. After correction for changes in $PaCO_2$, the gradients were found to be 0.64 ± 1.16 and 0.39 ± 0.30 %/% respectively.

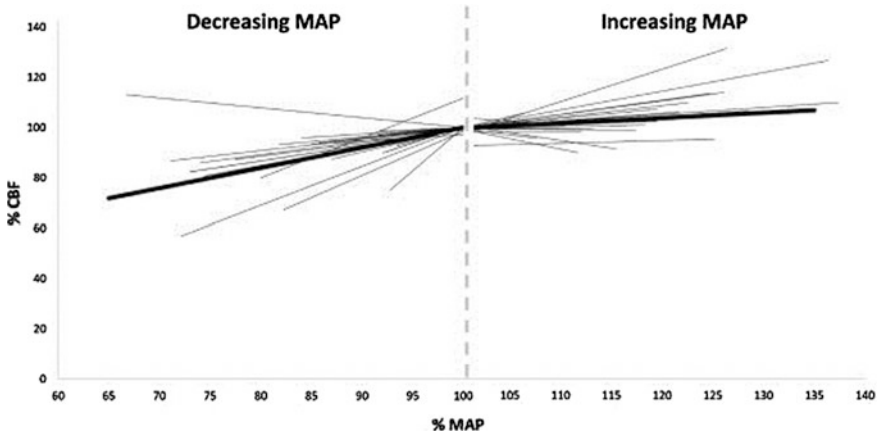

Fig. 5.1 Static relationship between changes in CBF and ABP, reproduced with permission from Numan et al. (2014)

It should of course be noted that this study is still based on the response of a number of populations and that a full study within individual subjects under the correct experimental conditions remains to be performed. Although some studies have examined the response in individual patients across a wide range of ABP, for example Schmidt et al. (1990), the data remain sparse. It is of course possible that the aggregation of multiple individual autoregulation curves, each with its own plateau region, results in a trend similar to that shown in Fig. 5.1: however, this remains to be investigated fully.

It is also worth noting at this point that all mathematical models of autoregulation are validated against the autoregulation curve obtained in a relatively small number of studies in a variety of animals; this is because there is as yet no fully established data set in humans that can be used for validation.

5.2 Ageing/Fitness/Exercise

The influence of ageing has been studied right across the age spectrum, both in the elderly and very elderly, and the young. There is widespread agreement that adult cerebral autoregulation is essentially maintained with age, even though this is accompanied by a number of changes, primarily the decrease in baseline CBFV found in the elderly. However, more recent studies have shown some interesting variations in these results in some subject groups.

The first studies, Carey et al. (2000, 2003), into autoregulation in the resting state in elderly subjects found that cerebral autoregulation (measured using ARI) is unaffected by physiological ageing, despite baroreceptor sensitivity and CBFV both reducing in elderly subjects. This was confirmed using Mx in subjects up to 70 years, Yam et al. (2005) and the review by van Beek et al. (2008), which found eight studies with subjects >75 years, and which concluded that, independent of the method used, cerebral autoregulation was maintained in the very elderly.

Hypertension has been shown to have no significant difference in either static or dynamic autoregulation in middle aged and older people, Eames et al. (2003). The response to orthostatic hypotension is preserved in healthy elderly subjects, Sorond et al. (2005), although the PCA territory appears to be more vulnerable to reduced perfusion during orthostatic stress in elderly subjects. Likewise, even when taking part in postural manoeuvres, there is no change in either cerebral autoregulation or cerebrovascular reactivity with age, even up to the very elderly, Oudegeest-Sander et al. (2014).

However, despite these conclusions, some studies have found some more subtle differences. It has been shown that when considering a group of individual healthy subjects, autoregulation (measured using ARI) was found to reduce, with an increase in coherence at 0.05 Hz, over a 10 year period, Brodie et al. (2009). A difference in gain with age has also been found by Ortega-Gutierrez et al. (2014) in healthy subjects. The response to the sit-stand manoeuvre was found to be different in the young and the elderly at the heart beat frequency (but not other frequencies), Narayanan et al. (2001). Autoregulation has been found to be better,

and vascular reactivity higher, in female subjects compared to male subjects over the age of 70 years, Deegan et al. (2009). Other gender-based differences have been found: women exhibit higher coherence and gain in the frequency bands 0.03–0.10 and 0.22–0.31 Hz when supine, whereas men exhibit higher coherence during tilt in the frequency band 0.05–0.26 Hz, Wang et al. (2005).

Wavelet phase coherence for ABP-O2Hb has been found to be different in healthy elderly subjects in certain frequency bands from values obtained in young healthy subjects; for example, in the sit to stand posture change, the wavelet phase coherence is lower in the 0.05–0.15 Hz frequency band in elderly subjects. However, this does not necessarily indicate impaired autoregulation in elderly subjects, since baseline flow values are very different, Gao et al. (2015).

In children, the evidence base is much smaller. Although no age-related changes in autoregulation were found between children during sevoflurane anaesthesia and adults, using four age groups from under 2 years old up to 14 years old, Vavilala et al. (2003a), ARI has been shown to be lower in adolescents (12–17 years) than in adults, when measured using the thigh cuff test, Vavilala et al. (2002). No differences have been found in the lower limit of autoregulation in healthy children related to age, although older children have a higher lower limit reserve (LLR = MAP-LLA) and autoregulatory reserve (ARR = LLR/MAP), Vavilala et al. (2003b).

The effects of exercise and fitness on autoregulation have also been investigated in both young and elderly subjects. In healthy young adults, progressive physical exercise has no impact on autoregulation, despite increases in heart rate, ABP and CO_2, Brys et al. (2003). However, exhaustive exercise results in a temporary decrease in phase angle in healthy subjects, Ogoh et al. (2005), and in athletes, Koch et al. (2005). During hypoxic exercise in healthy subjects, low frequency phase is reduced, indicating impaired autoregulation, even though CBFV is maintained and there is marked hypocapnia. The impairment seems to more than compensate for the effects of hypocapnia, Ainslie et al. (2007a). Intense exercise has been shown to increase BBB permeability, with no associated damage, following a free-radical-mediated autoregulation impairment, Bailey et al. (2011).

In elderly subjects, cerebral autoregulation is not different between those who have engaged in lifelong exercise and those who are healthy sedentary subjects, despite baroreflex gain being more than doubled in the active group, Aengevaeren et al. (1985). This is also the case in sedentary and exercising young healthy subjects, Jeong et al. (2014), tested using head-down-tilt bed rest. However, although RoR was found to be the same in normal subjects and endurance-trained individuals, the onset of autoregulation was found to be delayed in endurance-trained individuals, Lind-Holst et al. (2011).

Finally, it has been shown that there is a significant decrease in ARI between evening and morning, likewise a significant drop in cerebrovascular reactivity, suggesting one possible partial cause for the increased risk of cardiovascular events at this time, Ainslie et al. (2007b).

Overall, it appears that autoregulation is well maintained with ageing, despite some subtleties, and in response to postural changes. There does appear to be some development of autoregulation in children, although the evidence for this is much

less clear. Fitness levels seem to have no impact on autoregulation, even in the elderly. Exercise results in impaired autoregulation only at extreme levels.

5.3 Pregnancy

Apart from a single early case report by Oehm et al. (2003), studies into cerebral autoregulation have only been performed very recently. The single case study into a woman with postpartum preeclampsia showed that phase angle was severely decreased, indicating impaired autoregulation. Despite this sample size of one, this finding has been reproduced in larger studies by other authors.

Women with preeclampsia exhibit impaired cerebral autoregulation, as shown by a reduction in ARI, with no correlation being found between ARI and ABP. It was suggested that this might explain why eclampsia can occur even without increases in blood pressure, van Veen et al. (2013). The same impairment in autoregulation was also found by van Veen et al. (2015a), who showed that ARI is reduced in preeclampsia and in chronic hypertension, but not in gestational hypertension, in pregnant women at rest. In fact, phase (but not gain) has been found to be significantly higher in pregnant (25–28 weeks) women, compared to normal subjects, Janzarik et al. (2014).

ARI is lower in women with chronic hypertension who go on to experience preeclampsia, compared to those who do not; this is not the case for women with gestational hypertension or control subjects who went on to experience preeclampsia. It is not yet clear whether or not the decrease in ARI is due to pre-existing conditions, van Veen et al. (2015a). A history of preeclampsia during a previous pregnancy has been found to be associated with lower phase in both the MCA and the PCA, Janzarik et al. (2014).

Cerebral autoregulation has been found not to be impaired in pregnant women who have non-vasculopathic diabetes or who are overweight. The increased risk of preeclampsia in these cohorts is thus not associated with impaired cerebral autoregulation, van Veen et al. (2015b). It is clear that autoregulation can be impaired in pregnant women and that this can provide a useful marker of preeclampsia, although there are other markers for preeclampsia, which is clearly a multi-factorial condition.

5.4 Neonates

It is noticeable that this is the area of autoregulation where NIRS has been the most widely used. As discussed in Chap. 2, this opens up the possibility of gaining a substantial amount of information, but does make the interpretation of whether or not autoregulation is affected much more complicated. In particular, the conclusion that any changes seen in optically measured parameters are directly assignable to

changes in autoregulation status needs to be carefully justified, particularly when using advanced time series analysis techniques.

For example, the study by Riera et al. (2014) that used bivariate autoregressive spectral coherence between ABP and TOI was commented upon by Greisen (2014), who pointed out that the use of oxygenation index, rather than CBFV, needs care in its interpretation, particularly given the choice of analysis technique, even though TOI has been shown to reflect changes in CBF, Caicedo et al. (2012). Likewise Hbdiff and TOI have been shown to give very similar results on preterm infants, de Smet et al. (2009). The need for long recordings with this analysis method was commented on by Greisen (2014) and a reliable detection of cerebral autoregulation using NIRS to discriminate between preterm infants has been shown to take of the order of a few hours, Hahn et al. (2010).

It has been shown that neurologically healthy term infants have preserved autoregulation, see for example Boylan et al. (2000). Studies have thus primarily focussed on the behaviour in preterm neonates and those at higher risk; likewise the effects of drugs administered both during pregnancy and post-birth have also been investigated.

