REGULATION OF CEREBRAL BLOOD FLOW IN HUMANS: PHYSIOLOGY AND CLINICAL IMPLICATIONS OF AUTOREGULATION

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Keywords: cerebrovascular, cognitive function, hypertension, ageing, stroke, Alzheimer's disease, vascular dementia, vascular cognitive impairment, exercise, small vessel disease, microcirculation, neurovascular coupling, hypercapnia, resistance vessels

Total number of words (text+references): 62, 079

Title page+abstract+table of contents: 780

Figures: 8

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ABSTRACT

Brain function critically depends on a close matching between metabolic demands, appropriate delivery of oxygen and nutrients, and removal of cellular waste. This matching requires continuous regulation of cerebral blood flow (CBF), which can be categorized into four broad topics: 1) autoregulation, which describes the response of the cerebrovasculature to changes in perfusion pressure, 2) vascular reactivity to vasoactive stimuli [including carbon dioxide (CO_2)], 3) neurovascular coupling (NVC), i.e., the CBF response to local changes in neural activity (often standardized cognitive stimuli in humans), and 4) endothelium-dependent responses. This review focuses primarily on autoregulation and its clinical implications. To place autoregulation in a more precise context, and to better understand integrated approaches in the cerebral circulation, we also briefly address reactivity to CO_2 and NVC. In addition to our focus on effects of perfusion pressure (or blood pressure), we describe the impact of select stimuli on regulation of CBF (i.e., arterial blood gases, cerebral metabolism, neural mechanisms, and specific vascular cells), the inter-relationships between these stimuli, and implications for regulation of CBF at the level of large arteries and the microcirculation. We review clinical implications of autoregulation in aging, hypertension, stroke, mild cognitive impairment, anesthesia, and dementias. Finally, we discuss autoregulation in the context of common daily physiological challenges, including changes in posture (e.g., orthostatic hypotension, syncope) and physical activity.

Terminology and abbreviations

Arterial oxygen content: CaO_2

Autoregulation index: ARI

Blood-brain barrier: BBB

Blood flow: blood flow through a blood vessel, often expressed in ml/s or ml/min.

Blood pressure: BP

Brain-derived neurotrophic factor: BDNF

Cerebral blood flow: CBF

Cerebral metabolic rate of O_2: $CMRO_2$

Computed tomography: CT

Delayed cerebral ischemia : DCI

Intracerebral hemorrhage: ICH

Intracranial pressure: ICP

Left ventricular assist device: LVAD

Magnetic resonance imaging: MRI

Near-infrared spectroscopy: NIRS

Neurovascular coupling: NVC

Nitric oxide: NO

Partial pressure of arterial carbon dioxide: $PaCO_2$

Partial pressure of arterial oxygen: PaO_2

Partial pressure of carbon dioxide: PCO_2

Partial pressure of oxygen: PO_2

Perfusion: blood flow, expressed as rate of blood flow per unit of tissue (i.e., ml/100g/min)

Perfusion pressure: under normal conditions, perfusion pressure for brain equals arterial BP minus ICP or venous pressure. Under conditions where ICP is relatively low and constant, changes in BP equal changes in perfusion pressure.

Position emission tomography: PET

Randomized controlled trials: RCT

Subarachnoid hemorrhage: SAH

Transcranial Doppler: TCD

Transfer function analysis: TFA

I. INTRODUCTION: Regulation of cerebral blood flow in humans

A. *Historical perspective*

Some of the earliest knowledge regarding cerebrovascular anatomy, and specifically the circle of Willis, dates back to 1664 when Thomas Willis published his thesis 'Cerebri Anatome' (623). In 1783, Alexander Monro, who also named the 'foramen of Monro' in the brain's ventricles, deduced the brain's high demand for blood flow. He did so by taking the weight of the arm and the diameter of the subclavian artery - its source of blood supply – and comparing this with the weight of the brain and its blood supply - the combined diameters of the carotid and vertebral arteries (391). Monro, however, is perhaps best remembered for the Monro-Kellie doctrine, which states that because the brain is enclosed in the skull, there must be an equilibrium between its volumetric components (brain parenchyma, interstitial and cerebrospinal fluid, arterial and venous blood volume) (181). In the early 1900s, this doctrine led to the view that there was no regulation of CBF. Rather, CBF and changes in CBF, were restrained by this equilibrium. In other words, large increases in CBF were thought to be impossible because it would cause disequilibrium in intracranial pressure (ICP) (181), a view supported by the influential physiologists Hill (249) and Bayliss (40). Their idea was that there was no active control of CBF, rather CBF passively followed changes in BP. If the brain demanded an increase in CBF, this was achieved by vasoconstriction in the rest of the body, increasing BP and thereby CBF (249).

In 1868, the physiologist F.C. Donders (141) may have been the first to hint at active regulation of CBF in response to cognitive activation (i.e., neuronal stimulation), a concept now referred to as NVC or functional hyperemia (see also Sections **I**.C and **III.**A for further information on NVC). Donders wrote *'[because]… hemorrhage, or reduced cardiac function, are associated with loss of consciousness..[we conclude]..that a regular supply of blood to the brain is a*

prerequisite for cognitive processes, indicating a central role for brain metabolism [in cognitive activation]…which consumes oxygen and produces carbon dioxide.'(141). In the late 19th century, the physiologist Angelo Mosso published the first work related to regulation of CBF in humans (396). Mosso recorded pulsations of the brain in a patient with skull defects following a neurosurgical procedure, in which Mosso reported immediate increases in pulsations whenever the subject was spoken to, or when the subject began to think actively (e.g., arithmetic). Mosso also introduced the "human circulation balance", which represents a measurement technique using a balanced table that tipped downwards if the weight on either end were increased (506). Using this balance, he found that the moment emotional or intellectual activity began in a subject, the balance would tip down at the head end, reflecting a redistribution of blood toward the brain.

An experiment by Roy and Sherrington in 1890, wherein they injected a solution of homogenized brain intravenously in a dog, revealed an increase in brain volume (used as an index of increased CBF) without any increase in BP (493). This experiment formed the first evidence for the metabolic hypothesis of NVC (181). The interpretation was that this brain extract, from a dog that had died from hemorrhagic shock four hours earlier, contained chemical substances that induced cerebral vasodilation. They hypothesized these substances had been located in the perivascular fluid. Of note, however, this experiment could not be replicated by Bayliss and Hill (40).

These early experiments (by Donders, Mosso, Roy and Sherrington) were largely ignored in their time, or seen as incorrect, because Hill (249) found contradictory results and was convinced there was no relationship between brain function and its circulation, and therefore no active regulation of CBF (465).

Whilst the study by Roy and Sherrington from 1890 is often cited for the experiment (based on just one animal) that suggested the presence of NVC, their paper contains many other experiments and represents one of the more comprehensive publications on early integrative physiology of the cerebral circulation (493). In a series of studies using dogs, cats, and rabbits, they investigated effects of sensorimotor stimulation, vagal-sympathetic stimulation, brain stem stimulation, hypoxia, hemorrhagic shock, acid-base changes, and several drugs (493). They may also have been the first to indirectly describe autoregulation, as will be discussed in Section **II.**A. It is also interesting to read their description and recognition of brain lymphatics and perivascular spaces, topics for which there is now renewed interest (471, 604).

In 1895, Bayliss et al reported contrasting findings compared to the work from Roy and Sherrington. Bayliss and colleagues examined the brain circulation by performing simultaneous recordings of arterial and venous pressure, ICP, and cerebral venous pressure (40) with a design comparable to Roy and Sherrington (493). They concluded "*there is no evidence supporting the existence of cerebral local vasomotor mechanisms*", and that "*the cerebral circulation passively follows the changes in the general arterial and venous pressures*" (40). Bayliss is well known for the 'Bayliss effect', which refers to the response of vascular muscle to changes in pressure (see Section **III** D) based on experiments in the peripheral circulation, but not the cerebral circulation. Indeed, combining experiments, Bayliss concluded that "*there is, up to the present, no satisfactory evidence of the presence of a vasomotor supply to the brain; so that when an increased blood-supply is required in that organ it is provided by constriction of vessels throughout the rest of the body, which is, in this respect, so to speak the slave of the brain*" (40). The 'Bayliss effect' was in his opinion, not present in the brain, but only in the systemic circulation, most notably the splanchnic circulation.

Contrary to the belief of Hill and Bayliss, the concept that the cerebral circulation is responsive to neuronal activation and changes in BP, as earlier suggested by Donders, Mosso and (indirectly) Roy and Sherrington, was confirmed in subsequent decades (175, 178, 534) (see review by Rosenblum) (491). This research may have been sparked by work from Fulton (186), who obtained evidence of NVC in the occipital cortex upon visual stimulation in a patient with a cortical defect, very similar to the work of Mosso (181, 465).

Although the observations by Mosso in humans are now 140 years old, thorough insight into the integrative nature of the regulation of CBF in humans has proven difficult for a variety of reasons. For many years, the presence of the skull made the brain something of a 'black box' as it prohibited direct observation of blood vessels, measurements of blood flow, or blood flow-mediated changes in volume or pulsatility, approaches that were feasible in the systemic circulation.

A milestone in this field was the nitrous oxide method developed by Seymour Kety in 1948 (298, 301). This method applies the Fick principle (conservation of mass) and measures changes in cerebral arterial and venous concentrations of nitrous oxide following its inhalation. The Kety-Schmidt method yields an estimate of CBF averaged over 10-15 minutes. An adaptation of this method was introduced by Lassen and Ingvar in 1961, who used intra-arterial injection of radioactive Krypton^{85} or Xenon^{133}. Using a camera, the intracerebral concentration of the tracer could be recorded to derive both global CBF and estimates of regional CBF (329). Other adaptations of the Kety-Schmidt method have been adopted since, for example in position emission tomography (PET) and SPECT.

A second important development was the introduction of advanced techniques from the 1970s onwards that could be applied safely in humans, starting with computed tomography (CT), followed by PET and magnetic resonance imaging (MRI) (445, 626). These techniques have

significantly contributed to improved understanding of the anatomy, physiology and pathophysiology of the cerebrovascular system, and currently play a key role in diagnosis and research focused on diseases that affect the cerebral circulation. Despite continuous technological advances that provided more detailed insight, these techniques are still limited by a poor temporal resolution, that would be needed to record rapid changes in CBF in response to physiological or pathophysiological stimuli (445). Although the introduction of transcranial Doppler (TCD) ultrasound in the 1980s (2, 4) helped resolve this limitation because of its very high temporal resolution, the method has its own limitations in that it measures blood flow velocity, without knowledge of vessel diameter (or cross-sectional area). Therefore, any changes in vessel diameter during interventions and measurements affect estimates of CBF using TCD.

B. *Relevance of CBF for brain function and consequences of hypoperfusion*

The vertebrate brain is a unique organ. In the human, the brain represents only 2-3% of total body mass while requiring ~15% of cardiac output and consuming ~20% of the available O_2 under normal conditions. The high metabolic rate of the brain, combined with limited energy stores, highlights the importance of CBF for nutrient and O_2 delivery, but also for removal of cellular, metabolic, or toxic by-products. The importance of controlling CBF is highlighted by the acute consequences that occur following substantial reductions in CBF, a change that can rapidly lead to unconsciousness, life-threatening complications, and brain damage if sustained (133, 349). In a clinical context, acute reductions in global CBF can occur with cardiac arrest (349) or with a sudden profound reduction in BP, which can lead to global reductions in CBF, termed syncope [for a recent review and overview of guidelines on syncope, see (199) and Section **XI**.A.*ii*]. Focal reductions in CBF occur in stroke, where there is an acute vessel

occlusion leading to hypoperfusion and ischemia. Examples are the classic clinical stroke of the middle cerebral artery, or downstream microinfarcts in the case of small vessel disease or migrating microthrombi. Experiments in non-human primates and other preclinical models have shown that a reduction in CBF to below ~50% of normal induces an immediate loss of neuronal function (133, 349). Normal global CBF in awake humans is approximately 50 ml/100g/min, and loss of function is observed below ~22 ml/100g/min (133). This loss of function is responsible for the clinical symptoms of hypoperfusion, which include slowing of mental processing. These symptoms are followed by loss of consciousness, often within 10 seconds after the onset of hypoperfusion or ischemia (349). With rapid recovery of CBF, function can be restored without permanent cellular injury. In contrast, persistent lowering in CBF causes irreversible damage. There are no exact thresholds beyond which ischemic injury occurs, but estimates are that a sustained fall to 20-30% of baseline CBF causes ischemia within minutes (27, 349, 521). This estimation is obviously an oversimplification, because effects of ischemia vary between different populations of brain cells, between the core and penumbra in the case of stroke, and because apart from these immediate effects of hypoperfusion on cell function, a cascade of responses are triggered that lead to further damage and delayed ischemia, hours to days later (349). A detailed description of such changes is beyond the scope for this review, we refer to the extensive review by Lipton (349).

Other than acute effects of ischemia, an increasing literature describes the clinical relevance of chronic, but more modest, reductions in CBF that potentially contribute to loss of brain health in neurodegenerative diseases such as Alzheimer's disease, vascular dementia, or mixed dementia (see Section **V**). Here, hypertension is suggested to play a central role through its effects on CBF. Hypertension is a key risk factor for overall disease burden and health loss worldwide (184, 386). Hypertension is associated with chronic mild cerebral hypoperfusion, which may explain why hypertension is a risk factor for Alzheimer's disease. Recent research

(see Section **V.**B) suggests that BP-lowering treatment in hypertension may restore CBF to normal, which may explain why antihypertensive treatment can reduce the risk of Alzheimer's disease. This clinical example illustrates the complexity and implications of regulation of cerebral perfusion. Both hypertension itself and medications used to treat hypertension can affect CBF, most likely via effects on vascular function, vascular structure, or vascular mechanics (260), as well as effects on the autonomic nervous system. In addition, hypertension increases the risk of orthostatic hypotension, which poses an additional challenge to autoregulation (See Section **VI.**A.*i* and *ii*). This example, focusing on hypertension, highlights the importance of understanding the integrative nature of CBF regulation, and how alterations in BP may contribute to the development and progression of a series of clinical conditions that share a final common pathway involving CBF (Figure 1).

C. *Integrative approach to regulation of CBF*

Control of CBF involves a spectrum of overlapping regulatory mechanisms that collectively facilitate optimal O_2 and nutrient delivery to individual brain cells (444, 445). Mechanisms that influence CBF include arterial blood gases [partial pressure of arterial CO_2 ($PaCO_2$) and arterial O_2 (PaO_2)], tissue levels of PCO_2 and PO_2 (56, 254), central hemodynamics (BP, including effects of hydrostatic pressure gradients), cerebral metabolism, and neural mechanisms including extrinsic autonomic and sensory nerves, and intrinsic neurons in close association with the vasculature within the brain parenchyma (225). In addition to their individual impact, there are strong interactions between these regulators. Some of these mechanisms are unique to the brain, explaining the generalized observation that the peripheral vasculature represents a poor model or predictor for the cerebral vasculature in health or disease (152).

An important characteristic of CBF regulation is mechanistic redundancy, i.e. overlapping mechanisms contribute to maintaining CBF under highly challenging conditions. Studies exploring the regulation of CBF are importantly impacted by this, because the overlap in pathways makes it difficult to explore the relative importance of individual pathways or identify key contributors. From a teleological perspective, this redundancy makes the regulation of CBF a robust system where multiple strategies are present to ensure precise control, and thus protect against potential brain damage.

The regulation of CBF can be affected by certain processes in the rest of the body, because they can influence the sensitivity of the various systems that affect CBF. For example, $PaCO_2$ and PaO_2 are determined primarily by pulmonary gas exchange, local lung perfusion and body posture, yet they have a major influence on cerebrovascular resistance (56, 254) (Figure 1).

Using a simplified approach, one can divide mechanisms that regulate CBF into four distinct components or adaptive responses: autoregulation, chemoregulation, neuronal regulation, and endothelium-dependent regulation. The first mechanism, termed autoregulation, relates to the response of the cerebral circulation to changes in cerebral perfusion pressure (327, 328, 427, 444, 445, 581, 622). Cerebral perfusion pressure is determined by BP, ICP, and venous pressure. Under physiological conditions, cerebral perfusion pressure is mainly determined by arterial BP and body posture [supine or prone *versus* seated or standing in humans], because venous BP and ICP are relatively low and normally exhibit only small changes. Some key exceptions are traumatic brain injury or intracranial hemorrhage (ICH), where ICP can be substantially elevated and affects perfusion pressure. Cerebral autoregulation (henceforward referred to simply as ‘autoregulation’) will be the focus of this review, and will be discussed in detail in Sections **II, V** and **VI**.

The second mechanism is chemoregulation, another class of vascular reactivity. This includes vascular responses to changes in CO_2 (and subsequently pH), PO_2, or O_2 content. Changes in these variables (e.g., hypocapnia and hypercapnia) elicit strong CBF responses (56, 97, 254). Of these mechanisms, reactivity to CO_2 has been the most widely studied in controlled laboratory-based setting in humans, and has also been termed cerebral vasomotor reactivity to CO_2 (254).

The third mechanism consists of the influence of nerves or neurons on CBF. This includes NVC - the local CBF response to nearby intrinsic neuronal activation within the brain parenchyma (193, 265) - but also includes effects of autonomic and sensory nerves (extrinsic innervation) on the extra-parenchymal segments of the cerebral vasculature (225).

A fourth mechanism relates to the effects of vascular endothelial cells on vascular tone and therefore CBF. In response to hemodynamic stimuli (e.g., shear stress), ions, neurotransmitters, metabolic stimuli, and therapeutic agents, among other factors (160, 165, 260, 294, 357). This ability of endothelial cells to cause vasorelaxation importantly contributes to NVC. Studies using selective injury of endothelium or cell-specific genetic manipulation have shown that this cell plays an essential role in propagated (or ascending) vasodilation during NVC, eventually reaching arterioles and arteries on the pial surface (79, 357). Other studies that examined genetic alterations of signaling molecules in endothelial cells, but did not focus on propagated vasodilation, provide further direct evidence that endothelial cells play a major role in the vascular component of NVC in pial and parenchymal arterioles (84, 252). While still supporting a key role for endothelium, one study provided some evidence against a role for endothelial cells in propagated vasodilation (from capillaries to small parenchymal arterioles) in that vasodilation in response to whisker stimulation in mice occurred in precapillary arterioles before changes in diameter of capillaries (252). Endothelial dysfunction, a feature of

many forms of large and small vessel disease, can therefore have multiple consequences, not only on CBF, but also on other endpoints related to brain health.

Unlike myogenic responses (discussed below), in which a single cell type mediates most (or all) of the response to changes in transmural pressure, endothelium-dependent responses cannot occur without endothelial cells exerting effects on vascular muscle or other cellular targets via molecular or electrical signalling. Further, endothelium-dependent effects on platelets, immune cells, neurons, and glia, each involve target cells, highlighting that this signalling is not based on a single cell response(265).