One of the first studies into preterm neonates, Zernikow et al. (1994), suggested that cerebral autoregulation might be a non-linear control system, based on the entrainment of frequency components. This study was based on the use of TCD, as was the study by Panerai et al. (1995), who suggested that coherent averaging of the CBFV response to ABP could be helpful in classifying preterm neonates. They later showed that in neonates, normal autoregulation was associated with significantly smaller values of coherence in the frequency ranges 0.02–0.10 and 0.33–0.49 Hz, also showing a significantly more positive phase response and a significantly smaller amplitude in the frequency range 0.25–0.43 Hz, Panerai et al. (1998). Similarly, the critical closing pressure, as measured using TCD, has been suggested as having the potential to differentiate between intact and impaired autoregulation in preterm neonates, Michel et al. (1995).

Autoregulation has been shown to be impaired in high-risk (of neurological injury) term and preterm neonates as well as in preterm control infants, Boylan et al. (2000). A significant relationship between autoregulation strength and gestational age (but not with $PaCO_2$ or postnatal age) in a group of 62 healthy term and preterm neonates has also been shown, Verma et al. (2000).

Menke et al. (1997) investigated cerebral autoregulation in high risk preterm infants of 25–32 gestational weeks. Spectral analysis found a low frequency phase shift between CBFV and MBP oscillations that was about 0° at 24 h after birth, increasing significantly to 55° at 96 h. The authors suggested that this indicated a perinatal depression of autonomic nervous centres, with this initially low phase shift potentially indicating impaired autoregulation.

Kaiser et al. (2005) examined static autoregulation in very low birth weight infants. They found that with $PaCO_2$ in the range 30–40 mmHg, the slope of the autoregulation curve was not statistically significantly different from zero, but that autoregulation was lost as $PaCO_2$ increased above this range. They thus cautioned against the use of permissive hypercapnia, since this could make the brain more vulnerable to injury.

More recent studies have focussed on the use of NIRS to assess cerebral autoregulation in neonates, see for example Caicedo et al. (2011a), Eriksen et al. (2015). It has been shown that there are few differences between different NIRS metrics, indicating that a range of such metrics can be used to assess autoregulation, Caicedo et al. (2011b), although interpretation of any of these metrics needs to be done with care. A critical score value for coherence has been proposed to separate infants with impaired autoregulation from those with normal autoregulation, de Smet et al. (2010).

NIRS has been used to measure coherence and gain between MAP and cerebral oxygenation index in the first day after birth for preterm infants. It was suggested that the impairment of cerebral autoregulation increased with decreasing MAP (although this metric is not yet standard for quantifying impaired autoregulation); however, no significant relationship was found between either MAP or autoregulation and intraventricular haemorrhage or neonatal mortality, Hahn et al. (2012). A 12 channel NIRS was then used on six infants on life support (ECMO) to show that ABP-O2Hb WCC increases with decreasing ECMO flow; the use of multiple channels enables regional variations in dynamic cerebral autoregulation to be assessed, Papademetriou et al. (2012).

The use of labetalol for the treatment of hypertensive disorders in pregnant mothers has been shown to cause impaired cerebral autoregulation, measured by higher gain, in neonates and lower pulse pressure values in the first day after birth, this effect disappearing by day three, Caicedo et al. (2013). This has been shown to be due to vasodilation, Caicedo et al. (2014).

Conversely, the use of indomethacin, when prenatally administered for the treatment of fever, pain, stiffness and swelling, has no effect on cerebral autoregulation in new-born infants, Baerts et al. (2013). Indeed cerebral autoregulation was better preserved in very low birth weight preterm infants after indomethacin treatment of a haemodynamically significant patent ductus arteriosus when compared with surgical ligation, Chock et al. (2012). Dopamine therapy in preterm infants has been shown to be associated with a lower value of CO_x, although it is not known whether or not dopamine directly affects cerebral autoregulation, Eriksen et al. (2014).

Autoregulation, which is normal in healthy term neonates, is thus impaired in a number of different conditions in neonates. This impairment is related to gestational age and other neurological conditions and can be affected in the period shortly after birth by the use of treatments during pregnancy.

5.5 Altitude

It is now well known that high altitude substantially affects cerebral autoregulation. The first major study to investigate the effects of altitude compared 10 subjects at sea level and at 4243 m altitude with 9 Sherpas at the same altitude. All Sherpas and the majority of the other subjects showed impaired autoregulation, with

considerable variability amongst the other subjects, Jansen et al. (2000). A follow-up study compared the effects of different altitude, with subjects living above 4,243 m showing almost entirely impaired autoregulation, whereas at an altitude of 3,440 m and below autoregulation remained functional. There is thus a transitional region, over the course of which SaO_2 drops from around 93 % to around 88 %, Jansen et al. (2007). At higher altitude, autoregulation can be improved or restored when oxygen is administered, Jansen et al. (2007), or during acute hyperoxia, Ainslie et al. (2008).

Cochand et al. (2011) found that acute mountain sickness scores increased markedly at high-altitude and that inverse relationships were found between sea-level ARI scores and high-altitude induced increases in the Lake Louise and Environmental Symptoms Cerebral Symptoms scores. They concluded that a lower baseline ARI, measured using recovery from transiently induced hypotension, "may be considered a potential risk factor for AMS". However, autoregulation has not been found to be associated with acute mountain sickness (AMS) symptoms, Subudhi et al. (2010), Subudhi et al. (2015), suggesting that changes in cerebral autoregulation are related to hypoxia rather than AMS, Subudhi et al. (2014).

Acclimatization has been found not to affect the impairment in autoregulation, Subudhi et al. (2014), where autoregulation was found to be impaired on arrival at altitude and after 16 days. This has also been shown to be the case after 1 month, Iwasaki et al. (2011), similarly to acute hypoxia at sea level.

One recent study has suggested that the cerebral vasculature maintains strength in terms of regulation of small changes (since transfer function analysis showed no change at altitude) but not in terms of larger changes (since the thigh cuff test showed a decrease in ARI at altitude), Subudhi et al. (2015). This still needs further investigation, however, since other studies have shown impairment using transfer function analysis, for example Ainslie et al. (2008).

Finally, one extreme study investigated the response of healthy volunteers in a hypobaric chamber up to the altitude of Mount Everest. The transient hyperaemic response at 8,000 m was found to be depressed, possibly indicating impaired autoregulation, although the response in the small cohort was found to be quite variable, Ter Minassian et al. (2001).

5.6 Diabetes

The evidence surrounding autoregulation in diabetes is complex, partly because diabetes is often found in subjects with other pathologies. The two types of diabetes, a group of diseases where blood sugar levels are elevated, are known as Type 1 and Type 2. Type 1 is caused by insufficient insulin production in the pancreas, whereas Type 2 is caused by cells failing to respond to insulin, with a lack of insulin also resulting sometimes. Type 2 is by far the more common. If diabetes is left untreated diabetic ketoacidosis can develop, mostly in Type 1 diabetes. Diabetic

autonomic neuropathy is the most common complication of diabetes, leading to vasomotor and cardiovagal dysfunction.

Studies into **Type 1 diabetes** (T1D) can be divided into adults and children. The only study into adults with T1D found that there is an association between autonomic neuropathy and impaired cerebral autoregulation (measured using Mx) and that the magnitude of this impairment increases with the severity of cardiovascular autonomic neuropathy, Nasr et al. (2011).

In children with T1D, cerebral autoregulation (measured using ARI) has been found to be impaired during diabetic ketoacidosis, Roberts et al. (2006), Ma et al. (2014), although this effect reduces over time; children with just T1D have intact cerebral autoregulation, Ma et al. (2014). It has been suggested that cerebral oedema in diabetic ketoacidosis might result in a temporary loss of cerebral autoregulation, providing for a paradoxical increase in CBF and the development of vasogenic cerebral oedema, Roberts et al. (2006).

Studies into **Type 2 diabetes** have mostly concluded that cerebral autoregulation is impaired. Multi-modal analysis has showed that specific phase shifts were reduced over a wide range of frequencies in patients with T2D, Hu et al. (2008). The phase shift at 0.1 Hz has been shown to be significantly reduced in patients with T2D, although with no corresponding change in gain, Brown et al. (2008). RoR has also been shown to be reduced in patients with T2D, both at baseline and during low-intensity isometric handgrip, with the impairment larger during the handgrip exercise, Vianna et al. (2015). This could place such patients at greater risk for cerebral events during activity. The only contrary study that showed that dynamic cerebral autoregulation is not impaired in patients with T2D was performed by Huq et al. (2012), although it was explicitly noted that the study was relatively poorly powered.

There have been two studies with **no differentiation** of diabetes type, both of which concluded that cerebral autoregulation is impaired in diabetes. Higher correlation dimension values between ABP and CBFV, lower values of Lyapunov exponent and higher values of Kolmogorov entropy were all found in diabetic subjects with autonomic neuropathy in comparison with normal subjects, Liau et al. (2008). They suggested that "impaired autoregulation would be more chaotic and less predictable" and that autoregulation "is more complicated in diabetics".

The response to standing was investigated in patients with either T1D or T2D, with and without cardiovascular autonomic neuropathy, the former group both with and without orthostatic hypotension. On standing, after 1 min CBFV dropped substantially in those patients with neuropathy and OH, did not change in those with neuropathy without hypotension or without neuropathy and dropped somewhat in controls, Mankovsky et al. (2003). The "instability" in those patients with diabetes and autonomic neuropathy with orthostatic hypotension "suggests impaired cerebral autoregulation".

The evidence base is thus reasonably strong for autoregulation in diabetes, indicating that there is a distinct impairment in T2D, but not in T1D unless accompanied by diabetic ketoacidosis, although it should be noted that the evidence base is somewhat weaker in T1D than in T2D.

5.7 Obstructive Sleep Apnoea Syndrome

There have only been a handful of studies into the effects of obstructive sleep apnoea syndrome on cerebral autoregulation. This syndrome is caused by an obstruction of the upper airway and the resulting pauses in breathing, lasting tens of seconds, are termed apnoeas. The resulting effects can include hypertension and lapses in attention and sleepiness during the day. The pauses in breathing result in periodic hypoxic-hypercapnic episodes and can cause hypoperfusion, Urbano et al. (2008), with some loss of grey matter in extreme chronic cases. A recent review of the impact of OSAS on brain function and cerebral autoregulation has been provided by Torabi-Nami et al. (2015).

Cerebral autoregulation has been shown to be impaired in OSAS subjects and this impairment to be correlated with the severity of OSAS, Nasr et al. (2009). Impairment was also found by Urbano et al. (2008), where it was additionally shown that baseline CBFV and SaO_2 are reduced, together with a lower rate of recovery to drops in blood pressure. As in altitude studies, it appears that the impairment is likely to be driven by hypoxia/hypercapnia.

This impairment in dynamic autoregulation has also been shown to occur in trained divers during maximal voluntary apnoea, Cross et al. (2014), as measured using phase synchronization during maximal apnoea. This effect has been shown to be related to the change in end-tidal CO_2 similar to the conclusion above.

5.8 Orthostatic Hypotension/Autonomic Failure

There are a number of conditions related to an impaired response to global challenges, which for convenience are considered together here. The most common of these is orthostatic (or postural) hypotension, which is the low blood pressure response to standing from sitting or lying down. In a similar manner, postural tachycardia syndrome is exhibited by an abnormal increase in heart rate upon standing. Although these are not in themselves serious, they can result in dizziness, syncope and falls, the last of which can result in injury. Vasovagal syncope is the result of fainting in response to some form of trigger.

Carotid sinus hypersensitivity is the syndrome where dizziness or syncope can result from carotid sinus baroreceptor stimulation. Autonomic neuropathy (or autonomic dysfunction) is a more serious condition where the nerves that control involuntary body functions are damaged. Pure autonomic failure is a degenerative disease of the autonomic nervous system. All of these conditions involve an impaired autonomic response in some way and are thus considered here together, although it should be noted that they do cover a wide spectrum of disease.

Orthostatic hypotension has been shown to result in a loss of autoregulation during head-up-tilt, Khandelwal et al. (2011), although a variable response has also been found in elderly patients, Wollner et al. (1979). Studies into subjects with

postural tachycardia syndrome have shown both that static and dynamic autoregulation are both impaired in response to head-up tilt, Ocon et al. (2009a), and that no differences in autoregulation are found in the same subject group in response to the same test, Schondorf et al. (2005), although the analysis methods were different between the two studies.

Autonomic nervous dysfunction has been found not to influence cerebral autoregulation, Ohashi et al. (1991), but to be impaired in subjects with **autonomic failure**, as measured through hypotension generated by reactive hyperaemia in the lower limbs, Lagi et al. (1994), and by head-up-tilt, Blaber et al. (1997). In this latter study, transfer function analysis showed that phase angle was unaltered, but that gain was higher, but decreasing with tilt angle.

In patients with **multiple system atrophy**, a greater phase angle in the 0.07–0.2 Hz range was found, but changes in the cerebrovascular resistance index on standing were unaltered, indicating preserved autoregulation, Pavy-Le Traon et al. (2006), in agreement with the study by Hetzel et al. (2003). In subjects with familial amyloidotic polyneuropathy (FAP), when tested using the Valsalva manoeuvre, the ARI response was smaller, indicating that the dynamics of autoregulation are impaired in this subject group, Castro et al. (2014).

Both static and dynamic cerebral autoregulation are impaired in patients with **malignant hypertension**, measured using during sodium nitroprusside and phase angle at 0.1 Hz respectively, Immink et al. (2004). In a subgroup of patients with **orthostatic intolerance**, but not orthostatic hypotension or postural tachycardia, although vasoconstriction in response to head-up tilt was the same as in normal subjects, relaxation both during and after tilt was impaired, suggesting that vasoconstriction was prolonged compared to normal subjects, Lin et al. (2011). The response in patients with symptoms of **orthostatic intolerance** has also been shown to be variable, with some exhibiting impaired autoregulation but others showing normal autoregulation, Schondorf et al. (2001a).

In young subjects with **vasovagal syncope**, about 2 min before fainting during head-up tilt, a rapid decrease in phase synchronisation is shown, this rising sharply and remaining high during both the faint time and the period shortly after return to supine. There appears thus to be a dynamic response to autoregulation, although how phase synchronisation relates to autoregulation is not entirely clear yet, Ocon et al. (2009b). In patients with **neurally mediated syncope**, when measured using transfer function analysis and head-up-tilt, autoregulation is preserved and unrelated to the degree of orthostatic intolerance, Schondorf et al. (2001b).

Franco Folino (2007) reviewed cerebral autoregulation in the context of **syncope**, both orthostatic and neutrally mediated. In some cases, particularly neutrally mediated syncope, autoregulation can be harmful, since it is implicated in a "paradox effect" that causes an increase in resistance in response to a drop in blood pressure (which normally causes a drop in resistance) and hence a very large drop in CBF. The involvement of cerebral vasoconstriction in neutrally mediated syncope also confirms its complexity and the need for further studies and clarification, Folino (2006). Static autoregulation is impaired in patients with posturally related syncope, when measured using head-up-tilting and LBNP in combination, Claydon et al. (2003).

Carotid sinus hypersensitivity (CSH), a condition associated with syncope, has been shown to be related to impaired cerebral autoregulation in symptomatic patients, but not in asymptomatic subjects (measured during LBNP), Tan et al. (2014). Cerebral autoregulation is also altered in patients with **carotid sinus syndrome**, measured using LBNP-induced hypotension, Parry et al. (2006).

A number of studies have investigated the response of healthy subjects in the context of syncope, in order to quantify the response in healthy subjects. For example, Zhang et al. (1998) used orthostatic stress in healthy subjects through ramped maximal LBNP to pre-syncope. Mean ABP remained relatively constant, whilst CBFV continuously decreased. At high levels of LBNP, both low and high frequency power in both pressure and velocity increased significantly, together with an increase in transfer function gain, showing that at high levels of LBNP autoregulation is impaired, potentially leading to the development of pre-syncope.

There is no significant difference between autoregulation as measured using TCD-measured CBFV in the MCA and VA, when measured during orthostatic stress to pre-syncope in healthy subjects, suggesting that this is not related to the posterior cerebral hypoperfusion indicated by symptoms of pre-syncope, Deegan et al. (2010). In head-down-tilt, there is no change in autoregulation, Cooke et al. (2003).

Autoregulation is also preserved during LBNP when combined with transient systemic hypotension, even though there is a decrease in CBFV associated with sustained central hypovolemia. It has been suggested that preserved autoregulation is key in preventing orthostatic syncope, Guo et al. (2006).

Finally in this section, the studies that have investigated the response to gravity are briefly presented. Cerebral autoregulation is maintained in astronauts and even shows signs of improvement (although this study was limited by the small sample size), Iwasaki et al. (2007). Autoregulation is also enhanced in subjects exposed to mild dehydration to mimic the effects of microgravity, agreeing with a previous study showing that autoregulation was enhanced during and after spaceflight, Ogawa et al. (2009). Acute exposure to hyper-gravity (+3 GX and +3 GZ) results in a leftward shift in the autoregulation curve, due either to vestibular activation (in GX) or to an adaptation to reduced CPP (in GZ), in healthy volunteers, Serrador et al. (2001).

In conclusion, it is clear that there is a tipping point in the response to orthostatic stress, even in healthy individuals, at which point autoregulation starts to become impaired. This tipping point can be reduced in patients with reduced capacity to cope with orthostatic stress and could indeed be considered to be a ‘safety valve’, whereby autoregulation will not maintain CBF in the face of other changes.

5.9 Stenosis

Stenosis, the abnormal narrowing of a vessel, which results in an increase in vessel resistance, is normally found in the carotid artery, since the division into the internal and external carotid arteries is a common focal point for the build-up of a plaque. This is a significant risk factor for ischaemic stroke, since any piece of plaque that

breaks off can lead to vessel blockage downstream. Reduced vasomotor reactivity is also a risk factor for both stroke and TIA in patients with either symptomatic or asymptomatic stenosis or occlusion, Diehl (2002).

A number of studies have thus investigated autoregulation in subjects with cerebral stenosis. Since the degree of stenosis varies widely, this is one of the key parameters in assessing autoregulation. The most common procedures for treatment of carotid stenosis are carotid endarterectomy (CEA) and carotid artery stenting (CAS), where care has to be taken post-treatment to avoid hyperperfusion, Kitagawa (2010) since impaired autoregulation could then result in potentially severe ischaemia.

Early studies showed that autoregulation was found to be significantly different in the ipsilateral MCA when compared to vessels with normal vascular reactivity, Tiecks et al. (1996). ARI was also found to be significantly lower in the MCA ipsilateral to a stenosed or occluded carotid artery and to non-stenosed carotid arteries, but to return to normal after endarterectomy, White and Markus (1997). Head-up-tilt showed that the resulting decrease in CBFV was significantly smaller in patients with unilateral carotid artery disease, suggesting that autoregulatory protection against ischaemia might limit vasoconstriction, Stoll et al. (1999).

A series of studies by Reinhard and colleagues then investigated autoregulation in this subject group. They showed that phase angle was significantly reduced on the affected side in patients with severe carotid artery stenosis, measured using the Valsalva manoeuvre and deep breathing, Reinhard et al. (2001a). The Müller manoeuvre in patients with severe unilateral carotid artery stenosis showed that the mROR, phase shift and CO_2 reactivity were all severely reduced on the ipsilateral side, with the reduction in mROR correlating significantly with a reduction in phase shift and CO_2 reactivity, Reinhard et al. (2001b).

The agreement between transfer function analysis results obtained using both spontaneous and deep-breathing induced oscillations in patients with severe carotid stenosis or occlusion has been found to be poor for phase and only moderate for gain; phase was found to be more reproducible when extracted from deep breathing, Reinhard et al. (2003a). The correlation indices Mx and Dx in patients with severe unilateral carotid stenosis are significantly higher in the ipsilateral hemisphere, increasing with degree of stenosis. Transfer function analysis results and CO_2 reactivity are significantly worse in patients with symptomatic stenosis or occlusion, Reinhard et al. (2003b). Impaired vascular reactivity has also been shown in a proportion of patients with high-grade (>70 %) asymptomatic carotid artery stenosis, Engelhardt et al. (2004), indicating that both autoregulation and reactivity measurements may be of use in stratifying patients.

The role of collateral circulation has been shown to be very important in this patient group. When patients were divided into three groups, dependent on spontaneously activated collaterals via primary and secondary pathways (types I and II) and functional stenosis in the anterior collateral pathways (type III), there was no sign of impaired autoregulation in type I, with reduced phase angle in type II and the most impairment in type III. Types II and III are also associated with higher proportions of clinically symptomatic patients. Dividing the patients by stenosis

level gave a less clear distinction, Reinhard et al. (2003c), although it has also been shown that autoregulation is maintained in patients with bilateral 75–89 % stenosis, but not in patients with bilateral critical stenosis or obstruction (90–100 %). Those patients with ipsilateral 90–100 % and contralateral 75–89 % had a significantly less severe reduction in phase shift on the ipsilateral side, Reinhard et al. (2003d).