As a final short note to illustrate the complexity of endothelial function in the brain, endothelial cells normally also inhibit processing of ß-amyloid and phosphorylation of tau – both major contributors to Alzheimer's disease (32, 294).

Because autoregulation, i.e. the focus of this review, does not operate in isolation, we have attempted to present an integrative approach, briefly discussing other interacting mechanisms. Studies of autoregulation need to consider overall integrated responses. For example, many studies of autoregulation only consider effects of BP on CBF. However, other parameters affecting CBF when measurements are made cause 'physiological noise' in the BP-CBF relationship (505). For this reason, studies of autoregulation need to control variables such as the amount of exercise and caffeine intake prior to testing, room temperature, cognitive activation or mental stress during the experiment, and measure $PaCO_2$ or end-tidal CO_2 during experiments to ascertain if this parameter remained stable, or to take changes in CO_2 into consideration when interpreting results (98).

Another reason for this integrative approach is that mechanisms can be confused in the literature. For example, some studies use the term autoregulation when describing vasomotor

reactivity to CO_2. Others use ‘pressure reactivity’ to describe autoregulation, which can be confused with CO_2 reactivity.

D. *Other roles for the cerebral circulation outside the scope of this review*

The focus of this review is on the role of the cerebral circulation in delivering blood flow to the brain, with the main purpose of delivering O_2 and removing CO_2. Other functions of the cerebral circulation receive little attention in this review. For example, the blood-brain barrier (BBB) plays an essential role in controlling or limiting the movement of ions, molecules, amino acids, nutrients, cells, and so forth, into and out of the brain parenchyma (5, 461, 550). Damage or dysfunction of the BBB can be caused by aging, abnormal hemodynamics (i.e., acute hypertension), and various diseases (e.g., stroke, chronic hypertension, dementias, traumatic brain injury, multiple sclerosis, neuroinflammation, and so forth) (461, 550). Such damage or dysfunction can in turn have multiple consequences, such as impaired transport of essential substances into the brain, reduced removal of waste products or toxins from the brain, and the entrance of molecules or cells (e.g., toxins, infectious agents, drugs, proteins, immune cells) that are neurotoxic and/or cause cellular damage. This topic is outside the scope of this review, so we refer to other recent reviews for further reading (461, 550).

Another proposed function of the cerebral circulation that has reemerged recently and has some overlap with BBB function, relates to clearance of waste and toxins from the brain (265, 554). Three mechanisms, or pathways, have been proposed to play key roles. It should be noted that there is still controversy regarding the physiological and pathophysiological role of these pathways (285, 528).

One mechanism is the transvascular pathway, where toxins are actively transported across the BBB, from the brain and into the blood. An example is the transportation of amyloid-β from the perivascular space into the blood vessel by LRP1 (low-density receptor-related protein).

Amyloid-β and other waste/toxins reach the perivascular space by diffusion from the brain parenchyma (265, 554). The second mechanism is the perivascular pathway. Here, toxins and waste that have diffused into the perivascular spaces that surround penetrating arterioles, are transported alongside these same arterioles towards arteries on the surface of the brain, followed by drainage into cerebral lymphatics (located in the dura mater and meninges) and eventually into cervical lymph nodes (265, 554). Pulsations in blood flow, influenced by the dynamics of vascular distention, or spontaneous vasomotion, may have a role as a pump that drives this perivascular flow of brain interstitial fluid (ISF) (34, 460, 471). The third proposed mechanism is paravascular transportation. This concept has recently been termed the 'glymphatic system' (471). Here, CSF is hypothesized to travel into the brain parenchyma, alongside penetrating arteries and arterioles (therefore also in the perivascular space, but in opposite direction from the perivascular pathway), where it would clear the ISF and then exit alongside venous perivascular spaces. This paravascular pathway is thought to rely on aquaporin-4 channels in astrocytic end-feet in the perivascular spaces, to transport the CSF into the ISF (265, 554). Changes in hemodynamics, structure, or mechanics of the cerebral circulation may affect these three pathways in several ways. For example, changes in the pulsatile dynamics, which occurs in hypertension with increased vascular stiffness, may affect perivascular transportation. A feature of small vessel disease are changes in the microvascular perivascular spaces, associated with hypertension and expansion of perivascular spaces (Virchow-Robin spaces), which may also contribute to impaired ISF dynamics (604). Using an animal model, others have suggested recently that spontaneous slow oscillations (vasomotion) in arteriolar diameter may drive clearance or drainage of solutes from the brain parenchyma (591). This clearance was enhanced when vasomotion was increased by visual activation of the occipital cortex and was reduced in the context of vessel wall dysfunction (e.g., cerebral amyloid angiopathy).

II. AUTOREGULATION: The static and dynamic responses of CBF to changes in BP.

A. *Historical perspective*

Lassen's publication in 1959 in this journal can be marked as the 'birth' of autoregulation research in humans (327), although Roy and Sherrington provided a description of what we now call autoregulation in 1890. Roy and Sherrington were unable to directly measure CBF, but estimated changes in CBF from changes in brain volume or increases in cerebral venous pressure. They noted that changes in CBF could be smaller than changes in BP, or show an earlier return towards baseline (493). Others such as Fog provided early data that confirmed and extended the concept of autoregulation (175). Using a cranial window approach in anesthetized cats, Fog described rapid changes in the diameter of pial arteries and arterioles in response to experimental manipulation in arterial BP (175).

Lassens's paper introduced a more integrative approach of linking central (systemic) hemodynamics and regulation of CBF (327). Lassen presented a now very well-known figure that plotted CBF against BP for 11 groups of patients with varying levels of BP. That figure revealed a plateau in CBF across a relatively large range of BP (mean arterial BP between ~50-150 mmHg) and was the first description of effective maintenance of CBF over a considerable range of BP, a concept that Lassen termed autoregulation, to suggest the dominance of local mechanisms. Lassen's conclusions regarding autoregulation, in combination with many subsequent studies in the following decades, evolved into a widely accepted concept in vascular biology and medicine regarding regulation of CBF in humans and in preclinical models. His work continues to be cited frequently in the literature.

B. Critical appraisal of Lassen's autoregulation curve

Lassen's original curve was an extrapolation, based on a cross-sectional comparison of 376 individuals from seven publications. It featured a straight line drawn across average CBF data from nine of the 11 groups, which varied around a mean CBF of 55 ml/100g/min, for mean arterial BP between 50 and 175 mmHg. The graph also featured a downward line that connected two data points well below and to the left of the horizontal line, from two studies with mean CBF of 30 ml/100g/min and mean BP values of 40 mmHg. Lassen's interpretation of these latter two data points was that they marked the 'lower limit of autoregulation'. There was no data at higher BP values, and therefore no 'upper limit of autoregulation'; that concept was added later. Questions have been raised about the validity of some of the data points used to fit Lassen's curve (241). For example, one of the seven publications could not be traced and verified, and one of the data points had been plotted in error. A corrected plot would no longer feature a straight line but a line with a slight upward slope (241). Furthermore, it is important to realize that the original curve contained no within-subject data on changes in BP with repeated measurements of CBF. The curve consisted entirely of group averaged CBF values for a set of patients with a specific BP level, linked to specific medical conditions. Lassen's curve nonetheless was commonly interpreted as reflecting what would happen to CBF if, in a group of people or within a single individual, BP was reduced or increased across the wide range depicted in the figure.

More direct evidence to support this interpretation of the autoregulatory curve came after this original publication, consisting mainly of findings from preclinical models. A series of generally well-controlled experiments in non-human primates and common laboratory species confirmed the substantial autoregulatory capacity of the cerebral circulation, where despite large changes in BP, CBF is held relatively stable (78, 166, 172, 173, 231-233, 242, 243, 251, 317, 367, 497, 543, 574). Figure 2 provides examples of such experiments (118, 166, 233, 242, 251, 287, 367, 543, 573). All these studies reveal a range of BP in which CBF was relatively

stable. In some studies, there is a portion of the curve where a slope is not apparent. In others, there is a small positive slope - an increase in CBF as BP is increased. Upper and lower limits of autoregulation are suggested or can be seen in some of these data (Figure 2).

In conclusion, if one combines animal and human experimental data (discussed below), the overall concept of Lassen's autoregulatory curve can be maintained, albeit with some important caveats and modifications. The existence of an autoregulatory range of BP, where autoregulation is highly effective and where CBF is relatively stable, is undisputed. We suggest it should no longer be called a 'plateau phase', because this implies a horizontal line with zero slope. In reality, the relationship between BP and CBF within this autoregulatory range can vary between an upward or even a downward slope (90, 350, 410). A better description than 'plateau' therefore might be the term 'gradient'. We suggest a more precise description for this 'gradient phase of autoregulation' would be that there is a range of BP where autoregulation minimizes variations in CBF when BP is altered. How wide this range may be, cannot be precisely defined from the available studies, as a large number only looked at one end of the autoregulatory curve or a limited range of change in BP. Studies that would be needed to obtain such data may be impossible to perform in humans, for both physiological and ethical reasons. Even if such data did exist, it is unlikely that a group-averaged range would apply to all individuals. What we do know, however, is that in most studies relatively slow reductions or increases in mean arterial BP between approximately -20 and +20 mmHg are associated with a stable CBF in humans (for details and references see section V.B. *ii* on Hypertension and static autoregulation).

C. *The importance of time: autoregulation is strongly affected by the rate at which BP changes.*

One of the reasons why it is difficult to study a wide range of BP changes in humans is the efficacy of the baroreflex. The baroreflex normally helps to maintain BP within a narrow range during normal daily activities and under pathophysiological conditions (296). As such, this neural reflex will limit or at least dampen large fluctuations in BP (296). Commonly, this only allows for the assessment of relatively small changes in BP that can be maintained for a longer period. An example is lowering or increasing BP over weeks by starting or stopping antihypertensive medication. Larger, but acute changes in BP are difficult to achieve and can only be maintained for shorter periods, usually only during an experimental setting. Examples are administration of intravenous drugs to acutely lower or increase BP (126, 350). Although pharmacological manipulations are a common experimental strategy to alter BP, it is important to realize that depending on the agent used and whether it activates endothelial cell receptors or crosses the BBB to reach vascular muscle, pharmacological agents sometimes have direct effects on the cerebral vasculature, independent of changes in BP.

Numan and Ainslie recently reanalyzed 40 studies in healthy humans that examined the relation between BP and CBF above and below resting mean BP (410). Largely independent of the technique used to assess CBF (i.e., TCD, MRI, PET, or Xenon-133 technique), these studies confirmed that the cerebrovasculature has autoregulatory capacity, but not that CBF was completely stable over an autoregulatory range. In fact, they reported a relatively small range of mean BP that is associated with a stable CBF within subjects. Moreover, the efficacy to regulate CBF seemed to differ based on the direction of change in BP, with a more effective capacity to stabilize CBF during acute (transient) periods of hypertension, compared to hypotension. However, the studies summarized in that review used a variety of techniques to increase and decrease BP, leading to potential confounders, such as effects of medications, autonomic activation, and differences in $PaCO_2$. Many studies applied BP changes over relatively short periods of time (i.e., minutes), as in the study by Liu *et al.* (350). This affects

the shape of the classic autoregulation curve, because these faster changes in BP lead to a smaller range of BP wherein CBF is kept relatively stable (the 'gradient phase' noted above), and to a steeper gradient within that range. The importance of time in autoregulatory mechanisms is captured in the terms static and dynamic autoregulation (561). Understanding these two concepts, and the difference between them, is important for a proper understanding of autoregulation.

D. *Static and dynamic autoregulation*

i. Static autoregulation

The classic relationship between mean arterial BP and CBF, derived from Lassen's publication (327), should now be referred to as 'static' autoregulation (427, 428, 430, 432, 433, 561, 581). This does not relate to physiological characteristics *per se*, but rather refers to experimental characteristics that only measure the steady-state relationship between CBF and BP. The term *static* refers to the concept that BP and CBF are measured under conditions where individual variables (BP, CBF) have reached a steady state (427, 437). BP may have been experimentally increased or decreased, but it has reached a new stable, steady-state level (427, 581, 622). BP and CBF are measured over longer time intervals (10 minutes or more) and the resulting values represent the average BP and CBF during that period. This approach was a consequence of the fact that historically, measurements of CBF in humans required at least 10 minutes to perform. Due to this averaging, both BP and CBF will not display their short-term variability. Using this definition of static autoregulation, especially when applied to between-subject changes in BP and CBF, CBF is held relatively stable between various levels of BP under normal physiological conditions. This interpretation is a close approximation of Lassen's data presentation and conclusions (see also Figure 2).

ii Dynamic autoregulation

The concept of dynamic autoregulation only emerged once techniques with high temporal resolution became available to measure faster changes in CBF (427, 581, 622). Now, instead of values that took 10 minutes or more to obtain, these techniques allowed for measurements of changes in BP and CBF (or CBF velocity) occurring over seconds (210, 407, 408). It became clear that during more rapid changes in BP, there was much greater variability in CBF than was hitherto assumed based on Lassen's concept of static autoregulation (Figure 3 and 4). The ability of autoregulation to respond to rapid changes in BP across seconds or minutes (e.g., during postural changes, coughing, or physical activity), is referred to as dynamic autoregulation (427, 428, 430, 432, 433, 561, 581) (Figures 3-5).

TCD to measure CBF velocity (typically using the middle cerebral artery), with simultaneous beat-to-beat recordings of BP, has become a popular technique to measure dynamic autoregulation (4). Aaslid and coworkers examined the temporal relationships between BP and CBF in response to deflation of BP cuffs placed around the thigh to induce rapid, transient hypotension (3, 4, 370). The resulting drop in BP was accompanied by a proportional decrease in middle cerebral artery blood flow velocity -which was assumed to provide an accurate index for changes in CBF. In healthy individuals, CBF recovered more quickly than BP. These observations highlighted in humans that autoregulatory mechanisms were unable to maintain CBF perfectly stable during rapid changes in BP. Instead, dynamic autoregulation results in a relative, time-dependent buffering of changes in CBF.

This idea of a relative CBF buffering capacity for rapid changes in BP was later expanded by Birch *et al.* (46). They identified that the capacity to buffer changes in CBF was strongly dependent on the speed of BP changes (46). The slower the change in BP, the smaller the impact on CBF, to a point where CBF becomes almost unaffected. However, for more rapid changes in BP, the buffering capacity is progressively reduced and changes in CBF become larger, until a point where changes in CBF become as large as the change in BP. At that point,

CBF passively follows BP. This concept is illustrated in Figure 3, where oscillations (a change occurring at a specific frequency) are transmitted or blocked depending on the frequency, and is comparable to a high-pass filter that transmits high frequencies, but blocks low frequencies (136, 137).

This relationship between CBF and BP is analogous to the application in acoustics, where a high-pass filter transmits high frequency signals from an audio source to a tweeter. This led Giller to apply transfer function analysis (TFA) to dynamic autoregulation, a mathematical concept based on this example of acoustic signals. TFA quantifies how different frequencies and amplitudes in BP are transmitted (transferred) to CBF. Specifically, Giller applied the concept of coherence [i.e., a measure of the strength of the relationship between oscillations (frequencies) in BP and CBF] (192). As a simplified explanation, coherence can be compared to *r* in a linear regression. A coherence of 0 means no relationship between oscillations in BP and CBF. A coherence of 1 indicates that the oscillation in CBF is fully explained by the oscillation in BP. A coherence of 1 also means that CBF is passively following BP, and there is no dynamic autoregulation. Giller therefore proposed coherence as a measure of autoregulation efficacy: indeed, coherence increased for faster oscillations (higher frequencies). Further applications of TFA to dynamic autoregulation involved the use of TFA gain and phase by Panerai (436, 437, 439), Blaber (47) and Zhang (648). In summary, these groups reported that TFA characteristics between oscillations (fluctuations) in BP and CBF resemble a high-pass filter, wherein higher frequency fluctuations are more linearly transferred (i.e., higher coherence) to the cerebral circulation than lower frequency fluctuations (581). The parameter gain, as in acoustics, quantifies damping (i.e., smaller oscillations in CBF compared to BP oscillations). Phase - or more appropriate, phase shift - indicates that the oscillations in BP and CBF are no longer synchronized. In other words, because in every oscillation, CBF returns towards baseline before BP does, the CBF oscillations show a phase shift compared

with the BP oscillations (see Figures 4 and 5). TFA, with estimates of coherence, phase and gain, has become the most widespread method to quantify dynamic autoregulation (98, 382, 384, 581).

E. *How is dynamic autoregulation assessed?*

TFA has become popular because it allows assessment of dynamic autoregulation from a 5 minute (or longer) recording of BP and CBF, without the need for an experimental intervention to change BP (95, 437, 648). This approach is feasible because BP normally exhibits spontaneous changes (oscillations) that occur at specific frequencies. These BP changes influence CBF, but how they are transmitted is determined by dynamic autoregulation (577). The benefits of this method are being able to perform measurements while subjects rest quietly, either supine or sitting. This makes the technique more suitable for patients who cannot tolerate or perform interventions to experimentally manipulate BP (95). These benefits are in part offset by a number of disadvantages (524). The assessment of dynamic autoregulation can be hindered by a low signal-to-noise ratio. This can occur because BP oscillations can sometimes be too small (586) in relation to the level of noise that is always present when performing non-invasive recordings (156, 504, 505). The signal-to-noise ratio is also reduced because CBF is affected not only by BP, but by various other parameters during these measurements, such as changes in $PaCO_2$ or cognitive activation (505). This has led to the development of methods to enhance BP oscillations (94, 524). Several methods are now used, including repeated squat-stand (94, 527) or repeated sit-stand maneuvers (122, 585), paced breathing (135, 136), repeated occlusion/deflation of thigh cuffs (293), or oscillatory lower body negative pressure (226). Each procedure has in common that the frequency of the maneuver determines the frequency of the BP oscillation.

An example of how this method can be used to study dynamic autoregulation is illustrated in Figure 4. This figure shows an example of repeated sit-stand maneuvers that cause large oscillations in BP and CBF (middle cerebral artery blood velocity) at a frequency of 0.05 Hz. Visual inspection might indicate that BP changes are passively transmitted to CBF, implying absent or poor autoregulation. Upon closer inspection, with each oscillation in BP, CBF recovers before BP. This leads to a phase shift between the BP and CBF signals (Figure 5). Figure 5 also illustrates the concept of gain (or the ability for damping) by comparing the relative magnitude of CBF oscillations to those in BP. With normal dynamic autoregulation, a faster return towards baseline of CBF compared to BP will result in damping of CBF oscillations (581).

The frequency of 0.05 Hz is one where dynamic autoregulation is very effective. Autoregulation can be even more effective with slower changes in BP (lower frequencies). This phenomenon can, at least theoretically, be extended to changes in BP that become progressively slower, occurring over hours, days and weeks, and resulting in progressively smaller changes in CBF. These very low frequency fluctuations in BP represent the transition between dynamic (faster changes) and static (very slow changes) autoregulation, represented in Figure 3. Empirical evidence supporting this notion was recently published, in experiments wherein progressively slower oscillations in BP were induced with oscillatory lower body negative pressure (227), but is also supported by long-duration observations of spontaneous changes in BP (650).