Recanalization has been shown to restore autoregulation in patients with severe unilateral stenosis, Reinhard et al. (2004). Before recanalization, all correlation coefficient and transfer function parameters showed clearly impaired ipsilateral autoregulation compared to the contralateral side. After recanalization, phase, Dx and Mx all showed early normalization of autoregulation after both endarterectomy and stenting, with the improvement being highly significantly related to the degree of previous impairment. Follow-up showed no significant further change in autoregulation. It has also been shown that dynamic autoregulation only rarely improves over time in ICA occlusion, indicating that autoregulation is largely stable, without any temporary improvements that might allow for optimal times for surgery, Reinhard et al. (2011). Carotid stenting improves autoregulation, measured using aMx based on ABP, in the stenting side, but not in the contralateral side, in patients with both moderate and severe stenosis, Tang et al. (2008).

Other studies have investigated disease in other arteries, with the effects of stenosis in one vessel impacting autoregulation measured in a second vessel. Dynamic autoregulation is impaired to varying degrees in patients with severe bilateral VA disease, Haubrich et al. (2005). Dynamic autoregulation is impaired in patients with MCA stenosis, with low ARI values mostly seen in patients with higher degrees of stenosis and particularly in those with insufficient collateral compensation; after MCA angioplasty, there was a significant increase in ARI, Gong et al. (2006). RoR, phase and CVR are all significantly lower in patients with moderate (≥ 50 %) MCA stenosis and all three metrics are significantly correlated with the degree of stenosis, Chen et al. (2014).

Although there was no significant change in phase shift and gain between Basilar Artery (BA) stenosis subjects and controls in the MCA, phase angle decreased significantly in severe stenosis (≥ 70 % occlusion) subjects in the PCA and the gain in the PCA increased for moderate BA stenosis (50–69 % occlusion) subjects and decreased for severe BA stenosis, Gong et al. (2013).

ASL MRI has also been used to quantify spatial vascular reactivity, measuring changes in CBF in response to acetazolamide administration, in patients with symptomatic ICA stenosis. Reactivity was found to be lower in the symptomatic ICA flow territory than in the arteries of control subjects, with the reactivity in the relevant territory in patients with asymptomatic stenosis similar to that of the control subjects, Bokkers et al. (2010). Neurovascular coupling has also been found not to be affected in patients with (>50 %) PCA stenosis, Fritzsch et al. (2010).

More recently, spatial variations in autoregulation have been investigated through the use of multi-channel NIRS in this patient group to show significant side-to-side differences in phase angle between ABP and O2Hb at 0.1 Hz, Reinhard et al. (2014).

The link between baroreceptor sensitivity (BRS) and autoregulation in patients with carotid stenosis has been examined, Kitagawa (2010). In patients with severe carotid stenosis undergoing carotid endarterectomy, BRS is impaired but does not improve post-CEA, whereas autoregulation is impaired and improves post-CEA, independent of changes in CBFV, Mense et al. (2010). An inverse correlation between autoregulation and BRS has been shown in patients with atherosclerotic unilateral carotid stenosis or occlusion, and it has been proposed that this might be due to an increase in sympathetic activity, Nasr et al. (2014). It has thus been suggested that improvements in BRS need to be targeted in this subject group. The decrease in vasomotor reactivity in subjects with high-grade stenosis or ICA occlusion is associated with decreases in microstructural and functional connectivity of brain networks, which might be a mechanism whereby severe occlusion can lead to cognitive decline, Avirame et al. (2015).

In subjects with stenosis, the degree of stenosis and the collateral circulation thus both play an important role. Recanalization can restore autoregulation, but the role of the baroreceptors remains not fully understood.

5.10 Dementia

In comparison with other cerebrovascular diseases, there has been relatively little work examining cerebral autoregulation in patients with dementia. Likewise, the understanding of autoregulation in mild cognitive impairment (MCI) patients remains poor, although a better means of predicting the development of AD in MCI patients would be of considerable clinical value, particularly given an increasing prevalence of dementia in the adult population.

Although early animal models had suggested that autoregulation was impaired, early studies into patients with Alzheimer's disease (AD) seemed to show that autoregulation was not impaired, Claassen and Zhang (2011). Later studies have shown, however, that there are significant changes in cerebrovascular function. AD patients have been shown to have increased cerebrovascular resistance compared to both mild cognitive impairment (MCI) patients and controls, Gommer et al. (2012), although no significant differences in cerebral autoregulation parameters were found. They proposed that CVR might have predictive value in MCI patients developing AD, although this would need further validation.

In contrast, den Abeelen et al. (2014) did not find a significant increase in cerebrovascular resistance, as assessed using the sit-stand manoeuvre, in patients with mild to moderate AD; however, they did find a significantly larger relative increase in CBFV in response to standing, which was attributed to impaired autoregulation. Patients with MCI have been shown to have lower baseline cerebral TOI than control subjects, Tarumi et al. (2014), but no changes in transfer function gain or phase were found in these subjects. However, within the MCI patients, larger oscillations in cerebral TOI and a higher transfer function gain between TOI and CBFV were found to be associated with lower scores on delayed recall,

indicating that the severity of MCI did relate to changes in cerebrovascular function, even if this was not shown by cerebral autoregulation metrics.

The most recent study investigated non-demented older subjects and showed that reduced cerebral autoregulation (measured by phase angle at 0.1 Hz) is associated with increased amyloid deposition and increased white matter hyperintensity volume, the latter two also being positively associated with each other, Brickman et al. (2015).

There is thus strong evidence that there are changes in cerebrovascular function in both MCI and AD patients, with some correlations being found between these changes and clinical status; however, the evidence that there are changes in autoregulation is much weaker. These studies do open up the possibility of using cerebrovascular metrics as markers of progression and further studies in this population could prove highly valuable in improving understanding and developing clinical tools.

5.11 Anaesthetic and Other Drugs

The need to monitor patients undergoing surgery and to ensure continuous cerebral perfusion has meant that there has been interest in the effects of anaesthetic drugs on cerebral autoregulation, since any impairment will potentially make the brain more vulnerable to changes in ABP during the procedure. For example, one very early study in humans showed that morphine-nitrous oxide anaesthesia does not significantly affect cerebral autoregulation in normal subjects, Jobes et al. (1975). It has also been shown that static TCD measures are the most robust, Dagal and Lam (2009).

Using the thigh cuff test, isoflurane and desflurane have been shown to impair both static and dynamic autoregulation at 1.5 minimum alveolar concentration (MAC), but propofol does not affect autoregulation at any dose, Strebel et al. (1995). The addition of 50 % nitrous oxide to patients following a propofol infusion for anaesthesia had no additional effect on autoregulation, Harrison et al. (2002). Desflurane impairs autoregulation with almost total abolition at concentrations of 1.5 MAC, Bedforth et al. (2001). Autoregulation is maintained during 2.0 MAC sevoflurane anaesthesia, but not during 1.0 MAC equivalent, Endoh et al. (2001a). In healthy individuals autoregulation and CO_2 reactivity are both preserved under 0.5 MAC of sevoflurane and small-dose remifentanil, Rozet et al. (2006). In children, cerebral autoregulation is maintained when anesthetized with up to 1.5 MAC sevoflurane, Wong et al. (2006). Dynamic cerebral autoregulation is better preserved during sevoflurane than isoflurane anaesthesia in human subjects undergoing non-intracranial neurosurgical procedures, Summors et al. (1999).

The transient hyperaemic response and the phenylephrine response in subjects at 0.5 and 1.5 MAC desflurane were found to give the same response, Tibble et al. (2001). The use of propofol anaesthesia and sevoflurane anaesthesia resulted in a significant difference in the threshold of the $PaCO_2$ required to impair autoregulation significantly, McCulloch et al. (2000).

There have been relatively few studies into the role of other drugs on autoregulation, as summarised briefly here. Autoregulation is impaired in normal adult subjects during nicardipine-induced hypotension, as measured using dRoR, Endoh et al. (2000). Autoregulation is unaffected under the influence of either nitrogylcerin or prostaglandin E1, Endoh et al. (2001b). Dexmedetomidine causes an impairment in cerebral autoregulation, as measured using both RoR and transfer function analysis: since this is often used for patients with compromised circulation, it could further impair the cerebral response to decreases in blood pressure, Ogawa et al. (2008). Flumazenil has been found not to reverse the decrease in transfer function gain induced by midazolam, used for sedation, in healthy young males, Ogawa et al. (2015).

5.12 Cardiac Arrest and Surgery

Following on from the previous section, a substantial number of studies have been performed in patients undergoing **cardiopulmonary bypass** (CPB), since careful monitoring is required of such patients to ensure that the brain is sufficiently perfused continuously during the procedure. It has been suggested that the inclusion of cerebral autoregulation metrics in blood pressure management during CPB could help to improve patient outcome, Ono et al. (2014). For example, ABP going above the upper limit of autoregulation during CPB is associated with post-operative delirium, Hori et al. (2014).

Both static and dynamic autoregulation are maintained after mild hypothermic CPB, Preisman et al. (2005). During normothermic CPB, autoregulation (measured by gain, phase and ARI) is maintained in normocapnia and hypocapnia, but not in hypercapnia, Ševerdija et al. (2015a). In patients undergoing normothermic CPB, haemodilution down to a haematocrit of <28 % together with hypercapnia has also been found to decrease ARI (this was not found in normocapnia or hypocapnia), Ševerdija et al. (2015b). Cerebral autoregulation has also been shown to be better preserved when $PaCO_2$ was maintained at approximately 40 mmHg, Murkin et al. (1987) in this patient group.

It has been shown that 20 % of patients undergoing CPB showed impaired autoregulation. Multivariate logistic regression analysis showed that time-averaged cerebral oxygenation index during CPB, male gender, $PaCO_2$, CBFV and preoperative aspirin use were all independently associated with impaired autoregulation. Peri-operative stroke was found to occur more frequently in patients with impaired autoregulation, Ono et al. (2012). It has also been shown that apoE genotype does not affect static autoregulation, Ti et al. (2001), that diabetic patients lose cerebral autoregulation during CPB, Croughwell et al. (1990), and that there is no effect of age on the static autoregulation response in CPB patients, with changes in cognition not being associated with autoregulation, Newman et al. (1994).