F. *Static versus dynamic autoregulation*

The concept that dynamic and static autoregulation are two ends of a spectrum, has several consequences. First, a measurement at one end of the spectrum may not correlate with measurements at the other end. More precisely, dynamic autoregulation may not reflect static

autoregulation (126), even though this was originally suggested when dynamic autoregulation was introduced (561). Methodological differences may explain the opposite findings of De Jong *et al.* (126), who found no association between static and dynamic autoregulation when tested in the same subjects, *versus* Tiecks *et al.* (561) who found a strong linear relationship between static and dynamic autoregulation. The main methodological difference is that Tiecks *et al*. performed experiments during surgery, where isoflurane anesthesia was used to impair autoregulation (see section V.*G Anesthesia and autoregulation)*. This drug-induced impairment of autoregulation may have driven the correlation between static and dynamic autoregulation (126). Further research is needed to evaluate how assessment of dynamic autoregulation relates to static autoregulation. For example, can a finding of normal dynamic autoregulation be used to predict a normal static autoregulation response (e.g., to BP lowering treatment)? It is conceivable that in an individual, impairment in autoregulation manifests as a slowing of the adaptive response, starting with impairment to counteract faster changes in BP (i.e., impaired dynamic autoregulation), while the adaptation to slow changes in BP is still intact (i.e., normal static autoregulation) (438). Nonetheless, in the study by De Jong *et al.*, the lack of association between dynamic and static autoregulation was observed in subjects with normal static and normal dynamic autoregulation (126). Ideally, studies performing repeated within-subject comparisons of static and dynamic autoregulation could shed more light on this controversy.

A second consequence of the ‘two ends of a spectrum’ concept is that the outcome of studies in humans that try to measure static autoregulation are affected by the timing and magnitude of BP changes. A clear example of this is the study by Tan *et al.* which plotted a static autoregulation curve using induced BP (and CBF) oscillations at a frequency of 0.03 Hz (552). This frequency is much more in the dynamic range than in the static range, which explains why

that study found a very narrow gradient phase ('autoregulation plateau') of only 10 mmHg, and a steep slope for this gradient (552).

G. *Revisiting historical experiments*

When we revisit early studies with the current knowledge of dynamic autoregulation, we can explain initial observations of Roy and Sherrington (493) and Bayliss and Hill (40). Based on the heart beat traces in the figures in Bayliss' publication, we can tell that the perfusion pressure changes in the various experiments were of short duration (i.e., seconds). We know now that for such rapid changes in perfusion pressure, isolated cerebral blood vessels and CBF passively, but transiently, follow such BP changes, without effective regulation of CBF. Figure 6 compares one of Bayliss' figures with a recent human experiment wherein rapid changes in BP were provoked by repeated transitions between squatting and standing (94). In both experiments, the sudden increases and decreases in BP occur within 15 seconds, and these transient changes in BP appear to be passively followed by CBF, as interpreted by Bayliss (40). Closer inspection however indicates a more rapid return of the CBF trace in both experiments. In retrospect, a more precise interpretation of Bayliss' experiments should have been that this control was unable to maintain a stable CBF under the experimental conditions that were used (rather than that there was no active vasomotor control in the cerebral circulation). Another important message from Bayliss' experiments is the value of presenting individual findings, something that is often omitted in the current literature. In this case, presenting individual data made it possible to reinterpret findings, even >100 years after the original publication.

H. *Mechanisms that underlie autoregulation*

Some key phenotypic features of autoregulation have been known for many decades. For example, using a cranial window to measure vascular responses in anesthetized cats, Fog described rapid changes in the diameter of pial arteries and arterioles (within 1-2 minutes) in

response to experimental manipulation of arterial BP (175). These changes included vasoconstriction, with vascular diameter decreasing below baseline values, in response to a rise in BP and vasodilation following a reduction in BP (175). This work provided direct early examples of the rapidity of the cerebrovascular response following increases or decreases in arterial BP. In addition to insight regarding the temporal nature of the response, these studies revealed that BP-induced changes in the diameter of smaller arterioles were greater on a percentage basis than in larger arteries. Although it was not yet known that arteries and arterioles in this segment of the cerebral circulation are resistance vessels (128, 164, 233, 265), Fog speculated that reductions in vessel diameter during increases in BP would prevent a rise in capillary pressure and thus protect against brain edema (175). This concept remains widely accepted today (Figure 1)(85, 448).

With respect to autoregulation-related terminology, *myogenic tone* is defined as the state of partial vasoconstriction that occurs in an isolated blood vessel when maintained at a constant pressure (85). Arteries and arterioles in the pial and parenchymal circulation respond to pressurization with development of myogenic tone (85). As an example, isolated brain parenchymal arterioles from both humans and mice develop substantial myogenic tone when pressurized to physiological levels (115, 128, 130, 155). *Myogenic reactivity* reflects changes in vascular tone in response to changes in pressure (85). The term *myogenic response* seems to be used as a more general or global term, representing alterations in vascular tone that result from changes in intravascular or transmural pressure *in vitro* or *in vivo*. Myogenic responses of isolated cerebral blood vessels are more commonly studied during increases in pressure (rather than reductions in pressure). Many *in vitro* studies have confirmed the basic concept described *in vivo*, that changes in vessel diameter occur relatively rapidly in response to changes in intravascular BP (128, 130, 155, 162, 313, 380, 601, 603).

Arteries or arterioles from the pial or parenchymal circulation exhibit myogenic reactivity

following changes in transmural pressure (85, 342). In response to reductions in arterial BP, these vessels respond by reducing myogenic tone and increasing lumen diameter – thus reducing resistance through each vessel. Conversely, an increase in arterial BP activates mechanisms that increase myogenic tone and reduce vascular diameter – thus increasing vascular resistance. This suggests that rather than regulating vessel diameter *per se*, the physiological variable that is being regulated is transmural wall tension (85). With increases in BP, a reduction in vessel diameter helps to normalize wall tension. This concept is supported by the fact that similar phenotypic changes are seen in isolated vessels studied under pressurized conditions *in vitro*, but where blood flow is absent. Such behaviour of isolated arteries or arterioles *in vitro* during increases or decreases in transmural pressure (128, 130, 155, 162, 313, 380, 601, 603) confirm the changes in vascular diameter that have been described by many laboratories performing *in vivo* experiments in which arterial BP was altered (for examples, see (162, 175, 232, 233, 317, 573)). It is important to stress that, as the name implies, the myogenic response is intrinsic to vascular muscle. For example, this response remains intact if endothelial cells are removed or selectively injured (85, 162, 313, 380, 601, 603).

An important step in the development of the myogenic response relates to depolarization of vascular muscle, which has profound effects on vascular tone (Figure 8A and 8B). Work by Nelson and others demonstrated the high sensitivity of vascular tone to changes in membrane potential of vascular muscle (234, 312). Data based on direct recordings during alterations in intravascular pressure demonstrated changes in membrane potential of only a few millivolts. Under physiological conditions (i.e. baseline -40 mV), such changes cause significant alterations in intracellular Ca^{2+} and subsequently vascular diameter (Figure 8A)(234, 312, 402).

Increases in intraluminal pressure within an isolated artery or arteriole results in mechanotransduction, depolarization of vascular muscle, and Ca^{2+} mobilization (Figure 8B).

The increase in intracellular Ca^{2+} following a rise in intravascular pressure is due primarily to influx of Ca^{2+} across the plasmalemma (mainly via voltage-dependent Ca^{2+} channel, $Ca_V1.2$) or release of Ca^{2+}-stores from the sarcoplasmic reticulum (local Ca^{2+}-signals) via IP3 or ryanodine receptors (85, 234), resulting in activation of contractile proteins (phosphorylation of myosin light chain, MLC) and a reduction in vascular diameter (Figure 8B). When voltage-dependent Ca^{2+}-channels are blocked, or when extra-cellular Ca^{2+} is removed, the vasoconstrictor response to pressure (development of myogenic tone) is abolished, thus confirming an essential role of Ca^{2+} (312). Conversely, hyperpolarization of the cell membrane, due to stimuli that include Ca^{2+} sparks, closes $Ca_V1.2$ channels, reducing Ca^{2+} entry and intracellular Ca^{2+} concentrations, resulting in vasodilation (Figure 8A and 8B)(85, 234, 312). Together, these changes are believed to be major contributors to the maintenance or relative stability of CBF during increases or decreases in perfusion pressure *in vivo* (85, 234)(Figure 8). In addition to changes in subcellular concentrations of Ca^{2+}, myogenic tone is regulated by mechanisms that influence Ca^{2+} sensitivity, including protein kinase C and Rho kinase (ROCK)(Figure 8B)(85, 342). For example, in brain parenchymal arterioles, pharmacological inhibition of ROCK, or the ROCK2 subtype, eliminates the vast majority of myogenic tone (128, 340).

In relation to the control of myogenic responses and autoregulation of CBF, a major unanswered question continues to be: “what is the sensor responsible for mechanotransduction underlying the myogenic response and subsequent depolarization of vascular muscle?” Although this aspect of myogenic responses remains relatively poorly defined (particularly *in vivo*), multiple candidates have been proposed to be involved. These candidates include integrins (eg, $\alpha_5\beta_1$), mechanosensitive G-protein-coupled receptors (GPCRs) [eg, angiotensin AT1, sphingosine-1-phosphate (S1P), purinergic (P2Y)], G protein subunits (G_{12}/G_{13}) linked to activation of ROCK, and stretch-activated ion channels such as transient receptor potential

(TRP)(eg, TRPC6, TRPM4) and epithelial Na^+ channels (βENaC) (Figure 8C) (53, 82, 84, 85, 148, 342, 344, 593, 611, 641). Another potential mediator, the PIEZO1 stretch-activated ion channel in vascular muscle, has been investigated, but does not appear to play a role in regulating myogenic tone in isolated cerebral arteries (480).

In addition to multiple pressure-sensitive candidates, defining myogenic mechanisms is further complicated by evidence that the role of putative mechanotranducers may vary depending on the vascular segment or zone in question. For example, pharmacological inhibition of the AT1 receptor has been reported to reduce myogenic tone in cerebral arteries, but not parenchymal arterioles (53), despite the fact that parenchymal arterioles develop greater levels of myogenic tone (85, 102, 115, 128, 129, 340).

Although myogenic responses are intrinsic to vascular muscle, there are additional determinants or modulators of this response including genomics, endothelial-, metabolic-, neural- and immune-related signalling, as well as other ion channels and signalling networks (Figure 8D)(85, 234, 641). For example, large conductance Ca^{2+}-activated K^+ channels *(*BK_{Ca}} in the cell membrane are activated by local release of Ca^{2+} sparks from the sarcoplasmic reticulum, resulting in local membrane hyperpolarization and attenuation of myogenic tone (Figure 8B)(234, 402). The cystic fibrosis transmembrane regulator (CFTR, a membrane protein and chloride channel) exerts inhibitory effects on myogenic tone by attenuating S1P-dependent signalling (341). Collectively, such mechanisms may limit the development of excessive myogenic tone *in vivo*.

While vascular muscle and the myogenic response appear to play a predominant role in relation to autoregulation of CBF during changes in BP *in vivo*, it is not the only mechanism or cell type involved, making its precise contribution to overall autoregulation difficult to quantify. Thus, when new mechanotransducers, cell types, or signalling events are implicated, based on

studies of myogenic responses in isolated vessels, one cannot assume that the relative impact of a given mechanism studied *in vitro* is the same *in vivo*. For example, during increases in arterial BP (the upper half of the autoregulatory curve), several lines of evidence suggest sympathetic and trigeminal nerves influence the vascular response (see Section III.D.). Mechanisms that control vessel diameter and vascular resistance during reductions in arterial BP are likely not mediated through inhibition of these mechanisms that are activated when BP is increased. With decreases in perfusion pressure, mechanisms involving tissue hypoxia, adenosine, calcitonin gene-related peptide (CGRP), ATP-sensitive K^+ channels, and eNOS have all been implicated to play a role (165, 261, 317, 320, 486, 519, 565, 641). In this context, genetic deficiency in *NOS3* (eNOS) shifts the lower end of the autoregulatory curve to the right, consequently leading to augmented reductions in CBF in response to decreases in BP (261). A loss of function mutation in the *NOS3* gene is associated with impaired autoregulation in response to carotid artery compression in humans (641). In contrast, other genetic variants enhance NO (eNOS-derived) signalling and are associated with long-term beneficial effects, including reducing the risk for stroke in humans (157). We speculate that such protective effects may relate, in part, to positive effects on autoregulation of CBF.

Based on a model in which vessels within a brain slice are perfused and pressurized *in vitro*, a role for astrocytes in modulating myogenic tone has been suggested (Figure 8D)(303). The potential impact of these cells in this context is difficult to define because the model elevated intravascular pressure by increasing vascular perfusion within the slice. In other words, arteriolar responses were not studied at constant pressure (with constant flow) making interpretation less clear. The slice model is also complicated by the fact it was studied under hypothermic conditions, which are known to affect myogenic tone and CBF (318).

Recent studies continue to provide insight into novel potential sensors or signalling events that may contribute to myogenic responses in isolated vessels. Unfortunately, the majority have not

tested the relative contribution of each candidate mechanism *in vivo*. For example, the AT1 receptor is reported to be mechanosensitive, with activation of the receptor increasing myogenic tone in isolated cerebral arteries (53, 381). In other studies, however, inhibition of this receptor does not significantly alter baseline diameter of pial arterioles, resting CBF, or impair autoregulation of CBF during increases in arterial pressure (23, 194, 374, 543, 607). It seems logical to assume that *in vivo*, myogenic responses contribute to resting tone of cerebral arterioles, baseline CBF, and changes in CBF with increased BP. Thus, the contribution of AT1 receptors in relation to autoregulation of CBF remains unclear (Figure 8B).

There are exceptions to the approach of only studying myogenic mechanisms in isolated vessels *in vitro*. For example, a recent study examined effects of smooth muscle-specific deficiency in G_{12}/G_{13} protein subunits or the Rho guanine nucleotide exchange factor ARHGEF12, both *in vitro* and *in vivo* (82). Overall, the study suggested a dual mechanism for development of myogenic tone, one that involves Ca^{2+}-dependent and G_{12}/G_{13} G protein subunits, along with ROCK-dependent signalling in vascular muscle (Figure 8B)(82). Additionally, links between ROCK and TRPM4 had been suggested previously (340). The investigators also observed that genetic deficiency in G_{12}/G_{13} subunits in vascular muscle increased baseline CBF (82), a phenotype that is consistent with reduced myogenic tone, although autoregulatory responses per se were not examined *in vivo*.

I. *Where in the vascular bed does autoregulation take place?*

Basic laws of hemodynamics dictate that blood flow is determined by pressure gradients and vascular resistance. As a consequence, autoregulation operates by changing vascular resistance in response to alterations in BP, to maintain blood flow (149, 299). For blood vessels with a fixed length and blood with a fixed viscosity, vascular resistance is determined by vessel diameter (62). Changes in the radius ‘r’ of a blood vessel (i.e., due to vasodilation,

vasoconstriction, or vascular remodeling) affect its resistance by r^4. This means that even small changes in vessel diameter can lead to large changes in vascular resistance, and therefore in blood flow (149, 299, 431, 444, 446). For example, an increase in vessel diameter of only 20% (at a constant pressure), which is within the physiological ability of arteries for acute changes in diameter, will increase blood flow by 207%.

The degree of myogenic tone that develops under normal conditions varies along the vascular tree. Based on work using isolated blood vessels, there is less myogenic tone under baseline conditions in larger cerebral arteries than in smaller pial and parenchymal arterioles (85, 102, 115, 128, 129, 340). These findings are consistent with the observation that effects of changes in arterial pressure on vessel diameter are size-dependent in pial arteries and arterioles *in vivo* (175, 317, 573). This suggests that also during autoregulation and changes in vascular resistance during changes in perfusion pressure *in vivo*, differences may exist in the relative importance between segments. Direct measurements of CBF and intravascular pressure under baseline conditions indicate that vascular resistance is distributed over different vascular segments (or zones), resulting in a reduction in pressure along the vascular tree. For example, intravascular pressure in pial arterioles on the surface of the brain is approximately half of systemic arterial BP (i.e. central aortic BP) (Figure 8E) (128, 160, 232, 233, 265). As part of this arrangement, pulsatile effects of the beating heart on intravascular pressure (pulse pressure) are attenuated as blood flows down the vascular tree, into the parenchymal circulation, and pial venules (164, 166, 232, 233, 377). Furthermore, the hemodynamic profile within the parenchyma may be influenced by precapillary sphincters or other structures at the transition from small arterioles to capillaries (213, 473). Venules and larger veins contribute modestly to overall vascular resistance under normal conditions (166, 232, 233, 377).

Increases or decreases in BP evoke changes in resistance of large arteries, arterioles on the pial surface, and within the brain parenchyma (39, 164, 167, 175, 233, 242, 317, 573). From these

experiments, we have learned that small vessel resistance, which was calculated based on measurements of intravascular pressure in pial arterioles and pial venules, accounts for approximately half of total cerebrovascular resistance (Figure 8E) (164, 167).

To our knowledge, the relative contribution of arterioles, capillaries and venules within the parenchyma to overall vascular resistance has never been directly determined *in vivo*. Because most of the decline in intravascular pressure in the pial circulation occurs at the level of arteries and arterioles (Figure 8E) (128, 164, 265, 331), we assume arterioles and capillaries within the parenchyma are the major contributors to the small vessel resistance component of total cerebrovascular resistance (164, 167). Indeed, during moderate increases in arterial BP (~40 mmHg), small vessel resistance increased by ~50% and CBF was maintained at baseline levels (167).

Although myogenic tone and reactivity have been studied in isolated parenchymal arterioles *in vitro*, little is known regarding the responses of these same arterioles to changes in BP *in vivo*. In one study that used multi-photon imaging, a reduction in cerebral perfusion pressure was produced by increasing ICP by 10-15 mmHg, resulting in vasodilation of penetrating arterioles by ~12% (368). Although this experiment demonstrates an autoregulatory response *in vivo*, details regarding its influence on CBF and effects of changes in perfusion pressure on the various subtypes of parenchymal arterioles (230, 494) are lacking.

As described elsewhere (Section V.), the clinical consequences of failed autoregulation and the mechanisms involved differ depending on which portion of the autoregulatory curve is affected (Figure 8F). Failure at the left side of the curve results in hypoperfusion, potential ischemia, and even death (Figure 1). If autoregulatory mechanisms are overwhelmed and fail at the right end of the curve, hyperperfusion, increases in pressure in arterioles, capillaries, and venules, disruption of the BBB, edema, increased ICP, and death can result (Figure 1) (85, 204, 448,

641). With moderate increases in arterial pressure (~40 mmHg), elevations in vascular resistance are sufficient to maintain CBF at normotensive levels and prevent increases in microvascular pressure in pial venules (167). However, when the ability to autoregulate is exceeded during acute severe hypertension, CBF increases substantially along with elevated pressure in pial venules (Figure 8E, 8F)(167, 377, 378). These microvascular hemodynamic changes are important because acute increases in venular pressure is a key determinant of disruption of the BBB, much of which occurs at the levels of venules (31, 377, 378). Although the BBB is present in cerebral arterioles, capillaries, and venules (620), proteins that comprise tight and adherent junctions between endothelial cells exhibit heterogenous features, including looser junctional strands in venules (620). These looser venular junctional strands may explain why the BBB in venules appears to be predisposed to disruption during acute episodes of hypertension that exceeds the autoregulatory capacity of the circulation (Figure 8E, 8F). The clinical aspects of hypertensive emergencies are discussed in Section V.B.

Anatomical differences in the cerebrovascular bed or other factors, either in physiological or pathological conditions, can result in regional differences in intravascular pressure. For example, intravascular pressure is predicted to be higher in lenticulostriate arteries than in the intraparenchymal arteries in the parietal lobe (537). In addition, regional differences in vascular anatomy and patterns of the vascular tree can affect the control of microvascular pressure and vascular resistance. This could cause regional differences in susceptibility to ischemic events, such as lacunar infarction, which is predominantly seen in brain regions supplied by the lenticulostriate arteries (48, 537). Under pathophysiological conditions, such as small vessel disease, distinct changes in structure and function of small arterioles in the parenchyma may increase local intravascular pressure in upstream arterioles (473). This increase in arteriolar pressure may increase local wall stress and contribute to the development of arteriolar rupture and the pathogenesis of microbleeds (473).

In some, but not all studies, changes in diameter of capillaries have also been described during vasoactive stimuli (213, 214, 224, 250, 357, 610). When changes in capillary diameter are detected *in vivo*, to what extent these changes are active or passive - that is, due to alterations in the contractile state of local pericytes versus changes in transmural capillary pressure - remains largely unstudied and a possibility that is not generally considered (161).

Under some conditions, changes in diameter or cross-sectional area of venules may also occur (376). For example, increases in diameter of small venules occur during hypercapnia (376). A caveat when measuring venous or venular diameter is that veins often do not maintain a circular shape at low pressures (or when not pressurized), exhibiting an oval or collapsed shape (295). A similar limitation is a potential issue when measuring diameter of any vessel using *in vitro* brain slice preparations, where no pressurization is typically present.

Overall, multiple lines of evidence indicate that vascular muscles in cerebral arteries and arterioles are sensitive to changes in BP, and that smooth muscle is the primary effector cell driving acute changes in vascular resistance in response to increases or decreases in BP (Figure 8A, 8B, 8E, 8F). Based on the assumption that the primary mechanism contributing to autoregulation of CBF is myogenic responses of vascular muscle, then cerebral arteries and arterioles (pial and parenchymal) play a significant role in mediating substantial changes in myogenic tone . Capillaries, despite their large surface area, make a smaller contribution to total vascular resistance (Figure 8) and are unlikely to have a major contribution to autoregulation as capillaries do not actively alter their diameter in response to changes in transmural pressure. Whether pericytes can respond to physiological changes in capillary pressure by actively adjusting local capillary diameter is an area of ongoing investigation.

In relation to potential neural control of autoregulation, a few studies have examined whether specific regions within the brain may influence autoregulation of CBF globally. For example,

electrolytic lesions of the fastigial nucleus in the cerebellum had little or no effect on resting CBF or autoregulation of CBF during reductions in arterial BP (produced by hemorrhagic hypotension) in conscious rats (551). In contrast, electrolytic lesions of the nucleus tractus solitarii (NTS) in the medulla impaired autoregulation in multiple brain regions during phenylephrine-induced increases in arterial BP in anesthetized rats (276). This suggests that neurons that originate or pass through the NTS may play an important role. What mechanism(s) could account for such an effect remains unclear as the neural pathways from the NTS do not project to most of the brain regions that were affected (276).

The hypothesis that central pathways might be essential for intact autoregulation contrasts with the concept that local myogenic responses play a major role in this adaptive vascular response. That isolated arteries and arterioles studied in vitro exhibit myogenic responses that phenocopy key elements of autoregulation, argues that the presence of specific brain nuclei or dependent signaling pathways are not essential. Having said that, modulation of autoregulation by neural pathways (e.g., sympathetic nerves), has been described and will nbe further discussed (Section III. D). Thus, neural modulation of autoregulation via specific central pathways remains a possibility, albeit one that remains poorly defined at this time.

In conclusion, because of the physiological and evolutionary relevance of maintaining CBF during changes in perfusion pressure that follow from the various postural challenges in daily living, it is not surprising that autoregulation is normally so effective and that multiple mechanisms and cell types modulate the response (Figure 8). From an evolutionary perspective, the choice for relatively simple (but robust) myogenic responses as the main mechanism for autoregulation is logical, as they appear well positioned to withstand effects of aging and some diseases.

J. *Summary*

Various methods currently exist to; 1. assess CBF (or CBF velocity), 2. measure and manipulate BP, and 3. quantify the efficacy of autoregulatory mechanisms through several analytical approaches, each with their respective limitations and caveats that must be considered. Consequently, research examining autoregulation can be challenging, which may contribute to results that appear to be conflicting at times. Nonetheless, collectively these approaches have provided strong evidence that autoregulatory mechanisms maintain CBF relatively stable across a range of BP values in humans.

In the remainder of this review, we focus on improving our understanding of dynamic autoregulation of CBF in humans under resting conditions, in the presence of relevant disease states, as well as during daily life challenges. We first address other important mechanisms that affect CBF (e.g., arterial blood gases, cerebral metabolism, neurogenic stimuli), but also the inter-relationships between these stimuli. We discuss how and where these mechanisms or stimuli regulate CBF (i.e., at the level of large arteries and/or the microcirculation). With that background, we then focus on autoregulation, discussing clinical implications that may arise as a consequence of impaired autoregulation. We address clinical conditions where CBF seems to play an important role: hypertension, vascular dementia, Alzheimer's disease, mixed dementia, ischemic cerebrovascular disease, and cerebral hemorrhage (Figure 1). Finally, we discuss the consequences of daily life challenges for CBF, such as postural challenges (e.g., orthostatic hypotension, syncope) and the impact of physical activity (or inactivity).

III. OTHER MECHANISMS THAT REGULATE CEREBRAL BLOOD FLOW

Factors that we discuss below collectively influence CBF regionally or globally, serving to match CBF to demands for O_2 and removal of CO_2, or other mechanisms including the impact of blood gases or neural mechanisms (445). Many textbooks and reviews state that autoregulation operates through 'myogenic, metabolic, and neurogenic' mechanisms, implying that all these mechanisms are involved. It may therefore appear confusing if we list metabolic and neurogenic mechanisms as 'additional factors'. For autoregulation, in the definition of the adaptation of CBF to changes in BP, it remains uncertain whether all these mechanisms contribute in an orchestrated manner or whether they represent redundant or fail-safe mechanisms (162, 353, 429, 434, 447). For example, if BP falls, and a major mechanism influencing autoregulation (myogenic responses) should fail to maintain CBF, cerebral metabolism may be affected. Such a change could prompt metabolic mechanisms to promote vasodilation and restore CBF. Similarly, in response to a large rise in BP, increases in myogenic tone and activation of sympathetic nerves promote protective vasoconstrictor responses, thus attenuating increases in CBF and hemodynamic consequences that include disruption of the BBB and edema. With such a combination of mechanisms, all working synergistically and showing redundancy, it is difficult to discern which could be viewed as a primary mechanism in autoregulation, or simply an independent mechanism that provides redundancy or synergy due to overlapping functional effects. For example, the role of the autonomic nervous system in autoregulation can be investigated through inhibition or activation (e.g., pharmacological, denervation, or genetic approaches), followed by studying the response of CBF to changes in BP under such contrasting conditions (9, 43, 198, 228, 644, 649). However, such experiments can be riddled with confounding factors. For example, sympathetic blockade causes hypotension and affects respiratory control, causing changes in $PaCO_2$ (9). Similar 'side effects' may be observed in experiments that aim to inhibit endothelial function (162, 404,

615). This means that, even though some experiments have suggested that myogenic responses are independent of endothelial cells or the autonomic nervous system *in vitro*, experimental designs that can definitely exclude a role for endothelial cells or nerves are difficult to achieve *in vivo*. We have therefore chosen to discuss these factors or determinants of CBF, that may operate independently from autoregulation (even leading to confounding, or 'physiological noise', under some conditions) (95, 504, 505).

A. *Cerebral metabolism and NVC*

The regulation of CBF is tightly coupled to cerebral metabolism (63, 207, 466, 535). The observation that both variables are closely linked has been acknowledged for more than a century (141, 493), although the precise mechanisms underlying this coupling are not fully understood. The term metabolism suggests a role for reductions in tissue molecular O_2 and increases in CO_2 (which result from metabolic activity) in this coupling (141). The effects on CBF of O_2, CO_2, and associated changes in pH will be discussed in Section **III**.B. In addition to O_2 and CO_2, changes in metabolism may also affect CBF through local production of other vasoactive substances, including adenosine or potassium ion (265).

The metabolic 'coupling' pathway has been described as a 'feedback system', where changes in O_2, CO_2, pH and other vasoactive substances [i.e., adenosine, nitric oxide (NO), prostanoids, potassium ion] drive local vasodilation and increase CBF (265). For at least some brain regions, these factors alone are unlikely to account for the local increase in CBF that occurs in response to increases in neural activity (265). Indeed, the increase in CBF following neural activation can exceed metabolic demand (467). Moreover, increases in CBF following neuronal activation also occur under conditions of an abundance in glucose and O_2 (29). Metabolic processes alone may be too slow to explain the fast increase in CBF following changes in neural activity. Therefore, a 'feed forward' theory has also been proposed, wherein coupling largely takes place

between neurons, glia (responsible for consuming O_2 and the demand for nutrients), and the microvasculature (responsible for supplying blood, nutrients and O_2), within elements of what is commonly referred to as a neurovascular unit (265). Excitatory and inhibitory neurons form synapses on both astrocytes and GABAergic interneurons (225). With neural activation and NVC, endothelium-dependent propagation of vascular signals occur, which lead to remote vasodilation of upstream arterioles and arteries, including within the pial circulation (79, 185, 269, 357). These actions participate in mechanisms that maintain a close coupling between neuronal activation and local CBF. For example, activation of the occipital cortex by visual stimulation leads to a rapid increase in posterior cerebral artery blood flow, which supplies the occipital lobe (1, 411). This coupling can be observed through various techniques and allows for detailed insight into the ability to closely match regional demand with the supply of blood and O_2 (411). Recent work indicates that there may be regional differences in the timing and the precise nature of vascular responses to neural activation, but it should be noted that it remains uncertain how experimental conditions (e.g., anesthesia) may affect these results (214). It is now thought that the coupling of CBF to brain activity derives from a combination of the 'feedback system' and 'feedforward' mechanisms (265). Our overview of all factors that influence CBF includes factors that play a role in the CBF response to changes in metabolic or neural activity (NVC): arterial blood gasses, pH, endothelium, vascular muscle, and (autonomic) neural innervation.

Research into defining precise mechanisms that underlie NVC is an active area that is still unfolding (84, 213, 265, 357) and has implicated a role for neurons, endothelial cells, astrocytes, pericytes, and more recently, precapillary sphincters (84, 213, 265, 357). These topics are beyond the scope for this review. Instead, we refer to two excellent reviews covering these topics (214, 265).

In summary, cerebral metabolism and NVC regulate local CBF in response to neural activation. The constant and rapid changes in brain activity explain the relevance of this system, including a hypothetical condition where BP is fully stable, and autoregulation has no active role in regulating CBF. Therefore, we consider metabolic control of CBF and NVC as mechanisms of their own, independent from autoregulation, despite some obvious redundancies. Components of NVC will be discussed in Sections B-D below.

B. *Regulation by arterial blood gases and pH*

i. Partial pressure of carbon dioxide

Brain perfusion is highly sensitive to changes in $PaCO_2$ or tissue levels of CO_2 (11, 56, 97, 209, 254, 300, 479). An increase in $PaCO_2$ (hypercapnia) produces vasodilation, reductions in cerebrovascular resistance, and increases in CBF, whereas a drop in $PaCO_2$ (hypocapnia) increases cerebrovascular resistance and reduces CBF (56, 97, 209, 272, 300, 479). As summarized recently (254, 388), studies adopting TCD for assessment of the middle and posterior cerebral arteries or duplex ultrasound of internal carotid and vertebral arteries (extra-cranial conduit arteries) all demonstrated an approximately 3-6% increase in CBF per mmHg rise in $PaCO_2$ and a 1-3% decrease in CBF per mmHg reduction in $PaCO_2$ (97, 116, 272, 370). Differences in methodological design, assessment of CBF, analysis of the responses, magnitude of manipulation of $PaCO_2$, and correction for PaO_2, and especially differences in BP - as changes $PaCO_2$ can affect BP (97, 153, 245) - may contribute to varying results between studies. Nonetheless, the primary observation has consistently been that CBF shows a high sensitivity to changes in $PaCO_2$. This behavior of the cerebral circulation is clearly distinct from most of the systemic circulation (8, 315, 470). This basic observation in humans is consistent with many studies using preclinical models and multiple species, with only a small representation presented here (56, 163, 200, 235, 243, 244, 270, 302, 371).

Sensitivity to changes in $PaCO_2$ can be detected throughout the cerebrovascular tree – from large arteries, pial arteries and arterioles, and parenchymal arterioles (103, 163, 166, 256, 302, 418, 595, 609, 621). Based on changes relative to the original baseline diameter, the greatest response to hypercapnia occurs in the smaller arterioles (163, 200, 314, 418, 609). This may be related, in part, to a relatively larger content of vascular muscle, and to a higher degree of resting tone under baseline conditions. In a study using SPECT, the relative reductions and increases in CBF following hypocapnia and hypercapnia showed no relevant regional differences across various brain regions including gray and white matter (492). Note however that regional differences in baseline CBF (e.g., much lower CBF in white matter compared to gray matter) cause regional differences in absolute CBF responses to hypocapnia and hypercapnia. More recently, MRI techniques have been developed to measure global and regional responses in CBF to changes in $PaCO_2$ [for review see (351)].

Acidosis is known to be responsible for many of the biological effects of increased CO_2 (56). Classic work by Kontos *et al.* demonstrated that reduced extracellular pH, not increases in CO_2 *per se*, are responsible for vasodilation to local changes in PCO_2 (314). This suggests that vascular responses activated by increases in $PaCO_2$ relate to the diffusion of CO_2 across the BBB, subsequently leading to reductions in pH in the extracellular space and cerebrospinal fluid. Ultimately, a reduction in pH represents the primary stimulus that causes vasodilation of vascular muscle. While intermediate pathways involved in the response to hypercapnia have been studied for years, and include NO and prostanoids (56, 163, 263, 270, 419), molecular sensors that detect changes in extracellular pH have been more difficult to define. Recent studies suggest activation of a proton-gated cation channel [acid-sensing ion channel-1A (ASIC1A)] - particularly in neurons - by extracellular acidosis plays a critical role in CO_2-

induced vasodilation in brain (169). With very high levels of hypercapnia, additional mechanisms may be recruited and contribute to increases in CBF (169, 612).

ii. Partial pressure of oxygen

The cerebrovasculature is sensitive to variations in PaO_2 (or tissue PO_2). When PaO_2 drops below approximately 50 mmHg (equivalent to an arterial O_2 saturation of ~80%), this leads to cerebral vasodilation. This response also depends on the prevailing $PaCO_2$. The simultaneous presence of hypercapnia (i.e., another vasodilator) increases the sensitivity to hypoxia, strengthening the vasodilator response, whereas the presence of hypocapnia (i.e., a vasoconstrictor) attenuates the CBF response to hypoxia (3, 30, 179, 253, 262, 371, 416, 457, 490, 579). The practical consequence of this interdependency of cerebrovascular responses to changes in $PaCO_2$ and PaO_2 is that examining the impact of hypoxia in humans leads to a ventilatory response (i.e., hyperventilation), with resulting hypocapnia and vasoconstriction. In addition, regional differences in sensitivity to PaO_2 may be present. As a result, studies on the topic of cerebrovascular reactivity to hypoxia have produced results with significant variations (253). Although the overall impact of hypoxia is clear, these variations and dependency on alterations in $PaCO_2$ highlight the importance for simultaneous assessment of levels of $PaCO_2$ and PaO_2 in experimental conditions to correctly interpret outcomes.

A discussion of the impact of PaO_2 on cerebral perfusion should not omit the role of arterial oxygen content (CaO_2). The magnitude of changes in CBF during hypoxia are such that O_2 delivery (the product of CBF and CaO_2) is maintained at or near normal levels despite reductions in CaO_2, and appear linked to CaO_2, rather than PaO_2 *per se* (288). Situations that produce a reduction in CaO_2 (even in the presence of preserved PaO_2), such as carbon

monoxide exposure, acute or chronic anemia, or hemodilution procedures, lead to an increased CBF that maintains CaO_2 delivery at or near normal levels (288).

Several processes are suggested to play a role in the increase in CBF during hypoxia. The first relates to local decreases in PO_2 within neurons, glia, or vascular cells. Second, lack of local oxygen (PO_2 or O_2 delivery) may contribute to anaerobic metabolism, leading to extracellular acidosis, another vasodilator stimulus. Third, direct vascular mechanisms may be in place, where local hypoxia leads to the production and release of vasodilator substances. In this respect, adenosine is a popular and frequently studied vasodilator, partly because of various studies reporting increases in adenosine in response to hypoxemia (453). Indeed, several studies have observed increases in the CBF response to hypoxia when adenosine is enhanced and reduced CBF responses to hypoxia when adenosine is antagonized (e.g., by theophylline, caffeine, or more specific antagonists), although not all studies show similar results (316, 453). These partly conflicting data suggest that, although adenosine may contribute to cerebral vascular responses to hypoxia, redundancy in vasodilator pathways may be present and vasodilation may also be mediated through alternative mechanisms.

In summary, arterial blood gases can markedly affect CBF, but are not considered to be a mechanistic component of the autoregulatory response. These variables are however of clear relevance for studies of autoregulation, as changes in arterial blood gases affect autoregulatory control of CBF. This interaction is important in preclinical studies, as well as in clinical conditions where blood gases are altered, such as cardiopulmonary diseases, artificial ventilation (intensive care), anesthesia, exposure to high altitude, or exercise. Even everyday changes in posture, from lying to standing for example, cause changes in ventilation and lung perfusion, affecting blood gases and thereby CBF (and hence valid evaluation of autoregulation).