NIRS has been used in a number of these studies, with autoregulation metrics measured using both TCD and NIRS being shown to be correlated and in good agreement in CPB patients, Ono et al. (2013). Patients undergoing both carotid artery endarterectomy (CEA) and cardiac surgery have been shown to have higher values of cerebral oxygenation index before surgery when compared to patients either with prior CEA or with stenosis, indicating a potential value of this metric in selecting patients for CEA and for personalised patient management during surgery, Hori et al. (2015a). Likewise, in patients undergoing cardiac surgery with CPB, those with stenosis/occlusion and normal autoregulation showed no increased risk of stroke, but those patients with stenosis/occlusion and exhausted autoregulatory reserve did show an increased risk of stroke, Schoof et al. (2007).

The limits of cerebral autoregulation have been investigated during CPB using both TCD and NIRS, Joshi et al. (2012). A wide range of values for the lower limit of autoregulation was found with estimation of this value proving difficult during CPB. A paradoxical response in cerebral oxygen saturation, whereby cerebral oxygen saturation goes up when ABP goes down, was found in some CPB patients with intact autoregulation, Moerman et al. (2015).

A few studies have been performed in the context of **cardiac arrest**. An early study, albeit with a small sample size, suggested that cerebral autoregulation is impaired in patients resuscitated after cardiac arrest, Nishizawa and Kudoh (1996). A similar study by Sundgreen et al. (2001) also found impaired or right-shifted autoregulation in a majority of this population. Autoregulation has been shown to be disturbed in approximately one third of post cardiac arrest patients during therapeutic hypothermia. Optimal ABP is higher in patients with disturbed autoregulation than in those with undisturbed autoregulation, calculated using cerebral oxygenation index: the percentage of time under the optimal (oxygenation index predicted) ABP was found to be a considerably better predictor of mortality than the percentage of time under any fixed MAP target, Ameloot et al. (2015). It has also been shown that autoregulation is significantly altered in the post-operative period after hypothermic circulatory arrest procedures, in operations for thoracic aorta repairs, Neri et al. (2004).

5.13 Stroke

Stroke is normally divided up into two sub-types: ischaemic and haemorrhagic. The former, which is much more common, is caused by a blockage in a supply vessel to the brain, resulting in tissue being starved of oxygen, whereas the latter is caused by the rupture of a blood vessel, resulting in a pooling of blood in the brain and a rise in ICP. Although survival rates are high, there are high levels of disability associated with stroke, requiring very substantial resources over long periods of time in recovery and adapted living.

Very early studies into autoregulation in stroke patients were performed in the 1970s, where it was shown that autoregulation is influenced by the autonomic

innervation of blood vessels, with both alpha-adrenergic and beta-adrenergic blockade being shown to play a role in stroke patients, Fujishima (1971), Meyer et al. (1973), Meyer et al. (1974). Impaired (static) autoregulation was found, with the ability of cerebral blood vessels to constrict being improved when CPP was increased, due to an increase in vasoconstrictor tone. A decrease in CPP resulted in either unchanging or worsening autoregulation, Meyer et al. (1974).

One of the challenges in assessing cerebral autoregulation in stroke subjects is the fact that brain tissue responds over many different time scales to the infarction, with some tissue responding in minutes and other tissue responding over hours and days, dependent upon the severity and duration of the ischaemia. This makes stroke subjects a highly heterogeneous population and the timing of the autoregulation assessment very important in comparing the response of subjects both within and across studies. This has led to some seemingly contradictory reports in the early literature, although the increased awareness of this and investigations into the temporal variations and spatial heterogeneity in stroke patients have helped to clear this up in more recently published studies.

5.13.1 Ischaemic Stroke

It is worth noting that even within this sub-category, there have been five sub-types of stroke identified (the TOAST classification): large-artery atherosclerosis; cardio-embolism; small-vessel occlusion; stroke of other determined aetiology; stroke of undetermined aetiology, Adams et al. (1993). The ischaemic stroke population is highly heterogeneous and this is likely to result in a variety of findings from studies without clearly stratified population sub-types.

Early studies into acute ischaemic stroke (AIS) found that dynamic but not static autoregulation is globally impaired in AIS patients within 96 h of onset, measured using ARI assessed by the hand grip and thigh cuff tests, Dawson et al. (2000), and that global dynamic autoregulation is impaired in AIS subjects, measured using ARI assessed by spontaneous transient pressor and depressor stimuli, Eames et al. (2002). No differences were found between hemispheres, although baroreceptor sensitivity (BRS) was found to be reduced. This impairment in dynamic (but not static) autoregulation was also found in a group of ischaemic stroke patients both within 96 h of onset and 7–14 days later, using ARI for dynamic and the thigh cuff test for static autoregulation. Changes were found in both contralateral and ipsilateral hemispheres and were not related to previous antihypertensive treatment, blood pressure, age or stroke type, Dawson et al. (2003). Impaired dynamic autoregulation has also been shown by different maximum correlation strengths, measured using cross-correlation between instantaneous ABP-CBFV phase angle, in post-stroke subjects, Chen et al. (2006).

Analysis of different sub-types of stroke has, however, shown differences in autoregulation. In patients with large MCA territory ischemic stroke, dynamic autoregulation was impaired in the affected hemisphere; however, in patients with

lacunar ischemic stroke, dynamic autoregulation was impaired in both hemispheres, measured using phase angle, Immink et al. (2005). In patients with lacunar stroke, phase angle and vascular reactivity have been shown to be independent, Gommer et al. (2008). In patients with large MCA territory stroke, differences in static autoregulation between ipsilateral and contralateral hemispheres have been shown, Schwarz et al. (2002).

Differences in outcome have also been related to changes in autoregulation post-stroke: autoregulation, as measured by Mx and phase angle, deteriorated during the first 5 days after AIS in subjects with poor outcome, with phase found to decrease more on the ipsilateral side than on the contralateral side, whereas in patients with good outcome, autoregulation was preserved after rtPA thrombolysis, Reinhard et al. (2008). In AIS patients treated with moderate hypothermia, where alpha-stat was used for pH maintenance, static autoregulation was found to be intact, Georgiadis et al. (2002).

Analysis of stroke severity has shown that in patients with mild stroke there appears to be no impairment of autoregulation, measured using ARI, in either hemisphere once covariates (including ipsilateral carotid stenosis) have been adjusted for, Atkins et al. (2010). This was also found when assessing Mx and transfer function analysis in a cohort of early minor MCA stroke patients, Reinhard et al. (2005), although nearly every patient completing this study had a good clinical outcome. Likewise, no reduction in ARI has been found in TIA patients, Atkins et al. (2010).

The review by Aries et al. (2010) found twenty-three studies measuring autoregulation studies with TCD in stroke subjects. Despite the difficulties involved in coming to conclusions given the limitations of the different studies, the review concluded that the impairment of autoregulation in even minor stroke was generally agreed in both hemispheres. Autoregulation worsened in the first 5 days post-stroke and then recovered over the following 5 months. Impaired autoregulation was associated with neurological deterioration, the need for de-compressive surgery and poor outcome.

Subsequent studies have examined the temporal variations in autoregulation in further detail, as well as looking at additional sub-types and the role of therapy. An increase in Mx, indicating worsening autoregulation, has been found between 48 h and 5–7 days after onset, to a greater degree on the affected side. More severe stroke was related to increased values of ipsilateral Mx and lower phase angle and hence increasingly impaired autoregulation and poorer clinical outcome. Impaired autoregulation has been found to worsen and to spread to the contralateral side in the days after stroke onset, Reinhard et al. (2012a). However, Saeed et al. (2013) found no difference between hemispheres in AIS patients, with ARI significantly reduced compared to age-matched and BP-matched controls and the greatest impairment being found in cortical ischaemic stroke patients. The reduced phase angle measured in patients with large-vessel ischemic stroke at 1.3 and 4.4 days after stroke disappears at 9.75 days post-stroke, Petersen et al. (2015).

In large-artery atherosclerosis stroke patients, autoregulation, measured using phase angle at 0.1 Hz, is impaired in the affected hemisphere compared to the

unaffected hemisphere and control subjects; however, in small-artery occlusion stroke subjects, there is no significant difference between the two hemispheres, although the phase angles in both hemispheres are significantly lower than in control subjects, Guo et al. (2014a).

The contributions of ABP, $PaCO_2$ and neural activity have been quantified in AIS subjects within 72 h of onset. Vascular reactivity and the neurovascular coupling were both found to be depressed in this subject group compared to controls, but autoregulation was not affected, although the AIS subjects showed significant hypocapnia and the stroke severity in this cohort was mild-to-moderate, Salinet et al. (2015).

Alongside autoregulation, brain volume and functional status have also been measured in subjects with chronic ischemic stroke. In this population, subjects had bilaterally impaired autoregulation and exhibited grey matter atrophy in some areas on the ipsilateral side. Better cerebral autoregulation was found to be associated with less atrophy and better long-term functional status, Aoi et al. (2012).

The role of reducing ABP in subjects with acute ischemic stroke has been discussed: there is a balance between reducing ABP to protect brain tissue and the possibility of impaired cerebral perfusion, given the uncertainty of whether autoregulation capacity is reduced in patients with AIS. It is likely that there will be subgroups that will respond differently, Jordan and Powers (2012). The management of ABP in stroke subjects thus remains an open question and needs careful consideration, Petersen et al. (2015). This is particularly the case given the wide range of findings described above and the heterogeneity of autoregulation behaviour post-stroke.

5.13.2 Haemorrhagic Stroke

Early studies into aneurysmal subarachnoid haemorrhage (SAH) indicated that both autoregulation and vascular reactivity are impaired in SAH, Giller (1990) and Dernbach et al. (1988). Impairment was found in dynamic autoregulation relative to a control group with un-ruptured aneurysms, when measured using the thigh cuff test and ARI, with the impairment increasing significantly with the severity of the SAH, as measured using the Hunt and Hess and Fisher scales, Schmieder et al. (2006). Note that the former scale is based upon symptoms, with the latter scale being based upon CT imaging. Although SAH is only one sub-type of intracranial haemorrhage (ICH), it has been the most widely studied in the context of autoregulation.