C. *Role of endothelium, vascular muscle and pericytes*

All arteries, arterioles, capillaries, venules and veins are lined by endothelial cells (160, 165, 265). Arteries contain multiple layers of vascular muscle, with the smallest arterioles containing a single layer of smooth muscle (75, 255). During functional hyperemia or NVC (see also III A.), arterioles in the parenchyma dilate and this response is propagated in a retrograde direction so that the integrated response includes vasodilation of arterioles and arteries on the brain surface (269, 357, 411). Whether the diameter of capillaries increases or not during NVC (or other increases in local CBF) has been considered, but is currently controversial (161, 214, 224, 250, 357, 610). For example, recent studies indicate that red blood cells can rapidly deform under conditions of reduced O_2 (i.e., increased O_2 consumption during activation), thereby increasing the flow of red blood cells through the capillary, without the necessity for capillary dilation (214). Below, the role of endothelium and vascular muscle are discussed in relation to regulation of regional CBF.

Regulation of vascular tone by endothelial cells occurs via several mechanisms, including the release of signaling molecules that affect adjacent vascular muscle (85, 165, 247), but also the spread of electrical signals from endothelial cells to smooth muscle via myoendothelial gap junctions (33, 247). A family of endothelium-derived molecules have been identified that directly affect the contractile state of vascular muscle. The major molecular messenger in this context is NO. In addition, potassium ion, hydrogen peroxide, ATP, and other, yet unidentified endothelium-derived hyperpolarizing factors may contribute to affecting vascular smooth muscle tone under some circumstances (160). These vasoactive substances are released by the endothelium in response to mechanical shear stress, activation of endothelial cell receptors, and other mechanisms (160, 247). Collectively, these factors play an important role in the

endothelium-dependent control of vascular tone, along with elements of vascular structure, vascular mechanics, anti-thrombotic activity, as well as function of neurons, synapses, and glia (79, 85, 127, 160, 165, 247, 260, 265, 294, 357, 531, 603). Despite these advances, our understanding of this system is still relatively limited, particularly in relation to integration of responses between and within different cell types and segments (or zones) of the vasculature. Studies that specifically focus on cerebral arteries, arterioles, capillaries, and venules, preferably in an *in vivo* setting (214), are required to truly understand the diverse impact of endothelium-dependent mechanisms. The importance of better understanding into these mechanisms is emphasized by overwhelming evidence from experimental and clinical studies highlighting the central role of endothelial dysfunction in mediating and accelerating the process of atherosclerosis (509, 617).

Emerging evidence suggests endothelial dysfunction is also a major player in the pathogenesis of small vessel disease in brain (127, 550, 605). As one example, endothelial-dependent vasodilation plays a key role in NVC (79, 84, 252). To what extent endothelial cells modulate autoregulation *in vivo* is less studied (261), but most evidence to date suggests that myogenic responses *in vitro* are largely independent from endothelial function (6, 85, 162, 282, 313, 380, 601, 603, 646).

Morphological and molecular characteristics of pericytes have been reviewed in detail (22, 44). Although anatomical relationships of pericytes in the cerebral circulation are reasonably well defined (with the exception of transition zones such as precapillary arterioles and postcapillary venules), uncertainties regarding their molecular characteristics, and key aspects of their potential functional importance remain unclear (44, 214, 578). In contrast to vascular muscle, where closely associated cells are circularly arranged on a regular basis and oriented perpendicular to blood flow with essentially a zero-degree pitch (75), pericytes often extend

processes down the long axis of capillaries, occasionally encircling some or all of its circumference (22, 578). Activation of contractile pericytes at the capillary level could potentially reduce local diameter at specific sites and thus affect individual capillary blood flow. However, the concept that changes in capillary diameter due to activation or relaxation of pericytes occur in response to physiological stimuli is supported by some studies, but not by all (44, 214, 224, 250, 357, 610). In addition, much of the work on pericyte control of capillary diameter has used brain slices *in vitro*, a model that some experts conclude is not adequate to mimic *in vivo* conditions (214). Further, changes in capillary diameter are often quite modest in magnitude, raising questions as to whether commonly used microscopic techniques (multi-photon microscopy for example) can reliably detect physiological changes in capillary diameter (214). With respect to autoregulation, we are not aware of direct evidence supporting an active role for pericytes in regulation of CBF during changes in BP. However, pericytes might affect capillary blood flow under conditions of ischemia, where some studies suggest pericytes are sensitive to ischemia and respond with prolonged contraction, causing local entrapment of red blood cells (117, 118, 637). This concept is controversial, as others found that precapillary arteriolar smooth muscles, rather than capillary pericytes, contract under ischemic conditions (250).

D *Sympathetic, parasympathetic and sensory (trigeminal) innervation*

Large arteries and arterioles in the pial circulation are richly innervated by adrenergic (neurotransmitters: adrenaline, noradrenaline, dopamine, neuropeptide Y), cholinergic (neurotransmitters: acetylcholine, vasoactive intestinal polypeptide), and sensory (neurotransmitters: calcitonin gene-related peptide, substance P, pituitary adenylate cyclase-activity peptide) fibres within the sympathetic, parasympathetic, and trigeminal nerve systems, respectively (168, 225, 240). This innervation does not follow blood vessels as they dive into

the brain parenchyma (225, 240). The presence of adventitial sympathetic, parasympathetic, and sensory fibers, innervating a major segment of the cerebrovasculature, makes them distinct from most peripheral organs (440). In addition to this extrinsic innervation of the pial circulation, intrinsic innervation of parenchymal vessels is also present in brain (225). Extrinsic innervation of extra-parenchymal arteries and arterioles originates mainly from the superior cervical ganglia (sympathetic innervation), otic and sphenopalatine ganglia (parasympathetic innervation), and the trigeminal ganglion (sensory nerves). Upon entry into the brain parenchyma, arterioles and other microvessels are under influence of innervation from brain stem and other nuclei, including the nucleus basalis of Meynert (92, 225, 580). In addition to this innervation, sympathetic nerves potentially influence CBF through effects of circulating neurotransmitters (557), although an intact BBB may substantially limit such effects.

i. Sympathetic nervous system

When exploring effects of the sympathetic nervous system in the regulation of CBF, activation of these nerves is sometimes associated with a decrease in CBF. Studies that have examined patients that, as part of their treatment, underwent superior cervical ganglionectomy demonstrate that this procedure leads to an increase in CBF (222, 284, 549). Studies adopting local or systemic pharmacological ganglionic blockade have produced mixed results, although the majority report an increase in CBF (622). Methodological factors related to the pharmacological procedure used to block the ganglia (including potentially only partial inhibition, but also effects on BP and $PaCO_2$), may contribute to variations in findings. Nonetheless, it is generally accepted that the sympathetic nervous system prevents increases in CBF under resting conditions (151, 168, 240, 367). However, mechanisms other than the sympathetic nervous system (e.g., endothelial, chemical, or metabolic) are likely to be more important for the regulation of resting CBF (557).

While the contribution of the sympathetic nervous system to resting CBF may be modest, a key role for the sympathetic nervous system is its influence during rapid or acute increases in arterial BP. For example, sympathetic blockade doubled CBF during a Valsalva maneuver (644), and prevented the decrease in CBF associated with head-up tilt (289), although this finding was not replicated (645). In addition, non-selective α-adrenergic receptor blockade led to a stronger increase in CBF when BP was rapidly increased using intravenous phenylephrine (305). Inhibiting sympathetic innervation through ganglionic blockade also led to increased transfer function gain and reduced transfer function phase, implying reduced dynamic autoregulation (649). A complicating aspect for this and related studies, is that ganglionic blockade reduced BP and BP variability, thus affecting TFA. This was addressed by increasing BP using phenylephrine and by increasing BP variability using oscillatory lower body negative pressure (649). Such an example illustrates that it is nearly impossible to study effects of sympathetic activation or blockade in isolation, without affecting other confounding variables. Several other studies, adopting different paradigms or pharmaceutical strategies, but with the same caveats, suggest the sympathetic nervous system contributes to autoregulation of CBF during rapid changes in BP [reviewed by Ter Laan *et al.* (557)]. For example, during acute hypertension, the vasoconstrictor effects of the sympathetic nervous system buffers surges in downstream microvascular pressure, thus contributing to preservation of CBF and potentially the BBB (168, 367). It is important to realize that both the direct innervation of cerebral arteries, but also stimulation of adrenergic receptors by circulating neurotransmitters, provided they cross the BBB, may contribute to dampening increases in CBF associated with acute hypertension. Previous publications provide a more extensive discussion on whether or not autoregulation is influenced by the sympathetic nervous system (338, 589).

ii. Parasympathetic nervous system

Cholinergic nerve terminals are richly distributed throughout intracranial vessels, proximal to the Virchow-Robin spaces (225). Despite the anatomical presence of this innervation, a clear view on the role of the parasympathetic nervous system in the regulation of CBF in humans is still lacking. In animal models, cholinergic control of CBF seems species specific, with a role observed for the parasympathetic nervous system in dogs and rats (114, 512), among others. Although the traditional view considered cholinergic-mediated vasodilation to be of limited importance, some recent studies suggest the opposite. For example, systemic cholinergic blockade with glycopyrrolate led to increased transfer function coherence between BP and CBF, which could indicate a reduction in dynamic autoregulation (229). In addition, Seifert *et al.* found that glycopyrrolate abolished the increase in middle cerebral artery blood velocity during cycling and static handgrip exercise, with no change in cerebral metabolism (513). Although these data support a role for cholinergic effects on the regulation of CBF, the question remains whether a role for the parasympathetic nervous system *per se*, is indicated.

The role of the extrinsic parasympathetic nervous system must not be confused with the brain's intrinsic cholinergic innervation that derives from the basal forebrain (nucleus basalis of Meynert) (225, 333, 594). In rat models and in human experiments, stimulation of the basal forebrain increases CBF through direct cholinergic and indirect interneuron (that release NO) vascular innervation (333). Of note, Alzheimer's disease and Lewy's body dementia are characterized by early and prominent degeneration of these intrinsic cholinergic neurons originating from the nucleus basalis of Meynert (92, 580). It has been hypothesized that the reduction in CBF that occurs in these dementias may be related, in part, to this loss of cholinergic innervation and thereby its vasodilator influence, and that part of the clinical benefit of cholinesterase-inhibitors may be explained by increased cholinergic-mediated vasodilation

(92, 580). However, these relationships await further study. The current view is that in humans, cholinergic-mediated vasodilation is recognized for peripheral blood vessels, but not generally considered physiologically important within the brain (225).

In summary, cholinergic projections influence parenchymal neurons and the vasculature by releasing their neurotransmitters (i.e., acetylcholine; a potent vasodilator (333, 512)). In addition, cholinergic projections innervate interneurons that release NO locally (92, 163, 333, 580). This intrinsic cholinergic system can be pharmacologically influenced by cholinergic or anticholinergic drugs. Nonetheless, at this point, it seems unlikely that this system plays a major role in autoregulation.

iii. Trigeminal sensory nerves

In addition to sympathetic and parasympathetic innervation, cerebral arteries and pial arterioles are innervated by the trigeminovascular system (25, 26, 225). Roy and Sherrington provided evidence that stimulation of the trigeminal nerve increased CBF without a change in BP (493). Trigeminal nerve fibers release calcitonin gene-related peptide (CGRP), substance P, and pituitary adenylate cyclase-activity peptide (25, 26, 225). Released by stimulation of meningeal afferents, CGRP is an extremely potent peptide that mediates most of the effects of the trigeminal nerve on vascular tone. It has therefore become a new therapeutic target for treatment of migraine (25).

Using several approaches, including unilateral trigeminal ganglionectomy in a preclinical model, insight into vascular effects of the trigeminal vascular system have emerged. For example, increases in pial arteriolar diameter and CBF in response to severe acute hypertension (levels of BP that exceed the upper limit of autoregulation) are mediated in part by these sensory fibers (395, 499). One implication of this work is that increases in CBF during severe

acute hypertension are not only caused by autoregulatory breakthrough, with pressure-driven passive vasodilation (395, 499). In contrast, trigeminal ganglionectomy had no effect on regional CBF under baseline conditions (395, 499), suggesting the influence of this neural system on resting CBF is minimal.

IV. OTHER FACTORS THAT INFLUENCE CEREBRAL BLOOD FLOW

A. *Patterns of blood flow*

In the peripheral circulation, a significant literature focuses on patterns of blood flow in large arteries. Whilst resistance arteries and microvessels demonstrate a relatively smooth, continuous flow of blood, large conduit arteries exhibit fluctuations in blood flow across the cardiac cycle. These fluctuations relate to the functional and structural characteristics of large conduit arteries, blood volume, pressure-gradients (within the artery and across the arterial wall), and blood characteristics (e.g., viscosity).

The pattern of blood flow represents an important hemodynamic stimulus in relation to adaptation of conduit arteries in the systemic circulation (208). Blood flow in peripheral arteries is characterized by a large antegrade component during systole (i.e., blood flows towards the periphery), followed by a short retrograde component during diastole (i.e., blood flows back to the heart). Acute increases in antegrade blood flow are linked to immediate vasodilation, upregulation of anti-atherogenic gene expression and improvement of vascular function (403, 562, 563). In contrast, periods of increased retrograde blood flow lead to stimulus-dependent impairment, upregulation of pro-atherogenic genes and impairment of vascular health (403, 511, 559, 560). Sustained exposure to antegrade or retrograde blood flow can ultimately lead to changes in vascular structure or stiffness (208). These findings highlight the impact of changes in blood flow patterns on vascular health in the peripheral circulation. To date, few studies have focused on blood flow waveform patterns in the cerebral circulation, and to what extent they impact cerebrovascular health.

The common and internal carotid arteries have been a popular site for ultrasound-based assessment of arterial characteristics, largely because they are relatively easy to access and

exhibit a high susceptibility for development of atherosclerotic plaques (132). In addition, for clinical diagnostic purposes (e.g., to detect stenosis), ultrasound-based assessment of the common or internal carotid artery wall thickness demonstrate independent prognostic value for future cardiovascular or cerebrovascular disease (358). These structural characteristics may also affect blood flow profiles in the internal carotid arteries. Indeed, assessment of blood flow profiles is frequently used to evaluate the impact of a stenosis on downstream blood flow toward the brain. Analysis of intra- or extra-cranial artery blood flow and shear stress waveforms contribute to our understanding the development of atherosclerosis in these arterial segments, as low and turbulent levels of shear stress are associated with increased atherosclerotic plaque development and complexity in the internal carotid artery (514).

Structural (e.g., wall thickening, stenosis) or functional impairment (e.g., waveform) in large extracranial arteries supplying the brain may also affect regulation of CBF. Indirect evidence for this idea came from a meta-analysis, which reported that carotid atherosclerosis is associated with white matter lesions and silent brain infarctions (393). Moreover, in a 7-year prospective study in 6,025 dementia-free subjects, carotid artery plaque predicted development of vascular or mixed dementias (65). Whether development of atherosclerosis and plaques with resulting changes in blood flow patterns was a direct cause of progression of cognitive impairment, remains uncertain. In this context, recent work on dolichoectasia – an age-associated vascular disease characterized by increased vessel diameter, increased tortuosity, and altered blood flow - is of interest. Older people with dolichoectasia carried a higher risk of progression to Alzheimer's dementia (219).

More direct evidence for a link between cranial artery waveforms and cerebrovascular health was provided in a study reporting a correlation between diastolic (but not systolic) carotid

artery wall shear stress and cerebral infarcts (400). Others confirmed that low carotid artery wall shear stress was associated with white-matter lesions and cognitive impairment in older humans (354). Moreover, it was recently reported that carotid artery wall shear stress is independently related to progression of cognitive decline and occurrence of white matter lesions across a 5.4 year follow-up in 689 older humans (643).

The majority of work on blood flow and shear stress patterns in arteries supplying CBF comes from studies of the common and internal carotid arteries. Current techniques that lack high spatial and temporal resolution to measure cerebral artery diameter, make it challenging to examine shear stress patterns in intracranial arteries. CBF pulsatility, estimated from waveform characteristics of the middle cerebral artery using TCD, was investigated across a large group of healthy subjects ranging from 22 to 80 years (555). Advancing age was associated with a linear decline in middle cerebral artery CBF velocity, but also an increase in pulsatility of the waveform in this artery that started after midlife. A reduction in wall shear stress in cerebral arteries with aging was associated with increases in vessel diameter and increased BP (652). The potential clinical relevance of these findings is highlighted by the observation that higher CBF pulsatility correlated with a greater white matter lesion volume in older adults (608), and the finding that subjects with Alzheimer's disease exhibit increased levels of middle cerebral artery pulsatility (488). As a caveat, a 'chicken or the egg' dilemma on causality applies here. Do altered flow patterns cause vascular injury and then cognitive deficits, or is it the other way around where increased pulsatility is caused by increased vascular resistance due to vascular pathology?

Some work in this area has also been performed on the basilar artery. A cross-sectional study reported that lower diastolic (but not systolic or mean) wall shear stress in the basilar artery

was found in patients with mild cognitive impairment and Alzheimer's disease, whilst levels of wall shear stress correlated with the level of cognitive decline (588). Here, it is interesting to note that work on dolichoectasia (with potential effects on CBF) hinted at a relationship between a larger basilar artery diameter and markers of cerebrovascular disease (553).

Taken together, these studies suggest a link between conduit artery waveforms and cerebrovascular health. The exact underlying mechanisms are difficult to summarize at this stage. Changes in waveforms in arteries may result from a combination of proximal, upstream alterations (e.g., systolic or diastolic and pulse pressure), local factors (e.g., endothelial functional, mechanical or structural characteristics), and downstream (distal) variables in the cerebrovascular tree (e.g., increased resistance). Whether information on wall shear stress from different intracranial arteries provide distinct prognostic information for cerebrovascular health is currently unknown, and should be a topic for future research. For the purposes of this review, an interesting question is whether blood flow patterns play a role in autoregulation. Left ventricular assist devices (LVAD) for patients with heart failure offer an opportunity to investigate the effects of different flow patterns. Loss of pulsatile flow in patients with continuous-flow devices had no effect on dynamic autoregulation in a study of nine patients with continuous flow LVAD, five with pulsatile flow LVAD, and 10 controls (101). More work will be required to better understand if and how patterns of blood flow, rather than just the quantity of blood flow *per se*, affect the effectiveness of autoregulation and brain health.

B. *Brain-heart hydrostatic gradient*

The brain-heart hydrostatic gradient describes the potential influence of gravity on CBF. The influence of the brain-heart hydrostatic gradient has been debated since the earliest literature on the cerebral circulation (119, 195, 248, 398). For an overview and detailed explanation of

arguments for and against the relevance of a brain-heart hydrostatic gradient, we refer to a Point-Counterpoint discussion (195) and exchange in Anesthesia Patient Safety Foundation Newsletters in 2007-09. It is not the presence of the gradient itself that is debated, but whether or not the gradient affects CBF. The hydrostatic gradient between heart and brain refers to the pressure gradient in an imaginary fluid column between the level of the heart and the brain for a person in the upright position. There are currently two scientific opinions on how this gradient affects CBF. The first claims that the pressure gradient on the arterial side is compensated by the gradient on the venous side, so that the net effect on CBF is null (246, 398). The second opinion claims this assumption is not valid in the cerebral circulation, and therefore perfusion pressure is reduced in the upright body posture by the hydrostatic gradient (i.e., BP- hydrostatic pressure) (119, 195, 499).

Scientists that propose that there are no hydrostatic effects on CBF refer to the cerebral circulation as a closed-loop system, also referred to as a siphon model (246, 398). The siphon model is the concept of a length of rigid tubing containing fluid, where the pressure at either end is determined by the vertical position of these ends, but not by the position of the rest of the tubing. The closed-loop system is similar, but contains a pump that circulates fluid through a length of tubing. If this system is brought from a horizontal plane to a vertical plane, the pump will not require extra energy against the hydrostatic pressure gradient, because the returning flow now returns with a higher pressure.

Opponents of this view indicate that this comparison does not hold for the cerebral circulation, for reasons that include non-rigid tubing (collapsible veins), pressure differences across the system (intrathoracic pressure, ICP), and the cerebral circulation itself with its wide range of vessel diameters (119, 195).

This ongoing debate extends from humans to giraffes to sauropods (with their extraordinary hydrostatic gradient) (246, 516, 517) to species of snakes (the heart-brain distance is longer in snakes with a mostly horizontal habitat (i.e., aquatic) versus snakes in a vertical habitat (i.e., arboreal)) (343).

It is very complex to perform measurements to proof or disproof either theory. For example, one could study the effect of a change in posture from supine to upright on CBF. If the only parameter to change were the hydrostatic gradient, a reduction in CBF following the reduction in perfusion pressure (BP minus hydrostatic gradient) from supine to upright would suggest the hydrostatic gradient affects CBF. Indeed, CBF decreases in human subjects between supine and standing (upright) position (196, 197, 516, 517, 590, 618). Unfortunately, this change in body position affects multiple factors that also influence CBF, such as BP, central blood volume, $PaCO_2$, and ICP (196, 197, 590, 618). This array of changes make it difficult to isolate the single effect of a hydrostatic reduction in perfusion pressure on CBF. In addition, dynamic autoregulation will modify the effect of a change in perfusion pressure on CBF (see Section **II**.D on dynamic autoregulation).

Parabolic flight experiments offer the unique opportunity to modify effects of gravity without changing posture (176, 330). In a parabola following normal gravity (1 G), a period of ≈ 22 s of 0 G is preceded and followed by ≈ 30 s of hypergravity (1.8 G). These changes in gravity occur quickly (in about 1 s). For a hydrostatic gradient in a subject seated upright in this plane, this pressure gradient suddenly nearly doubles for 30 s (from 1 to 1.8 G), then equally suddenly drops to zero for 20 s (from 1.8 G to 0 G), only to rapidly return to double for another 30 s (from 0 to 1.8 G), after which it returns to normal (176, 310, 330, 415, 600). For autoregulation, these conditions create a series of step-wise, very fast changes in perfusion pressure (under the hypothesis that the gradient affects perfusion pressure) of ≈30 mmHg. Under the opposing

hypothesis (siphon), these changes in gravity should have no effect on perfusion pressure. Unfortunately (yet unsurprisingly), the sudden changes in gravity affect multiple physiological processes (176, 309, 330, 415, 600). For example, hypergravity increases BP whereas zero gravity reduces BP, but also ICP, and $PaCO_2$ (332).

Nonetheless, in 16 healthy volunteers, with 15 parabolas for each subject, the averaged traces of BP and CBF velocity revealed stepwise changes in CBF velocity during the transitions from hypergravity to zero-gravity and back, while BP remained stable during these changes (309). Plots for BP corrected for changes in hydrostatic gradient identified stepwise changes in perfusion pressure that could explain (from the viewpoint of autoregulation) the stepwise changes and subsequent adaptation in CBF velocity (309). This is circumstantial evidence that is not meant to end this debate. However, from a clinical perspective, incorrectly dismissing effects of a hydrostatic gradient on CBF carries more risk than incorrectly dismissing the siphon hypothesis. For example, in a patient with hypotension (mean arterial BP of 50 mmHg), if the siphon hypothesis is correct, the position of the head compared with the rest of the body (e.g., upright, supine or head-down tilt for example) has no effect on perfusion pressure, and therefore no effect on CBF. However, if the siphon hypothesis is false, the upright position may reduce perfusion pressure to ≈ 30 mmHg, whereas a head-down tilt could increase it to ≈ 70 mmHg. This simplified example ignores effects of body position on BP and ICP, but hopefully serves to explain our point. For further reading on such clinical implications, see Pohl *et al.* (455) and the call-out text for clinicians.

V. REGULATION OF CEREBRAL BLOOD FLOW AND CLINICAL IMPLICATIONS

Despite redundancy in mechanisms that regulate CBF, diverse clinical conditions have been linked to acute or chronic changes in brain perfusion. In this section, we describe the clinical implications of autoregulation in diseases commonly associated with cerebrovascular pathology [e.g., ischemic stroke, hypertension, dementias (vascular dementia, Alzheimer's disease, mixed dementia)] and dysregulation of CBF. Since older age is one of the most common risk factors in these clinical conditions, we start by discussing the impact of aging on regulation of CBF.

A. *Cerebral perfusion across the age span*

Although the impact of aging on CBF has been frequently studied, our understanding of the biology of vascular aging is relatively modest compared to its clinical impact (127). Independent of the techniques and designs used to measure CBF, blood flow to grey and white matter (or global CBF) decreases by about 0.5% per year from early adulthood (10, 55, 334). The potential relevance of a lower CBF may not only relate to its regulation, but may also be associated with age-related changes in cognitive function (631) and specific domains of cognitive performance (131). Recently, a prospective cohort study in 4,759 participants from the general Dutch population with a 6.9 year follow-up found that cerebral hypoperfusion at baseline was related to accelerated cognitive decline and increased risk for dementia, independent of known risk factors for dementia (628). Separate findings from the Alzheimer's Disease Neuroimaging Initiative reinforced these conclusions, reporting that a higher index of cerebrovascular resistance (*ergo* lower CBF) predicted cognitive decline (independent of reduced metabolism) and brain atrophy (independent of ß-amyloid) in older adults across a two-year period (638).

Mechanisms that account for age-related decreases in CBF are not fully understood, but are likely multi-factorial. One potential explanation relates to changes in the cerebral metabolic rate (see Section **III**.A.), which has been demonstrated to decline by ~0.5% per annum (334). Older age may impair neuronal or glial mitochondrial metabolism. Indeed, metabolic rates for neuronal tricarboxylic acid and glutamate-glutamine cycles are lower in older adults (50). However, other studies found progressive reductions in CBF, that were independent of changes in cerebral O_2 consumption (17, 131, 638, 643). These findings suggest that age-related changes in metabolism cannot fully explain the progressive decline in CBF that occurs as individuals age.

Somewhat related to cerebral metabolic rate is the presence of cerebral atrophy (and therefore lower cerebral metabolism). Even in healthy individuals, advanced age is associated with cerebral atrophy. Interestingly, age-related atrophy shows regional variability and seems more prominent in frontal and temporal regions (366, 417). Regional differences in cerebral hypoperfusion may also be present with older age (283, 360). These findings raise the hypothesis that regions of cerebral atrophy and hypoperfusion with older age may match. To understand this potential link, the spatial pattern of age-related changes in cerebral atrophy and CBF were explored (81, 360). Whilst these studies confirmed the presence of regional variation in age-related changes in CBF and brain atrophy, regional effects of age on CBF differed from that of grey-matter atrophy, and were not related to metabolism. Therefore, dissociation may be present between age-related hypoperfusion and cerebral atrophy in older humans. Atrophy may also affect the reliability of imaging through partial volume effects. This may affect imaging-based measurements of CBF, and lead to either underestimation or overestimation of CBF (334).

Aging and autoregulation, CO_2 reactivity, and baroreflex function. Changes in hemodynamics may also contribute to the age-related decline in CBF. Aging is associated with a gradual increase in arterial BP, which may be related to several mechanisms including endothelial dysfunction, aortic stiffening, and an increase in systemic vascular resistance (599). In addition, assuming ICP does not change significantly (106), an increase in arterial BP leads to an increase in cerebral perfusion pressure with aging. To compensate for such changes and prevent hyperperfusion, an increase in cerebrovascular resistance is required.

Another factor that may contribute to age-related reductions in CBF is impairment of autoregulation or related mechanisms. Oudegeest-Sander *et al.* examined the dynamic responses of CBF velocity (using TCD) and cortical oxygenation (using near infra-red spectroscopy) to changes in BP in response to sit-to-stand maneuvers and $PaCO_2$ in cognitively healthy individuals - young, elderly, and very elderly (422). While this study confirmed the presence of an age-related decrease in middle cerebral artery CBF velocity, the relative changes in CBF in response to these paradigms were similar across age groups, suggesting preserved dynamic autoregulation as well as preserved CO_2 reactivity with older age. Others have also reported preserved dynamic autoregulation in healthy older populations (7, 57, 66, 67, 138, 150, 348, 585, 633).

Previous studies have linked older age and neurodegeneration with impaired baroreflex sensitivity (296). Interestingly, such work suggested that baroreflex and dynamic autoregulation may interact in the regulation of CBF to counteract acute changes in arterial BP. One study found an inverse correlation between baroreflex sensitivity and autoregulation (576), suggesting counterregulatory functionalities between these mechanisms. However, a recent study examined both dynamic autoregulation and baroreflex sensitivity in a cohort of 136

healthy individuals (633). This study confirmed a reduction in CBF and impaired baroreflex sensitivity in the older population. However, autoregulation was unimpaired with aging, and there was no relationship between baroreflex function and autoregulation. Similar observations were found in a large dataset of healthy participants across a wide age range, showing preserved autoregulation and no relationship between autoregulation and baroreflex function (375). Together, these data do not support a link between baroreflex sensitivity and autoregulation in the older population.

Studies have also examined the impact of aging on cerebrovascular reactivity to changes in $PaCO_2$. While some studies found that increases in CBF during hypercapnia are impaired with aging (160, 292), others did not (127, 422). These conflicting findings may result from differences in the methods used to measure CBF (TCD, MRI), the range of $PaCO_2$ tested, the extent of aging, and the protocol used to induce hypo- and/or hypercapnia (388). Although some studies do not provide clear insight into the impact of older age on vascular reactivity, these results are largely in line with studies that examined dynamic autoregulation, in that older age does not demonstrate a clear age-related decline in the ability to regulate CBF in response to stimuli affecting BP, arterial blood gases, or pH.

It is important to note that studies of CBF in aging have a potential confounder due to age-associated neurodegenerative disease (e.g., Alzheimer's disease, vascular dementia, mixed dementia). Because the prevalence of neurodegenerative diseases increases sharply with advancing age (619), it is likely that some studies have unknowingly included older people with lower CBF caused by neurodegenerative disease. This can occur because many of these diseases remain asymptomatic, or at least not clinically recognized, in their early stages.

B. Autoregulation in hypertension

There are two widespread, yet incorrect concepts about autoregulation in hypertension. The first is that chronic hypertension (which is often combined with aging) leads to impaired autoregulation (static and dynamic), through hypertension-associated vascular dysfunction [see (518) or (564) for examples from review articles where this concept is presented as a fact]. The second, in partial contrast with the first, is that static autoregulation remains intact in hypertension, however its lower and upper levels are shifted towards higher pressure levels (542, 544, 546). In other words, the autoregulation curve has shifted rightwards (545, 564). With this concept, the brain can tolerate higher BP, but becomes more sensitive to low BP (545). The translation of these two concepts to clinical practice is explained in the following example. A 75-year old hypertensive patient has a habitual systolic BP of 160 mmHg. According to the first concept, further increases or decreases in BP, albeit fast or slow, would affect CBF because static and dynamic autoregulation are impaired. According to the second concept, an increase in systolic BP to 180 mmHg will not affect CBF, because the upper limit of the static autoregulation curve has shifted upward. However, a reduction in systolic BP to 120 mmHg may fall below the lower limit of autoregulation, which has also shifted to a higher pressure, leading to a reduction in CBF. With both concepts, older hypertensive patients are considered to be vulnerable to cerebral hypoperfusion when BP is reduced (205, 481, 545). Common clinical examples of BP reduction are those associated with antihypertensive treatment (mostly slow, gradual changes), and with postural changes in BP (fast changes, see also Section **VI.** A. on postural changes).

i. Dynamic autoregulation

One of the first studies of dynamic autoregulation in hypertension tested the following hypothesis: " … *that age and hypertension would impair dynamic autoregulation, resulting in*

relative cerebral hypoperfusion during acute hypotensive stress" (348). Ten young (24 years of age), 10 normotensive (mean BP of 125/68 mmHg) and 10 hypertensive (mean BP of 153/90 mmHg) older adults (72 years of age) underwent assessment of dynamic autoregulation during an active stand from sitting. This maneuver causes a transient reduction in BP, which usually reaches a maximum around 15 seconds after standing, and recovers within 30-40 seconds (348, 536, 585). Mean BP fell by 25%, leading to a reduction in CBF of 15% in old adults, and 19% in young adults. Autoregulation during spontaneous fluctuations in BP was also assessed using TFA, during five min of quiet sitting or quiet standing. An impairment in dynamic autoregulation would manifest as a lower phase and a higher gain (see section **II**. D.). However, phase was normal and gain was lower in hypertensive older adults. In contrast with the hypothesis, the authors concluded that there were no differences in dynamic autoregulation between young, older, and older hypertensive adults (348).

These results were confirmed by a study in 21 hypertensive patients (49 years of age) and 21 normotensive controls (566). Here, transient hypotension was evoked by standing up from a squatting position, which leads to a stronger drop in BP compared to sit-to-stand. The average 35-40% transient decrease in BP led to a reduction in CBF of 21% in hypertensive adults and 28% in controls (566). In the hypertensive group, there were no differences between those with well controlled BP (136/78 mmHg) and uncontrolled BP (154/95 mmHg) (566).

In a study of acute BP lowering in hypertensive crisis (190), 28 patients (55 years of age) with a mean systolic BP of 200 mmHg, were randomized to rapid BP reduction with sublingual captopril or nifedipine. CBF velocity was not significantly reduced following treatment with captopril, but was modestly reduced by nifedipine (190).

These three studies with relatively small sample sizes were followed by a larger study in 35 normotensive (mean BP, 124/76 mmHg) and 45 hypertensive older adults (mean BP, 152/89 mmHg, 68 years of age) (146). In this study, the range of systolic BP was wide in the hypertensive adults, up to 206 mmHg. The authors investigated a wider spectrum of dynamic autoregulation by looking at effects of decreases and increases in BP that were sustained for up to three minutes, as well as more rapid decreases and increases in BP. For all procedures, the changes in BP (up or down) were between 15 and 20 mmHg. The authors found no differences in dynamic autoregulation between hypertensives and controls (146).

A second large study recruited 60 older adults (72 years of age); 22 normotensives (BP <140/90 mmHg, no medication), 20 controlled hypertension (BP <140/90 mmHg on medication), and 18 uncontrolled hypertension (systolic BP >160 mmHg with or without medication)(515). Dynamic autoregulation was examined using TFA of spontaneous changes in BP at rest, and by studying transient BP changes during a single sit to stand protocol. This study was comparable in design to the smaller study by Lipsitz *et al.* (348). Following standing, the transient decrease in BP ranged between 20 and 25 mmHg. A transient reduction in CBF was observed, 15% in normotensives and 10% in controlled and uncontrolled hypertensives (515). TFA found similar values for phase in all groups, whereas, as in the earlier study by Lipsitz *et al.* (348), the gain was lower in hypertensives.

Summary of dynamic autoregulation studies in hypertension. In five studies with 240 participants and a range of ages from young, middle aged, to older, dynamic autoregulation was intact in hypertension during non-pharmacological changes in BP. Limitations of these studies are that no patients over 80 years old were included, and that participants were non-frail and had limited comorbidity.

ii. Static autoregulation

Studies using TCD. For clinical translation, the studies described above related mainly to faster BP changes evoked by daily life challenges such as postural changes. An unexplored area was how slower, more gradual reductions in BP using antihypertensive treatment, would affect CBF. There are two arguments why this is relevant. First, antihypertensive medication could have direct effects on cerebrovascular function that may impair autoregulation. Second, BP lowering using antihypertensive treatment could reduce BP to the lower limit of autoregulation, such that any further reduction in BP (e.g., during a postural challenge), would lead to hypoperfusion. Ideally, therefore, studies exploring these relationships would combine measures of static and dynamic autoregulation.

In one study, normal static autoregulation was observed in 42 young (34 years of age) hypertensive patients (567). BP was reduced with atenolol from a mean arterial BP value between 100 and 105 mmHg to between 80 and 85 mmHg. CBF velocity was measured after 30 and 60 days, and was not reduced (567). In another study, older hypertensive patients were studied (346) in three groups: normotensive (n=19), controlled hypertension (n=18), and uncontrolled hypertension (n=14), with a mean age of 70.4, 72.4 and 72.4 years and ≈ 50% female. At baseline, mean systolic BP in the three groups was 124, 135, and 160 mmHg, respectively. Only the uncontrolled hypertensive group was treated, to a systolic BP target <140 mmHg. After six months of antihypertensive therapy, the group with uncontrolled hypertension had, on average, a 17 mmHg decline in systolic BP, while CBF velocity increased significantly. At baseline, dynamic autoregulation was similar between groups, and this did not change following BP lowering in the uncontrolled hypertensive group (346). Thus, preserved static autoregulation can be deduced from the observation that there was no decline in CBF following

BP reduction. The increase in CBF following BP reduction is not explained by autoregulation, but may point towards a negative effect of chronic hypertension on CBF. Chronic hypertension could impair vascular compliance, and through this mechanism reduce CBF. Indeed, antihypertensive treatment led to increased carotid artery distensibility, a measure of vascular compliance (346).