Post-SAH, a number of processes can occur that can contribute to deterioration in a patient's clinical status. Vasospasm (the narrowing of a large artery) can lead to delayed cerebral ischaemic (DCI), which is most prominent 5–7 days after onset. Vasospasm does not, however, reduce CBF without a second factor, such as a decrease in ABP, Budohoski et al. (2015a). Disturbed autoregulation in the 5 days after SAH significantly increases the risk of DCI at 21 days, Budohoski et al. (2012a).

Patients that go on to develop angiographic vasospasm in days 2–4 have been found to have a higher transfer function gain, whereas those that go on to develop DCI showed lower transfer function phase, both compared to SAH patients that developed neither, indicating that differently impaired autoregulation could be used to help to identify patients at higher risk of developing secondary complications post-SAH, Otite et al. (2014). A failure of autoregulation has been reported to occur before the onset of vasospasm, Lang et al. (2001), Budohoski et al. (2013a). Autoregulation has also been shown to increase during vasospasm and to be significantly impaired on the side of vasospasm compared to the contralateral hemisphere, Soehle et al. (2004).

In SAH patients, a unilateral failure of autoregulation is related to unfavourable outcome, with this failure being seen in patients who developed delayed cerebral ischemia (DCI), Budohoski et al. (2015b). Bilateral failure in autoregulation is observed more often in patients with unfavourable outcomes and is found on a median of day 4, compared to unilateral failure on a median of day 3. In DCI patients, a higher inter-hemispheric difference in autoregulation is seen than in non-DCI patients, Budohoski et al. (2015a). Three different metrics of autoregulation measured in patients in the 5 days following SAH, based on both spontaneous fluctuations and a compression test, were all able to predict DCI accurately, with a combination of all three giving best results, Budohoski et al. (2013b).

In patients with low-grade aneurysmal SAH within 4 days of aneurysm rupture, autoregulation is impaired at baseline and at day 7, returning to normal by day 14. Although neither autoregulation impairment nor large artery vasospasm are individually associated with DCI, in combination, vasospasm and increased autoregulation impairment from baseline to day 7 are significantly correlated to subsequent DCI, Calviere et al. (2015). A similar conclusion has been found in patients after aneurysmal SAH, where vasospasm alone did not seem to cause delayed ischaemic deficits, but in conjunction with impaired autoregulation, the risk seemed to be very high, Lam et al. (2000). Statin (pravastatin) use in aneurysmal SAH patients results in a shortened duration of impaired autoregulation and on days 3–5 the pressure-reactivity index correlates significantly with ipsilateral impaired autoregulation, Tseng et al. (2006).

As well as TCD, NIRS has been used in the SAH population, showing good correlations between correlation coefficients based on NIRS parameters, Zweifel et al. (2010a) and similar results for disturbed autoregulation, Budohoski et al. (2012a). PWI has been used to measure rCBF and rCBV in SAH patients, with these being related to different degrees of vasospasm. Simultaneous decreases in rCBF and rCBV were found in vascular territories, these decreases being related to increasing degree of vasospasm, although there was substantial variability between different territories, Hattingen et al. (2008).

In patients with spontaneous ICH, transfer function analysis has shown that autoregulation is impaired, with a higher gain (but no change in phase) in days 1–5, Oeinck et al. (2013) and days 1–3, Nakagawa et al. (2011). A reduction in phase is associated with larger ICH volume, lower ABP and poorer outcome, whereas gain is unrelated to clinical factors or outcome, Oeinck et al. (2013). On day 5, higher

values of Mx are significantly associated with lower GCS, ventricular haemorrhage and lower CPP on the ipsilateral side; with an increase in Mx from day 3 to day 5 being associated with lower GCS and ventricular haemorrhage. Higher ipsilateral Mx on day 5 is a significant predictor for poor outcome at 90 days. A secondary decline in autoregulation found in some subjects is associated with poor clinical outcome, Reinhard et al. (2010).

In conclusion, it is clear that autoregulation is impaired in stroke, both ischaemic and haemorrhagic, although this impairment is dependent upon the sub-type of stroke, its severity and the time post-stroke as well as the treatment pathway. The exact relationships between all of these variables are still far from being fully understood, but it is clear that a better understanding of this will be required to optimise patient treatment and to ensure that therapies are suitably targeted specifically to patient sub-groups.

5.14 Brain Trauma and Injury

There is a very substantial literature on cerebral autoregulation in brain injured patients, dating back to the 1970s, with a recent review summarising the findings from 56 papers, Czosnyka and Miller (2014). A study from 1978 in 18 patients with traumatic brain injury (TBI) using Xe133 showed a regional loss of static autoregulation in most patients, although no relationship was found with clinical outcome, with normalization occurring gradually 5 days after trauma, Cold and Jensen (1978). The role of CO_2 was first explored shortly afterwards, Cold et al. (1981), with impaired dynamic autoregulation improving in this population in hypocapnia even without changes in CPP, Newell et al. (1996).

The measurement of central perfusion pressure (CPP) as a driver of CBFV, measured with TCD, subsequently showed that autoregulation was impaired at low CPP values (<55 mmHg), Czosnyka et al. (1994), where it coincides with the lower limit of autoregulation, Czosnyka et al. (2000), and high CPP values (>95 mmHg), Czosnyka et al. (2003). The U-shaped curve between Mx and either CPP or ABP, Fig. 5.2, was first introduced by Czosnyka et al. (2001), based on 187 patients with head injury. Impaired autoregulation and elevated ICP were found more often in patients with unfavourable outcomes, Czosnyka et al. (2001, 2002a). It is worth noting the shape of the static autoregulation curve, Fig. 5.2a, given the studies presented earlier.

Mx has been shown to correlate with ICP, admission Glasgow Coma Score (GCS) and outcome, as has Sx (based on systolic blood pressure, rather than mean blood pressure), Czosnyka et al. (1996). Mx correlates significantly with static autoregulation, Czosnyka et al. (2003). Mx has been found to depend on outcome better than the admission GCS, with patients who died showing disturbed autoregulation in the first 2 days post injury, Czosnyka et al. (2000), and to discriminate strongly between patients with good and bad outcome, Czosnyka et al. (2003). TBI patients with intact cerebral autoregulation showed a good outcome,

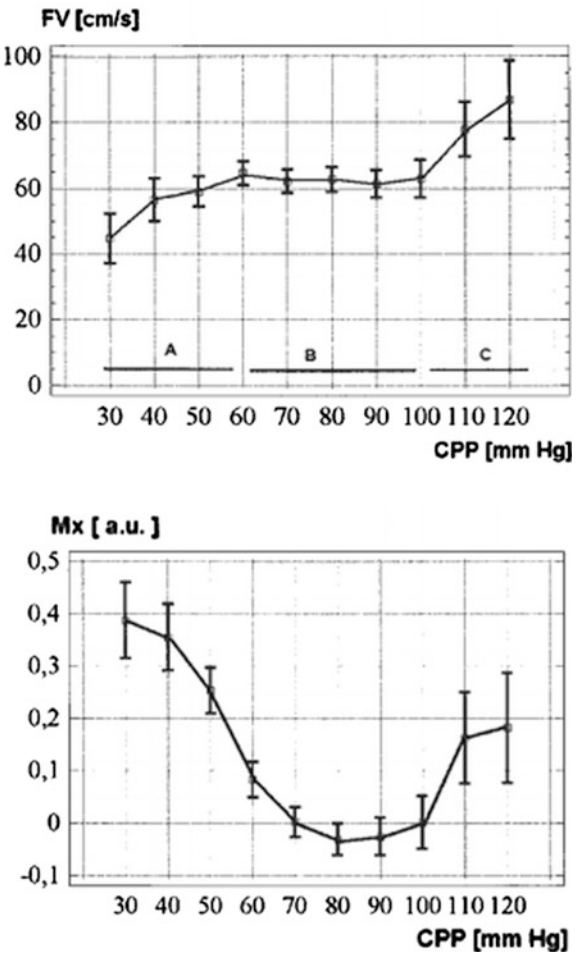

Fig. 5.2 Relationships between mean CBFV (*top*) and Mx (*bottom*) and CPP in subjects with severe head injury, reproduced with permission from Czosnyka et al. (2001)

with patients with impaired autoregulation having poor outcome, Puppo et al. (2008). Thresholds for Mx have been proposed, with values greater than 0.3 indicating "definitely disturbed autoregulation" and values lower than 0.05 being a marker of good autoregulation, the range in between being uncertain Sorrentino et al. (2011).

PRx has also been shown to be a significant predictor of negative outcome in TBI patients, Kirkness et al. (2001), and a significant relationship has been found between Mx and PRx and outcome that is stronger than the association between admission GCS and outcome, Czosnyka et al. (2002a).

In patients with minor head injuries, only a minority of patients have been found to exhibit impaired autoregulation (measured with ARI) with a significant correlation being found between lower ABP and decreased autoregulation but no

correlation between ARI and initial GCS or 1-month Glasgow Outcome Score (GOS), Jünger et al. (1997).

In addition to Mx, the step response and transfer function analysis have been used by a number of authors. The step response is different for subjects with mean ICP less than and more than 20 mmHg, with a high degree of correlation between CBFV and ICP in the second group, Panerai et al. (2002). A change in phase angle has been more frequently found in subjects with large lesions that in those with small lesions, Müller et al. (2003) and the phase angle between respiratory waves has also been recorded, Ragauskas et al. (2005). Phase angle and Mxa (based on ABP, rather than CPP) are well correlated during deep breathing, Lewis et al. (2008), and phase angle correlates with respiration rate and CPP, Lewis et al. (2012). Respiratory phase shift has been suggested as having some prognostic value for TBI patients, although no significant relationship between phase shift and outcome has been found, Lewis et al. (2012).

ARI has also been used, with median ARI being shown to be significantly lower for non-survivors of severe head injury compared to survivors. There is a significant correlation between ARI and GOS and the difference in ARI values between survivors and non-survivors is still significant when adjusted for GCS. No other variables have a significant contribution to predict outcome, Panerai et al. (2004).

Hemisphere-to-hemisphere differences in autoregulation (measured with Mx) have been shown to be a predictor of fatal outcome in patients with head injury, Schmidt et al. (2002). Cross-correlation values based on cortical flux (Lx) are significantly higher than Mx, indicating that cortical autoregulation is worse than cerebral autoregulation measured in the MCA when ICP is increasing and CPP is falling; when CPP is greater than 60 mmHg, the two are similar, Zweifel et al. (2010b).