Static combined with dynamic autoregulation were addressed in a study in 21 newly diagnosed (but untreated) hypertensive patients, 49 years of age (range from 27-66), and nine controls (647). Of the 21 hypertensive patients, 12 had mild (BP of 143/88 mmHg) and nine had moderate (BP of 163/101 mmHg) hypertension, diagnosed with 24-hour ambulatory BP monitoring. Within two weeks, BP was reduced using antihypertensive medications (losartan-hydrochlorothiazide) to 126/77 mmHg in mild and to 134/84 mmHg in moderately hypertensive patients, (i.e., an average reduction of systolic BP of 20-30 mmHg), thus lowering BP to or near the lower limit of autoregulation. At that point, CBF was measured during an orthostatic stress test using head-up tilt. This was repeated after longer-term treatment (three-four months). Acute (one-two weeks) reductions in BP brought about by antihypertensive treatment did not reduce CBF. Furthermore, CBF remained stable during the orthostatic stress test. After three-four months of treatment, BP remained at its reduced level, and CBF remained stable (647). Thus, combining assessments of static and dynamic autoregulation, this study found no evidence for impairment in autoregulation. Nor was there evidence for an upward shift of the lower limit of autoregulation (Figure 7). Similar to the findings of Lipsitz *et al.* and Serrador *et al.*, the patients with hypertension (but not those with only mild hypertension) had lower gain values than controls at baseline (515, 647). An interesting observation is that gain increased to similar values as in the control group following treatment. Lower gain could be interpreted as better autoregulation, however, it may also be explained by differences in

vascular compliance, supported by the observation in this study, but also several other studies of autoregulation (122, 201, 346, 515, 647), that increases in cerebrovascular resistance are associated with lower gain, and that normalization of cerebrovascular resistance increases gain (515, 647).

Summary of studies on static (combined with dynamic) autoregulation in hypertension. In n=123 subjects, including young, middle-aged and old individuals, static and dynamic autoregulation were investigated before and after pharmacological treatment to lower BP. Treatment had no effect on dynamic autoregulation, and follow-up CBF remained stable, suggesting normal static autoregulation. Beneficial effects of BP lowering on CBF (i.e., increases in CBF) were observed, possibly due to improvement in arterial compliance.

Studies using Xenon-133. In all studies described above, CBF was evaluated using TCD to measure changes in cerebral blood velocity in middle cerebral arteries. That artery supplies approximately 70% of the blood flow to the cerebral cortex. Investigators in this area use TCD because it has the high temporal resolution that is needed to measure dynamic autoregulation in humans. For static autoregulation, additional techniques are available that can provide measurements of global or regional CBF, some of which have been around for more than half a century. Perhaps the first studies to dispel the notion of impaired static autoregulation in hypertension were published in the late 1970s and 1980s (100, 211), but appear to have received little attention. Conen *et al.* investigated the effects of short-term (hours) and longer term (4 weeks) BP lowering on CBF, where CBF was measured using the Xenon-133 method – the same technique used by Lassen (327) and Strandgaard (231) in their work on static autoregulation (100). Patients (n=10, 37 to 70 years of age) with a mean arterial BP of ≈ 130 mmHg, requiring emergency BP lowering (for hypertensive encephalopathy, ICH, fundal

hemorrhage, or diabetic retinopathy) were studied. BP was reduced on average from 220 mmHg to 150 mmHg systolic in approximately 1 hour using intravenous nifedipine or clonidine, whereas CBF (≈ 60 ml/100g/min) remained stable overall (100). In that same study, 21 patients (10 female) with mild to moderate hypertension (50-89 years of age), were treated for four weeks with nitrendipine, verapamil, or chlorthalidone. Systolic BP was reduced from ≈170 mmHg to 145 mmHg, while CBF remained stable (≈ 50 ml/100g/min) (100).

In 1979, Griffith *et al.* investigated the effects of BP lowering using different antihypertensive agents (all ß-blockers) in a large number of hypertensive patients (27 per group, >100 in total). Mean BP was lowered from values between 135-140 mmHg to between 110-115 mmHg. CBF was measured using Xenon-133 (211). In all patients, and for all ß-blockers, despite this substantial BP lowering, CBF remained stable (211) (see also Figure 7).

A small study in 1987 using Xenon-133 in eight older hypertensive patients found no reduction in CBF following BP lowering with prazosin (469). In addition, in 23 older hypertensives (66-91 years of age), systolic BP was lowered using amlodipine from 177 to 156 mmHg (24 hr ambulatory BP) for daytime measurements, and from 157 to 140 mmHg for overnight measurements, in eight weeks. There was no reduction in global or regional CBF described using SPECT (Tc-HM-PAO) (426). However, in most instances (as in this study) SPECT only allows qualitative estimates of CBF patterns, not quantitative CBF, unless tracer kinetics are applied (426). Lastly, in 15 patients (nine men, 60-79 years of age), with hypertension and carotid artery stenosis, CBF (measured using Xenon-133) before and two hours after BP lowering (mean arterial BP from 110 to 102 mmHg) remained stable (443).

Studies using MRI. In 37 older (74 years of age) hypertensive patients (systolic BP >150 mmHg), CBF was measured using MRI (arterial spin labelling) before and after antihypertensive treatment in two different regimens: standard and intensive (569). After 12

weeks, systolic BP was reduced by an average of 15 mmHg in the standard treatment group, and 27 mmHg in the intensive treatment group. BP lowering did not result in lower CBF (Figure 7). In fact, in the intensive BP lowering group, CBF actually increased by approximately 10% (569).

The following is an illustration of how persistent the concept of impaired autoregulation in hypertension is in the literature. Despite accumulating evidence indicating preserved autoregulation in older hypertensive patients, a study was initiated in 2013 with the hypothesis that older hypertensive patients have impaired autoregulation, and their antihypertensive treatment would therefore cause cerebral hypoperfusion (392). It was also hypothesized that stopping their medication would increase BP and CBF, leading to improved cognitive function (392). This was a large important study in 102 older, hypertensive adults (81 years of age). Participants were randomized to continuation of antihypertensive treatment (n=47) or to stopping all antihypertensive medication (n=55). BP and CBF (arterial spin labelling) were evaluated at baseline and after four months. It was noteworthy that already at baseline, the findings were in contrast with the original hypothesis (180). Hypertension (i.e., higher systolic BP) was associated with lower, not higher, CBF. At follow-up, discontinuation of antihypertensive medication led to an expected increase in BP of approximately 10 mmHg systolic. Again in contrast with the original hypothesis, this did not lead to an increase in CBF (Figure 7) (180). An important contribution of this study is that it included subgroups of people with small vessel disease, diabetes, and mild cognitive impairment. In these subgroups, there was no evidence of impaired autoregulation (180).

Whether autoregulation is impaired in older hypertensive patients with cerebrovascular disease (small vessel disease) was further explored in the PRESERVE trial (104). Patients with severe

small vessel disease were included, i.e., a combination of clinically defined lacunar infarcts and white matter disease (a Fazekas score of 2 or 3 out of 3). Sixty-two patients (69 years of age) were included, with relevant comorbidity such as diabetes, cognitive impairment, depression and smoking. With treatment, mean BP was reduced from 150/83 to 141/79 mmHg in the standard group, and from 154/88 to 126/75 mmHg in the intensive treatment group over a period of three months. In both groups, CBF (measured using MRI arterial spin labelling), was unaffected by BP lowering (104).

Hypertensive emergency

In hypertensive emergencies, also described in the literature as hypertensive crisis, malignant hypertension or hypertensive encephalopathy, BP levels are extremely high and exceed the upper limit of autoregulation, (e.g., systolic BP of > 180 mmHg) (448). In this situation, an excessive increase in CBF and ICP may occur, which explain the signs and symptoms associated with hypertensive emergency: altered mental state, encephalopathy, infarction or bleeding, optic disc swelling and retinal bleeds. The presence of signs or symptoms of acute end-organ damage in a patient with very high BP levels (for example, diastolic BP >130 mmHg, systolic > 200 mmHg) should alert the clinician that the upper limit of autoregulation may have been exceeded, and therefore autoregulation is impaired (448). Impaired autoregulation (static and dynamic) in patients with hypertensive emergency was demonstrated in a small study using TCD (273), which reported a reduction in CBF following BP lowering treatment. It is possible however that the magnitude of reduction in CBF was overestimated due to changes in MCA diameter, affecting blood-velocity measurements (273). CBF was unaffected in a small study using Xenon-133, where systolic BP was reduced from 220 to 150 mmHg in one hour (100). The clinical relevance is that in a patient with a hypertensive emergency, a very fast and very large reduction in BP must be avoided to prevent cerebral

hypoperfusion. Current guidelines recommend a 20-25% reduction in BP (e.g., from 220 to 165 mmHg) in the first hour, followed by a target BP of 160/(100-110) mmHg in hours 2-6, using intra-arterial BP measurements and intravenous antihypertensive agents (448). The vascular biology in hypertensive emergency is discussed in Section II. *H.*

A hypertensive crisis is not only determined by how high BP levels are, but also by how fast they have risen (448). This follows logically from autoregulation: with a slow or gradual increase in BP, autoregulation adapts by a rightward shift of the upper limit of autoregulation, the result being that autoregulation can function effectively, even at very high BP levels (e.g., systolic BP of 200 mmHg). In contrast, in an individual with a habitual systolic BP of 120 mmHg, a sudden sustained increase in BP to 180 mmHg can exceed the upper limit of autoregulation and trigger a hypertensive crisis. In clinical practice, hypertensive crisis tends to be over-diagnosed because there are many (older) hypertensive patients with chronically elevated BP, and because the clinical symptoms in such individuals (altered mental state, confusion, encephalopathy) fully overlap with those characteristic of delirium and dementia, which have a high prevalence in older patients in acute care settings.

Summary of all studies on autoregulation in hypertension. Between 1979 and 2018, 747 hypertensive patients have been investigated. In 240 patients, dynamic autoregulation was studied (without evaluation of treatment). All studies found that autoregulation was similar to normotensive controls. In 507 older patients, autoregulation was evaluated before and after BP lowering treatment. In 384 patients, this was an evaluation of static autoregulation. In 160 patients, CBF was measured using Xenon-133 CT, in 23 with SPECT, and in 201 patients with MRI (arterial spin labelling). In 123 patients, both static and dynamic autoregulation were evaluated before and after treatment, using TCD to measure changes in CBF velocity.

Individuals that were included were not only otherwise healthy and non-frail, but included a substantial number of people over 70, and even 80 years of age with comorbidities (vascular disease, including cerebral small vessel disease, diabetes, depression) and cognitive impairment. All these studies came to the conclusion that autoregulation is not impaired in hypertension. Figure 7 provides a summary of studies that investigated static autoregulation in hypertension.

iii. Hypertension and adverse outcomes

Evidence suggesting normal autoregulation during hypertension can also be obtained from studies that did not measure CBF. Such studies investigated adverse outcomes associated with cerebral hypoperfusion, the feared outcome of BP lowering if autoregulation is impaired. Examples of adverse outcomes related to cerebral hypoperfusion include falls, dizziness, cerebrovascular lesions, mild cognitive impairment, or dementias. Interestingly, in a prospective cohort of almost 600 older hypertensive patients (70-97 years of age), the use of antihypertensive medication to lower BP was associated with a substantially lower odds ratio (0.6) for the risk of falls (347). This result strongly argues against the concept of impaired autoregulation with aging and hypertension, and also against the concept of an upward shift of the lower limit of autoregulation (347). The increased risk of falls in patients not using antihypertensive medication may be explained by the observation that untreated hypertension (in older people) increases orthostatic hypotension. Orthostatic hypotension is a strong risk factor for falls (86, 291). The findings by Lipsitz at al. have subsequently been confirmed by others, as summarized elsewhere (291). These studies highlight that hesitance to treat hypertension in older people, based on the assumption of impaired autoregulation and fear of induced cerebral hypoperfusion, is unsupported and may in fact have the opposite effect on the risk of falls (291, 347). Untreated hypertension can increase the risk for orthostatic

hypotension, with large transient reductions in BP, which may not be prevented by autoregulation and cause cerebral hypoperfusion and falls.

There have also been prospective, randomized trials that have evaluated the outcome of BP lowering on cognitive decline. The SPRINT trial was a study of intensive versus standard antihypertensive therapy. It included patients >75 years old, with a subgroup of moderately frail participants. The SPRINT-MIND sub-study (n=9361) was specifically designed to evaluate cognitive function (212). If autoregulation were impaired in hypertension, the expected outcome would have been that intensive BP lowering, through cerebral hypoperfusion, would promote cognitive decline. The contrary was found. The intensive treatment group had less risk of developing mild cognitive impairment or dementia than the standard treatment group (212). Equally, there was no increase in risk of falls or fractures in the SPRINT study (212, 423). The prevalence of syncope was not increased (see Section **VI.**A.*ii* - note that syncope is a disorder of BP regulation, much more than a disorder of autoregulation). In the subgroup of patients >80 years old, intensive treatment was associated with increased risk of a decline in kidney function (423). The clinical consequences of this reduction in kidney function (which was defined as a 30% or more reduction in estimated clearance) remain uncertain. A recent study indicates that these reductions in estimated creatinine clearance do no really represent clinically relevant reductions in renal function (99). In addition, this older subgroup demonstrated reductions in cardiovascular events and mortality, and reductions in cognitive decline with intensive BP lowering, without increased risk of reduced mobility (gait speed) or falls (423). Of note, the benefit was influenced by baseline cognitive function: in those with poor cognitive function at baseline (defined as a MoCA score below 18 or 20 depending on level of education), there was no or limited benefit of intensive treatment on all endpoints, including cardiovascular events. This seems to

emphasise the role of early start of anti-hypertensive treatment in the prevention of cognitive decline.

The INFINITY trial also investigated effects of intensive versus standard antihypertensive therapy in older patients (199 randomized patients, 54% women, 80.4 years of age) (616). At study entry, subjects had a systolic BP >170 mmHg, or between 150-170 mmHg on antihypertensive medication. All subjects had evidence of white matter disease on MRI. They were then treated from a mean systolic BP (based on 24 hr ambulatory monitoring) of 149 mmHg to 128 mmHg (intensive) or 144 mmHg (standard), with a three-year follow-up (616). Outcome measures were gait speed, cerebrovascular lesions, volume of white matter lesions, falls, and syncope. Impairment of autoregulation would be predicted to manifest as a slowing of gait, an increase in white matter lesion volume, and/or an increase in falls. However, these were not found. In contrast, the time-dependent increase in white matter lesion volume was smallest in the intensively treated group (616). Finally, a meta-analysis of 31,090 individual participant data from trials performed between 1980 and 2019, investigated the risk of development of dementia associated with use of antihypertensive medication (139). Participants were 55 years and older (≈ 50% were >75 years, but only ≈ 5% were >85), and were followed for at least 5 years. In approximately 15,000 participants with a baseline systolic BP <140 mmHg, antihypertensive use did not increase dementia risk. In the approximately 15,000 participants with baseline systolic BP >140 mmHg, use of antihypertensive medication even reduced dementia risk (RR 0.88) (139). There were no differences between classes of antihypertensive medication.

Conclusions. Despite the evidence presented above, statements claiming that autoregulation is impaired in hypertension, and that older hypertensive patients require higher BP because of a

rightward shift of the autoregulation curve, are still found frequently in the literature. Very often, they are presented as facts, sometimes without references. Equally, there is an abundance of cross-sectional studies dealing with BP levels and treatment of hypertension, sometimes with - but often without - measurements of CBF, that nevertheless draw inferences regarding the relationship between BP and CBF. The bias in such studies almost always leads to observations that people with low BP have worse outcomes in mortality or cognition than people with high BP. Such anticipated outcomes may be explained because BP levels often decline in cancer, heart failure, or dementia. Nevertheless, and almost without exception, such studies end with a conclusion that the negative outcome can be explained by a low CBF, caused by low BP and impaired autoregulation.

Based on prospective studies that measured CBF as an outcome in >700 older hypertensive patients, however, there is no convincing evidence that autoregulation is impaired in hypertension. Nor is there evidence that older hypertensive patients require higher levels of BP to preserve CBF. This conclusion is further supported by the outcomes of three large prospective studies, and one recent large meta-analysis, of antihypertensive treatment (combining >25,000 patients >75 years of age), that found no evidence for adverse effects that could be attributed to cerebral hypoperfusion, including falls, cerebrovascular lesions, or cognitive decline and risk of dementia.

C. Cerebral perfusion and stroke: immediate and long-term changes

The key role of BP control in the management of acute ischemic and hemorrhagic stroke makes assessment of autoregulation a top research priority to inform clinical decision-making, with the aim of preventing secondary damage due to extremes of hypo- or hyperperfusion (Figure 1) (21, 598). The need for a better understanding of autoregulation following stroke has led to a substantial literature in this area as reflected by the number of reviews dedicated to the topic

(21, 72, 215, 260, 275, 290, 319, 342, 387, 424, 532, 546, 581, 632, 634). The main aim of this section is to assess progress with the understanding of autoregulation pathophysiology in human stroke and to identify priorities for future research.

Ischemia impairs CBF regulatory mechanisms, including autoregulation (193, 280, 319, 424), and hence it is not surprising that most studies of autoregulation have shown that autoregulatory mechanisms are often impaired following both ischemic stroke and ICH (21, 72, 275, 290, 369, 387, 546, 632). In addition, autoregulation has been shown to be impaired in most studies following aneurysmal subarachnoid hemorrhage (SAH) (12, 58-60, 64, 177, 187, 237, 281, 322, 326, 474, 507, 533, 570, 639, 656). The finding that autoregulation tends to be impaired in the main types of stroke (ischemic or hemorrhagic) has come from controlled and observational studies where patients have been compared to healthy controls as distinct groups. However, this cannot be generalized to all stroke patients as some studies, mainly involving mild strokes, have shown that many stroke patients maintain intact autoregulation (21, 72, 356, 369, 458, 459, 476, 478, 502, 568). Moreover, even in the case of patients with moderate to severe strokes, autoregulation is not impaired at all time points. Indeed, one of the main items of interest is the temporal evolution of autoregulatory efficacy post-stroke to inform treatment decisions in a timely fashion (369). In addition to the need to understand the time-course of impairment of autoregulation following stroke, individual heterogeneity due to phenotype, stroke etiology, severity, sub-type, location, co-morbidities and early intervention, as well as the different protocols and techniques used for assessment of autoregulation, represents a highly complex, multifaceted problem that has not been addressed in a comprehensive manner. The extent of impairment of autoregulation, and its post-stroke temporal evolution, also likely depends on the volumes of the core and penumbra regions (Sec. I.B.) and patterns of reperfusion (290, 349, 363, 477). The role of these multiple factors is well illustrated by one of the first studies of autoregulation in ischemic stroke that proposed a quantitative measure of

static autoregulation, as the ratio of changes in CBF [measured with hydrogen clearance and cerebral (A-V) CaO_2] and cerebral perfusion pressure (invasive measurements of BP and ICP) (385). Meyer *et al.* (385) found that dysregulation was associated with severity and location. In other words, there was worse autoregulation with brainstem or subcortical lesions as compared to cortical strokes. Moreover, they reported an inverse correlation with time of measurement (day one to 44) after ictus, suggesting less dysregulation with longer duration since ictus, without an influence of age or hypertension.

i. Methodological aspects of autoregulation assessment in stroke

Before reviewing the different factors that can influence autoregulation in ischemic or hemorrhagic stroke, it is important to call attention to the diversity of protocols and measures of both static and dynamic autoregulation that have been used in these studies and their potential to confound findings. Assessment of autoregulation based on static methods requires induction of changes in mean BP which have been performed by means of tilting (385) or the use of vasoactive drugs such as nicardipine or labetalol (458, 459). In addition to changes in physiological processes that can result from these manipulations of BP, such as changes in $PaCO_2$ with tilting, there are also concerns about estimating the slope of Lassen's static autoregulation curve using only two points, which can potentially lead to substantial errors (427).