ICP is a critical parameter in the monitoring of TBI patients and so some efforts have been made to investigate this parameter. Adaptive mathematical models of ICP have been used to improve the accuracy of non-invasive estimates of ICP, Schmidt et al. (2003). No correlation has been found between ICP and ABP amplitudes in TBI patients, Eide et al. (2007). Measurements of pressure volume index (PVI) in a group of comatose TBI patients showed that PVI is elevated when autoregulation is impaired, even though ICP and CPP show no difference, Lavinio et al. (2009). The relationship between ICP and CBFV (quantified using Fix) shows similar behaviour to Mx, with Mx showing a plateau and Fix a trough with CPP, both indicating a zone of optimal CPP, Lewis et al. (2014).

The use of different metrics to quantify autoregulation has been investigated in more detail recently. The association between Mx and Mxa (based on ABP) is moderately strong, with the difference decreasing with the degree of autoregulation impairment. The significant difference shown in Mx between groups with different outcomes was not found in Mxa, Lewis et al. (2007). Systolic-based metrics have been found to show a stronger association with outcome than mean-based metrics, with Sx having the strongest association for favourable/unfavourable and death/survival outcomes, when compared with diastolic and mean blood pressure metrics, Budohoski et al. (2012b).

A correlation coefficient metric based on the pulse wave amplitude of ICP, termed PAx, has also been proposed. On average, an increase in ABP causes a decrease in amplitude and there is a strong correlation between PAx and Mx and between PAx and age, with PAx having equally good predictive power as Mx for outcome, Radolovich et al. (2011). A recent comparison of time and frequency domain methods has been made, using ARI, transfer function phase, gain and coherence, and mean flow index (Mx) and patients' Glasgow outcome score. Only five metrics were found to be significantly correlated with patients' outcome, with Mx (based on CPP) showing the strongest association and a number of metrics showing significant correlations between each other, Liu et al. (2015).

Both TCD and NIRS have been used to assess autoregulation, as well as brain tissue oxygenation (measured invasively), Zweifel et al. (2014). Measurements of tissue pO_2 in patients with severe head injury have shown a plateau phase similar to that shown by CBFV; static autoregulation was also found to be significantly correlated with cerebral tissue oxygen reactivity, Lang et al. (2003). However, the challenge of interpreting NIRS measurements has recently been emphasised by a study that found significant correlations between some NIRS indices (PRx and THx, PRx and TOx, and Mx and TOx) but not others (Mx and THx), Highton et al. (2015).

Some studies have investigated the effects of clinical interventions. Red blood cell transfusion was found to result in increased PRx values in severe TBI patients, hence impaired autoregulation, Sekhon et al. (2015). Moderate hypocapnia has been proposed to provide a benefit to TBI patients, since impaired autoregulation was improved during moderate hypocapnia (measured using Mx) with no significant change in CPP, Haubrich et al. (2012). Glucagon has been shown to protect against impaired vasodilation by upregulating cAMP and inhibiting upregulation of tPA, possibly providing neuroprotection post TBI, Armstead et al. (2011). Indomethacin has been shown to decrease ICP and CBFV, thus increasing CPP in TBI patients and leading to a significant increase in dynamic autoregulation, Puppo et al. (2007). Morphine and fentanyl have been shown to cause a reduction in CPP, but with no change in CBFV, de Nadal et al. (2000), with ICP changes being the same in subjects with intact and impaired autoregulation. Hypotension after TBI is associated with significant secondary neuronal damage, Myburgh (2004).

Although there any many studies that use continuous metrics of autoregulation in TBI patients, there is only a moderate amount of evidence for their use in CPP management, with the use of an optimal CPP as a target still requiring prospective randomised trials, Czosnyka and Miller (2014). CPP-guided therapy has also been suggested as a means of reducing ICP, Ter Minassian et al. (2002).

Finally, there have also been a number of studies in children with TBI, which have shown considerable heterogeneity in this population, although it seems that the incidence of impaired autoregulation is greater in those children with severer head injury or worse outcome. For example, in children during external surgery, impaired autoregulation was most often found following moderate to severe TBI and was associated with poor outcome, Vavilala et al. (2004); hyperaemia was also associated with impaired autoregulation and poor outcome. Autoregulation was also

found to be impaired in 12 of 28 children with TBI, with ARI < 0.4 in the first 72 h being associated with GOS < 4 at 6 months, Vavilala et al. (2006).

ARI has been found to be lower in the affected side than in the unaffected side when there is isolated focal TBI, but there is no difference in patients with diffuse TBI, Vavilala et al. (2008). Glasgow Outcome Scores tend to be highest in patients with intact cerebral autoregulation on both sides. Age under 4 years and low GCS values have been found to be independently associated with impaired cerebral autoregulation, Freeman et al. (2008).

In inflicted TBI in both infants and young children, all children with inflicted TBI were found to have poor outcome and impaired autoregulation in both hemispheres, and children with non-inflicted TBI had better overall outcome than those with inflicted TBI, although it should be noted that the numbers are very small in this study, Vavilala et al. (2007). The time course of autoregulation post severe TBI in children is highly variable, so it is possible that this might be a measure of worsening TBI (although again this is a small study), Tontisirin et al. (2007).

5.15 Miscellaneous Conditions

Although cerebral autoregulation has been studied in different physiological conditions and in the expected cerebrovascular pathologies, it has also been studied in a wide range of other conditions. For convenience, these are grouped here, since there are often very few studies that have been performed.

For example, cerebral autoregulation has been shown to be impaired in subjects with **panic disorder**, Wang et al. (2010), but not during jaw movement in normal healthy subjects, Sakagami et al. (2011). Autoregulation has been shown to be impaired during **acute alcohol withdrawal**, potentially indicating an elevated risk for cerebrovascular disease, Jochum et al. (2010). The taking of a hyperthermic bath results in an increase in ARI (and a hypothermic bath a decrease in ARI), Doering et al. (1999).

Cerebral autoregulation has been investigated in patients with **Shy-Drager syndrome**, Briebach et al. (1989), and found to be impaired in patients with **Fabry disease**, measured using transfer function analysis, Hilz et al. (2004). As in a number of other studies, impaired autoregulation is suggested to imply an increased risk of stroke in this patient group. Autoregulation is impaired in patients with **sickle cell disease**, as shown by a reduced phase angle and increased CBFV variability, Kim et al. (2009), and in subjects with **glaucoma**, both normal pressure and primary open angle glaucoma, as shown by increased transfer function gain, Tutaj et al. (2004).

Moyamoya disease (characterized by progressive ICA stenosis) exhibits impaired dynamic cerebral autoregulation, with a gradual decrease in gain and

phase throughout its different stages of progression, Chen et al. (2013). A significant correlation between autoregulation strength and resistance to CSF outflow has been shown in patients with clinical symptoms of **communicating hydrocephalus**, indicating that brain atrophy is related to impaired cerebral autoregulation, Czosnyka et al. (2002b).

Autoregulation has been shown to improve in patients with **epilepsy** after temporal lobe surgery, Dütsch et al. (2004). The presence of a **Ventricular Assist Device** does not seem to affect autoregulation, although coherence changes, Bellapart et al. (2011). Enhanced external counterpulsation, a technique to augment blood pressure rhythmically through diastolic lower-body compression, does not affect cerebral autoregulation, Marthol et al. (2005). Fifteen minutes of **transcranial direct current stimulation** has been found to impair cerebral autoregulation, although it can be safely applied when done in a particular way in both older subjects and in patients with cerebrovascular diseases, List et al. (2015). Even the position of patients during **shoulder surgery** has been shown to affect cerebral oxygenation index after surgery, Laflam et al. (2015).

In patients with **liver disease**, autoregulation has been found to be impaired in the most severe cases of liver cirrhosis (assessed using the Child-Pugh scale), measured using the response to deep breathing and head-up-tilt, Frøkjaer et al. (2006), with those subjects with impaired autoregulation also having severe parasympathetic and sympathetic autonomic dysfunction, and the level of liver dysfunction being associated with the severity of autonomic dysfunction. Patients that exhibit impaired autoregulation were found to have worse liver function, a higher cardiac index and lower peripheral resistance, Lagi et al. (1997). Likewise, although static autoregulation is preserved in most patients with end-stage liver disease, this is not the case in patients with hepatic encephalopathy or with low ABP, Strauss et al. (2000). Autoregulation is impaired in primary biliary cirrhosis patients in response to the Valsalva manoeuvre, with a link being suggested between the degree of impairment and structural changes in the globus pallidus, Hollingsworth et al. (2010). Large variability has been shown using NIRS in patients undergoing orthotropic liver transplantation, with some, but not all, patients exhibiting unimpaired cerebral autoregulation, Nissen et al. (2009). Interestingly, autoregulation is not significantly impaired by ethanol in healthy subjects, Blaha et al. (2003), despite the obvious link.

In patients with **sepsis**, autoregulation has been found to be maintained in the early stages, with assessment in the later stages being harder (the thigh cuff test used being unable to generate large enough changes in ABP), Berg et al. (2015). The majority of mechanically ventilated patients with septic shock have been shown to have impaired cerebral autoregulation, Taccone et al. (2010) and NIRS has been used successfully in this context, although the results are harder to interpret, Steiner et al. (2009). Phase angle was found to increase after a 4-h lipopolysaccharide infusion, unaffected by hyperoxia or hypoxia; this might protect the brain from ischaemia in the early stages of sepsis, Berg et al. (2013).

The studies into patients with **brain tumours** indicate that autoregulation is maintained, irrespective of tumour size, but only if the clinical status is good (this study was performed in patients scheduled for brain tumour resection), Schmieder et al. (2000), with patients with accompanying disease having significantly impaired autoregulation pre-surgery. Sharma et al. (2010) then found that in patients with large supratentorial tumours, preoperative autoregulation is impaired in 20 % of patients and that this impairment remains during the first 24 h post-surgery, whereas in the other 80 % of patients, autoregulation was maintained both pre- and post-operatively.

Although no differences were found in autoregulation parameters between patients with **migraine**, with and without aura, and normal subjects, Reinhard et al. (2007), later, more detailed studies have found that impaired autoregulation is found in subjects with migraine with aura (but not in subjects without aura) in both the posterior inferior cerebellar artery and MCA, Reinhard et al. (2012b). It was suggested that autoregulation might be one contributing factor to the cerebellar predilection for ischemic lesions in patients with migraine with aura. No significant relationships were found between autoregulation and clinical factors (such as migraine frequency and orthostatic intolerance). The most recent study showed that ABP-CBFV phase angle in patients with migraines and a right-to-left shunt is significantly lower than in those with migraines and no shunt, with this being most significant in patients with large shunts. A potential mechanism linking RLS, migraine and cryptogenic stroke was thus proposed, Guo et al. (2014b).

Studies measuring static autoregulation in patients with **Parkinson's disease** have found evidence of impaired autoregulation that appears to be independent of dopaminergic treatment, Vokatch et al. (2007), and larger reductions in CBFV at lower values of ABP than in control subjects in response to head-up-tilting, Debreczeni et al. (2005). This has been suggested as a component of the orthostatic intolerance of PD patients.

5.16 Conclusions

The studies cited in this chapter have covered a very wide range of both physiological and pathophysiological conditions. It is noticeable how there has been a considerable emphasis on clinical studies within the last 10 years and how this has resulted in a very substantial volume of information becoming available. This is particularly relevant with cerebrovascular disease becoming of increasing importance in an ageing population. It is perhaps worth noting that although impaired autoregulation is implicated in a wide variety of cerebrovascular diseases, it can be seen actually to be remarkably robust in many instances, with impairment occurring only in extreme cases. In the next, and final, chapter, the implications of this are examined.

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Chapter 6
Conclusions

6.1 Cerebral Autoregulation Today

The field of cerebral autoregulation has come a long way since Lassen's curve was first proposed in 1959. The development of new measurement techniques, allowing for bedside assessment of autoregulation, and analysis techniques, allowing for highly detailed assessment of a multivariate, non-linear and non-stationary relationship, have opened up many new avenues for exploration. In the last decade or so, there has been a considerable push to understand autoregulation in pathophysiological conditions, with a resulting acceptance of the complexity of the processes that act together to maintain near constant cerebral blood flow.

One of the motivations for this book has been the fact that, particularly in the last ten years, cerebral autoregulation has generated a very large number of publications that are spread over numerous technical and clinical journals. The exponential rise in the number of papers published in this field can be seen even by the very simple metric shown in Fig. 6.1. More than 150 different journals have been cited in this book alone (with many omitted). Perhaps for that very reason, it is very difficult to find a starting point for studying cerebral autoregulation, providing one of the motivations for this book.[1]

It is possibly this diversity and the complexity of cerebral autoregulation that has also led to some surprising gaps in our understanding of this phenomenon. Even the behaviour of static autoregulation remains unclear, over 60 years after Lassen's study; however, without a proper understanding of what autoregulation is and how it behaves in individual subjects, it will remain very difficult to translate findings into a clinical setting.

[1] Although see http://car-net.org/content/resources for a recent ranking of the most cited papers and reviews on cerebral autoregulation.

S. Payne, *Cerebral Autoregulation*, SpringerBriefs in Bioengineering,
DOI 10.1007/978-3-319-31784-7_6

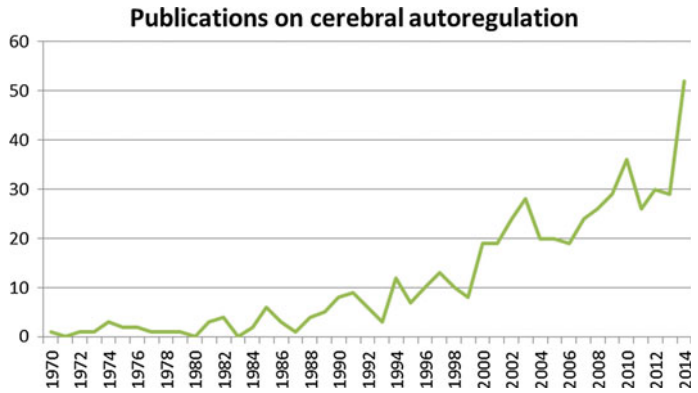

Fig. 6.1 Number of publications with cerebral autoregulation in the title up to 1/1/15, numbers taken from PubMed

In a similar manner, although autoregulation has been measured in many different contexts, it is currently only a metric that is recorded, rather than a parameter that is manipulated. For example, a diagnosis of hypertension will often result in treatment with anti-hypertensive drugs, yet a diagnosis of impaired autoregulation will not result in any treatment aimed directly to improve autoregulation, rather therapies will be targeted at the underlying cause with improved autoregulation as a side benefit. Often, this benefit is not even acknowledged and autoregulation, even when very important, for example when managing blood pressure post-stroke, is not accounted for in therapy or even mentioned as a consideration.

The interaction between autoregulation and the wider control of the cardiovascular system remains surprisingly poorly explored, despite the fact that the primary purpose of autoregulation is to ensure adequate supplies of nutrients to the brain from the rest of the body, but as part of a wider control system. Changes in one part of this control system might be counter-balanced by other compensatory changes in other components, with homeostasis maintained over a range of physiological statuses. The issue of blood pressure management in post-stroke patients again gives a clear indication of how a lack of understanding and translation impacts (or fails to impact) clinical decision making.

One possible reason for the lack of clinical usage of autoregulation is the fact that it is not clear whether autoregulation is the driver of clinical symptoms or simply one of many symptoms exhibited by pathological conditions. Is a failure of autoregulation a cause or a symptom of disease? There is a need to improve our understanding of what it is that the brain is trying to achieve through the mechanisms that have been termed autoregulation, and how this can be measured concisely in humans.

Its complexity, however, means that often it is simply stated that autoregulation is impaired, yet it is far from clear precisely what this means or whether there are multiple different ways in which it is impaired. This is of course a common problem in a measurement that is essentially very indirect in human subjects: it is not

obvious what, for example, a change in phase angle at 0.1 Hz means in terms of the actual physiology. This is an area where modelling, combined with analysis techniques, could play a substantial role in interpreting data more in terms of the underlying physiological changes than in simple metrics.

It is also worth noting in this context that even the control of blood flow is an indirect process: the brain actually requires oxygen and glucose rather than blood, and it is impairments in this supply that are of importance. The increasing use of NIRS unlocks a great possibility for exploring this supply in more detail, but also opens up associated difficulties in understanding what the signals mean and how they relate to the supply and demand of oxygen and glucose. This is likely to involve increased development of models of blood flow and metabolism that can be validated and used at the bedside. Even the question of what we really need to measure is unanswered thus far.

The current use of models also illustrates two major shortcomings. There is too little validation of models against human data, with animal models being used in their place, and there has been too little effort to draw upon expertise in different but highly related fields. It should be noted that this book has entirely focussed on studies in human subjects, in marked contrast with earlier books in related areas: this has been possible due to the substantial number of studies that have now been performed in humans. The reluctance to draw on other fields is likely due to the historically overwhelming use of a single modality (TCD) across the field, when there are many other studies available based on different modalities that could be used. By setting out the state of cerebral autoregulation in this book, it is hoped that it will enable the field to spread more widely through greater interaction with other researchers.

One very noticeable feature of the studies performed here is the enormous variety of analysis methods used to quantify autoregulation and to distinguish between different subject groups. The lack of reproducibility between centres means that using autoregulation to stratify patients remains challenging, since setting thresholds is extremely difficult. Also precisely what temporal variability actually represents and whether it is important or simply noise has not yet been addressed. If autoregulation is to move into the field of personalized medicine, it has to be shown that it can be measured in individual subjects robustly and reproducibly.

6.2 Cerebral Autoregulation Tomorrow

It is well known that making predictions is very difficult, particularly when they are about the future.[2] However, this does seem to be a suitable place in which to offer some comments, based on the preceding pages. It is hoped that one of the

[2]Rather aptly, the source of this (mis-)quotation remains somewhat obscure, hence the liberty taken both here and elsewhere in (mis-)quoting it.

advantages of this book is the opportunity it provides to reference a very large number of papers, to follow links across topics and to provide a feel for the state of the field and for what the future might hold for cerebral autoregulation.

Reading earlier reviews of cerebral autoregulation has highlighted the fact that some issues have been set out again and again, yet they remain tantalisingly out of reach, despite the enormous growth in the literature on this subject. The need to consider cerebral autoregulation in the context of lowering blood pressure in hypertension and cerebral ischaemia, as discussed by Strandgaard and Paulson (1984), remains acknowledged, yet there is still little or no evidence base for how this should actually be done, largely because of the lack of a standardised personalised metric of autoregulation and the absence of a randomised control trial that has proven clinical benefit.

One area in which progress has been made since the review by Paulson et al. (1990) is in developing a better understanding of the subtleties and heterogeneity of patients with, for example, brain injury and stroke, where autoregulation is known not simply to be impaired in a particular subject group; rather there can be significant variability between subjects. However, in the age of personalised medicine, there is a real need for personalised metrics of autoregulation that can be used in diagnosis and therapy and this remains a failing of the field at present.

It is very instructive to compare the two reviews by Panerai (1998) and Panerai (2008), where the importance of multi-variate analysis is emphasised and the need for reproducibility is highlighted. There is certainly a greater awareness of the multivariate nature of autoregulation, but the question of reproducibility remains largely un-tackled, even if some effort has been made to quantify this more recently. Without this, it is hard to see how personalised metrics can be taken into a clinical context in the required robust and reproducible form.

The most recent review, Tzeng and Ainslie (2014), picks up many of these themes, including a lack of understanding of the actual mechanisms of autoregulation and the wide variety of methods used to assess it, particularly in the context of why autoregulation has not been translated into a clinical setting.

It seems clear that there are thus four directions in which cerebral autoregulation needs to move if it is not to remain an interesting, but somewhat esoteric, avenue for study: fundamental understanding; convergence of analysis methods; reproducibility; clinical RCT to prove clinical benefit. These relate closely to the four questions posed by Donnelly et al. (2015): (1) what is it?; (2) how do we measure it?; (3) why is it important?; and (4) can we use it as a basis for therapy? These questions provide an excellent starting point for determining the role and potential impact of cerebral autoregulation in a whole range of clinical conditions.

Even in the context of TBI, where the first three questions have been well investigated with the concept of an optimal CPP based on autoregulation now well understood, there has yet to be a randomised controlled trial to prove any clinical benefit. This would appear to be one of the most promising avenues for finally moving autoregulation into the clinical treatment pathway. This would have a twin benefit, both showing how autoregulation can play a role in patient management as an exemplar for other pathologies, and opening up the possibilities of targeting

autoregulation directly, rather than using it solely as a metric. If in a further 10 years time, progress in this direction has been made, autoregulation may start to take its proper place in a clinical setting.

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