The majority of the literature is dominated by studies using the dynamic autoregulation approach. Although originally proposed in combination with sudden reductions in BP induced by the rapid release of compressed thigh cuffs (3, 561), dynamic autoregulation assessment has been increasingly based on spontaneous fluctuations in BP, whose convenience is particularly relevant in the acute stroke setting (577), where patients may be unable to perform or tolerate

postural changes or other interventions to manipulate their BP. Concern about the sufficiency of BP variability in spontaneous cardiovascular fluctuations (524) has led many investigators to revert to the thigh cuff approach (120, 147, 177, 191, 498), or to use alternative ways to provoke rapid changes in BP, such as rhythmic handgrip (321), tilting (191), paced breathing (203, 326, 575), Valsalva maneuver (409), rapid changes in head position (323), brief carotid artery occlusion (12, 61, 322, 474, 570), or elbow flexion (501). The concomitant changes that these maneuvers can induce in co-variates of autoregulation, such as $PaCO_2$, heart rate, cardiac output, and activity of the sympathetic nervous system, need to be kept in mind when comparing studies using different protocols (577). A few studies used spontaneous fluctuation recordings, but attempted to improve reliability of autoregulation parameters by using only larger pressor or depressor transients in BP identified in the data (145, 147, 191, 274).

A relatively large number of indices have been adopted for estimation of autoregulation efficiency (428). By far, the main approach has been TFA, in conjunction with spontaneous fluctuations in BP, with the use of the amplitude (gain) and phase frequency responses as metrics of dynamic autoregulation (326, 362, 413, 421, 437, 475, 648). At each frequency, gain reflects the ratio of output (i.e., CBF or CBF velocity) to input (i.e., BP) amplitudes, while the phase expresses the time delay between output and input. With failing autoregulation, one would expect the gain to increase (that is reduced buffering of BP fluctuations) and the phase to decrease (that is the tendency of output to follow the input). A recent systematic review and meta-analysis has shown that phase is a more reliable parameter than gain to detect changes in autoregulation in ischemic stroke (275), something that had been highlighted in previous reviews (98, 428). When comparing studies that used phase or gain, it is important to consider the different settings that are required in TFA, which may confound comparability. To address this problem, a White Paper proposed standardization of TFA settings aimed at improving

comparability of future studies (98). When BP changes were induced by means of thigh cuffs, efficiency of autoregulation was expressed with the rate of regulation (3) and autoregulation index (ARI) (120, 147, 177, 191, 498, 561) indices. The rate of regulation was adapted to express the rate of recovery of the CBF velocity response to a step change in BP (calculated via TFA) (80, 216, 362), and also to studies of autoregulation in stroke based on MRI estimates of CBF (435). Following the demonstration that the ARI can be calculated by means of TFA, using spontaneous fluctuations in BP (439), several studies have used this approach in both ischemic and hemorrhagic stroke (28, 323, 356, 389, 498, 500, 502). This alternative has a number of advantages as it abbreviates several choices that need to be made when using phase or gain directly (98).

When using spontaneous fluctuations in BP, one alternative to TFA is the Mean Velocity Index, usually referred to as Mx (or Mxa) that has been adopted in autoregulation studies of both ischemic and hemorrhagic stroke (including SAH) (59, 64, 475-478, 533, 634, 656). A variant of the Mx, the Sx index, using the systolic value of CBF velocity, instead of the mean value, has been adopted in SAH studies (59-61, 533). The Mx/Mxa is correlated with the ARI (111), but hitherto it has not been scrutinized regarding its sensitivity to noise, measurement errors and choice of parameter settings. In situations when measurements of ICP are available, the PRx index, expressed by the correlation coefficient between mean arterial BP and ICP, has also been used, mainly in studies of SAH (187, 472, 522, 571). In a few studies, indirect measures of CBF were obtained with methods reflecting the utilization of O_2, leading to correlation indices, similar to the Mx or Sx, labelled TOx (60, 61, 522, 656) or ORx (187, 281), from measurements with NIRS or an invasive tissue O_2 tension probe, respectively.

Finally, modelling of autoregulation in stroke has been performed with the Multimodal Pressure-Flow (MMPF) method (19, 257, 409). This approach generates estimates of phase differences between fluctuations in BP and CBF velocity (either spontaneous or from Valsalva

maneuvers), but these should not be confounded with phase differences derived by TFA as there are substantial differences in the data processing involved. In fact, the authors have shown that MMPF seems to provide greater sensitivity than TFA in detecting deterioration of autoregulation in stroke and other conditions (258, 259, 362, 409, 413, 437, 475, 648).

ii. Temporal course of changes in autoregulation following stroke

Most studies of autoregulation in ischemic stroke have performed assessments in the acute (<48 hours) and sub-acute phases (<14 days after ictus) (21, 72), with a much smaller number of studies performing measurements several weeks or months after stroke onset (19, 147, 191, 202, 217, 257, 321, 323, 385, 409, 500). Given the considerable heterogeneity of patient conditions and autoregulation assessment methodology, inferences about longitudinal changes in autoregulatory metrics can only be made from a relatively small number of studies that performed two or more intra-patient measurements. In addition to the time period encompassing measurements, it is also relevant to take into consideration whether autoregulation parameters were found to be altered in comparison with controls, or not. In studies that did not have a control group, or indications that autoregulation was impaired at any time following stroke, autoregulatory metrics were found to deteriorate within the first five days following stroke (476, 477). In contrast, others detected improvement over time, mainly in the acute and subacute stages (451, 478), although Kwan *et al.* (321) found increased values of TFA phase and decreased gain three months after stroke onset. When control groups were included, measures of autoregulation indicated that impairment was present from the acute to the subacute stages, up to 28 days after stroke onset (28, 121, 147, 361). Noteworthy, two studies reported normalization of the ARI after three months, following significantly reduced values of this index at approximately five days (323) and after two weeks (500), respectively.

On the other hand, Guo *et al.* (217) obtained reduced values of TFA phase, suggesting impaired dynamic autoregulation, at <48 h after onset that were not altered six months later. Although serial assessments were not performed, Novak *et al.* (409) and Hu *et al.* (257), also found that the phase, derived with the MMPF method, was lower in comparison with controls, an average of 18 and six months after stroke onset, respectively, but other investigators reported normal values of autoregulation parameters one month up to 63 months after ictus (191, 202). In summary, most studies assessing the evolution of autoregulation parameters in ischemic stroke, have shown a deterioration of autoregulation metrics in the first two weeks after ictus, with return to normal values between one and three months later.

Although the corresponding number of studies in ICH is much smaller, there seems to be a similar pattern. Based on TFA phase and the ARI, respectively, Oeinck *et al.* (413) and Minhas *et al.* (389) have not observed any changes in the TFA phase and ARI, respectively, in the first five to 14 days after ictus. Reinhard *et al.* reported Mx index values not different from controls, on day one, but by day five, higher values of the Mx index (indicating worse dynamic autoregulation) were a significant predictor of outcome (475). A longer follow up (362) indicated that TFA phase was lower than controls from days one-two, reaching a minimum by days 10-12, but then recovering to comparable values as controls at 30 days after ictus. Therefore, these data on TFA phase and ARI support the earlier temporal changes in autoregulation after stroke, with a decline in the first two weeks after ictus and a return to normal values thereafter.

In SAH, several studies reported impairment of autoregulation from days one-four after admission (12, 58, 59, 64, 177, 187, 281, 421, 474, 507, 639, 656), in some cases with temporary improvement, followed by further deterioration around days 7-14 (60, 177, 187, 326, 474). The occurrence of vasospasm, often followed by delayed cerebral ischemia (DCI), show an interaction with autoregulation impairment.

The temporal evolution of effectiveness of autoregulation, as suggested by different metrics, needs to be taken into account to inform the clinical management of patients with either ischemic or hemorrhagic stroke, but cannot be considered in isolation from a number of other factors, such as the severity of stroke.

iii. Influence of stroke severity and sub-type on estimates of autoregulation

When examining the influence of stroke severity, controlled studies in ischemic and hemorrhagic stroke indicate that indices of autoregulation show normal values in mild strokes, but have a greater tendency to present abnormal values in moderate and severe strokes (21, 72, 290, 319, 634). The volumes of the core infarct and penumbral regions (349) likely influence the relationship between autoregulation and stroke severity, but distinguishing the core and penumbral regions has been elusive (290). In many studies, the association of autoregulation with severity is incidental without formal statistical testing. However, a reasonable number of studies have used a nominal or ordinal scale to assess the relationship between indices of autoregulation and corresponding measures of severity. The *National Institutes of Health Stroke Scale* (NIHSS) is the main tool for quantifying severity in stroke, with values 1-5 indicating a mild stroke and very severe strokes corresponding to values >25 (145, 356, 361, 476, 502). Other measures of severity that have been used are the *Glasgow Coma Score* (GCS) (362, 413, 459, 475), the *Barthel Index* (145), degree of stenosis (80, 203, 238, 602), or other scales (385). Using MRI or CT imaging, classification of severity has also been based on the volume of infarct or hematoma (71, 73, 363, 458, 459, 475, 477), the presence of brain atrophy (19), hemorrhagic transformation in ischemic stroke (71), or ventricular hemorrhage in ICH (389, 475). In SAH, the most common measures of severity are the GCS, the Hunt and Hess score, the World Federation of Neurological Surgeons Scale (WFNS), or the Fisher scale (489).

In summary, independent of the measures used to express stroke severity, or the parameter adopted for assessment of autoregulation, these studies found no association between autoregulatory metrics and stroke severity for mild strokes (145, 238, 361, 458, 459, 476, 502). However, in moderate and severe strokes, there is a positive association between stroke severity and worse autoregulation, independently of stroke etiology (19, 71, 80, 140, 203, 238, 356, 362, 363, 385, 413, 475, 477, 502, 602). The influence of stroke severity on autoregulation in SAH is more complex, due to the development of vasospasm and DCI, entities that by themselves are dependent on severity. Direct association of the Hunt and Hess, WFNS, Fisher or GCS with autoregulation was reported in only a few cases (474). On the other hand, multiple studies suggested an association of indices of autoregulation with the occurrence of vasospasm (12, 177, 326, 507, 533, 571) or DCI (20, 59, 64, 187, 322, 474, 507). Given that autoregulation was found to be depressed after SAH, often before the development of vasospasm and DCI, several authors have proposed predictive models, showing that alterations in autoregulation indices were independent predictors of vasospasm and/or DCI (12, 61, 64, 421, 474, 507). The inter-dependence of stroke subtypes, severity, phenotype and co-morbidity makes it difficult to unravel the separate influences of these factors on autoregulation. Studies specifically designed to assess the influence of stroke subtypes on autoregulation have adopted either the Oxford Community Stroke Project (OCSP) or the TOAST criteria for classifying stroke subtype (16), but have not controlled for co-factors and usually involved a relatively small number of participants (16, 120, 145, 216, 356, 361, 498). Most of these studies have not found a significant, multi-class association of autoregulation status with either the OCSP or the TOAST classifications, with the exception of Ma *et al.* (361) who reported lower values of TFA phase in strokes due to large artery atherosclerosis when compared with small vessel occlusions. A larger number of studies however investigated inter-hemispherical comparisons of autoregulation parameters for different subtypes of ischemic stroke. In general, small vessel

disease and lacunar strokes result in bilateral impairment of autoregulation, as might be expected given their more diffuse distribution (161, 216, 217, 274, 409, 635). For large vessel occlusions though, a more complex pattern emerges, given the expectation that unilateral lesions should lead to impairment of autoregulation in the affected hemisphere, when compared to the unaffected hemisphere. This was shown to be the case in some studies (73, 216, 274, 451), but in other studies autoregulation was depressed in both hemispheres, despite unilateral occlusion (361, 635). In the majority of studies though, the population included a mixture of stroke sub-types, with small vessel disease or lacunar infarcts representing a variable proportion (usually <50%) of the sample. What is startling is that in all these studies, both hemispheres had depressed autoregulation, independently of the metric adopted for autoregulation (19, 28, 83, 120, 145, 257, 321, 323, 356, 435, 458, 498, 500). In ischemic strokes of undetermined etiology, Tutaj *et al.* found impaired autoregulation only in the unaffected hemisphere (575). In ICH, most studies did not find a difference in autoregulation parameters between sides, and an association with hematoma location was not reported (362, 363, 389, 413, 475). Of note, in some of these studies, the autoregulation metric was not different from controls. For SAH, we could not find any reports of an association between the extent of impairment of autoregulation and the location of the ruptured aneurysm. One possible explanation for this lack of specificity, is that the diffusion of blood in the subarachnoid space, and its effects of triggering endothelial dysfunction, reactive oxygen species formation, and hypersensitivity of vascular muscle to contraction (134, 342, 532, 632), make the corresponding loss of autoregulation independent of the site of bleeding.

Interim summary. Autoregulation parameters after ischemic or hemorrhagic stroke tend to show similar values in both hemispheres, independently of location or subtype, with only a few studies reporting unilateral impairment. The difficulty of explaining the extent of autoregulation impairment based on stroke subtype is undoubtedly related to the intervening

effects of stroke severity. A few studies highlight this interdependence (502, 602, 635), but much more work is needed to improve our understanding of how autoregulation is influenced by the confluence of stroke subtype and severity.

iv. The association of autoregulation with stroke outcome

The potential association of autoregulation efficiency with the outcome of stroke is of considerable interest, not only for its more immediate importance to guide patient management, but also to shed light on the causal mechanisms involved in the pathophysiology underlying alterations of autoregulation. The relevance of this association is reflected by the recent increase in the number of studies describing the relationship between autoregulation and outcomes. In these studies, outcome has been nearly unanimously expressed with the modified Rankin Scale (mRS) (37) at 90 days after stroke onset, dichotomized as good (0-2) or poor (3-6). In ischemic stroke, poor outcomes were associated with parameters indicating impairment of autoregulation; reduced TFA phase (73, 83, 203, 361), increasing Mx index (477, 478), increased TFA gain (70), or lower ARI (502). The short-term prognostic value of depressed dynamic autoregulation - lower TFA phase six hours after stroke onset - was shown by its association with hemorrhagic transformation and cerebral edema (71). Similar associations of TFA phase and the Mx index with outcome were observed in ICH (362, 413, 475). In patients with SAH, outcome was often assessed with the mRS at discharge, as well as at three, or sometimes six, months after discharge, with the majority of studies reporting a strong association with autoregulation (59, 177, 187, 281, 326, 472, 474, 522). A measure of functional independence and the efficiency of rehabilitation were also associated to severity of SAH and the shape of the autoregulation curve (58).

Interim summary. Taken together, the accumulated evidence that autoregulation is often impaired in ischemic stroke, ICH, and SAH, with significant associations to severity and outcome, suggests that further consideration should be given to incorporate autoregulatory assessment as part of routine protocols to manage patients with stroke. To progress in that direction though, there are important gaps in our knowledge about the pathophysiology of autoregulation in humans that need to be addressed.

The association of different indices of autoregulation with severity and outcome of ischemic and hemorrhagic stroke would suggest that one possible strategy to improve stroke treatment is to take autoregulation efficacy into account in treatment protocols. This approach has been gaining momentum in the critical care of patients with severe brain injury and also in premature newborns through the concept of optimal cerebral perfusion pressure or optimal BP (20, 108). Given the long monitoring times required by this approach, indices of autoregulation have been estimated with NIRS or from the BP-ICP relationship, with the pressure-reactivity index (109), rather than with indices derived from CBF velocity (TCD). By observing changes in pressure-reactivity index or a number of different indices obtained from NIRS (108), a U-shaped curve can be derived as a function of BP or cerebral perfusion pressure, with its minimum indicating the optimal value to maximize autoregulation efficacy (540). A recent NIRS-based study has demonstrated the feasibility of using the optimal-BP approach in ischemic stroke, in patients undergoing mechanical thrombectomy (452). A similar approach in SAH has shown a strong association between outcome and the time patients spent outside the boundaries of the optimal BP interval (472, 522). The possibility of individualizing optimal BP management, as compared to the adoption of fixed BP targets, and the better outcomes of the former (452, 472, 522), warrant further research, including large scale clinical trials. On the other hand, the fairly long observation times required with the optimal BP approach, which was 28±18 hours (452), 68 ± 51 hours (522) or an average of 95 hours per patient (472), might be a critical limitation

for extending this approach to all stroke patients. Moreover, unless mean BP is manipulated, its spontaneous variation might not necessarily cover a sufficient range to show a U-shaped curve and hence the identification of the optimal BP target. Alternatively, a simpler approach to restoring autoregulation to normality was proposed in the context of ICH (389), by using hyperventilation to improve dynamic autoregulation by means of hypocapnia (3, 388). The possibility of adopting a similar strategy in ischemic stroke, could be limited by the observation that spontaneous hypocapnia already seems to be prevalent in this population (503). Furthermore, the effects of hypocapnia on CBF are transient, as CBF starts to return to normal after four-six hours of hyperventilation (468).

Although restoration of autoregulation efficacy seems an intuitive target in the treatment of ischemic and hemorrhagic stroke, its judicious application to patients with different phenotypes, stroke subtypes, location and severity, will undoubtedly require more work to fill in the gaps in knowledge identified in the sections above. Considerably more data is needed to characterize the temporal course of autoregulation stratified by stroke subtypes, location and severity, for example. Likewise, the recovery in autoregulation, observed between one and three months after ischemic stroke onset (323, 500), needs to be better understood, in particular how individual time-courses relates to outcome, which hitherto remains unexplored.

Although targeting improvement of autoregulation as a potential coadjuvant in stroke therapy is an avenue that needs further exploration, the overall conclusion so far is that advances in clinical or surgical management of patients with ischemic or hemorrhagic stroke are unlikely to be achieved without due consideration for the key role of autoregulation in post-stroke pathophysiology and management.

v. Autoregulation and blood pressure control in stroke

Although the role of autoregulation has not been directly investigated in large randomized controlled trials (RCT) of BP management in ischemic or hemorrhagic stroke, some indirect evidence about autoregulation efficacy in stroke can be inferred from the results of several RCTs, and important lessons can be learned for improving the design of future trials. Following ischemic stroke, a significant number of patients present with hypertension (598, 624) which has been the main drive to test different approaches to lowering BP in the acute and subacute stages (18, 38, 456, 484, 485). Theories about autoregulation in stroke play an important role in the rationale behind such trials. For example, the increase in BP can be hypothesized as serving a purpose of maintaining CBF (specifically in the penumbra) and lowering BP may therefore be disadvantageous. On the other hand, if autoregulation is impaired in the penumbra, the increase in BP following stroke may cause hyperperfusion injury in the infarcted area, and BP lowering interventions may prove beneficial. However, excessive BP lowering may cause hypoperfusion injury if autoregulation is impaired. This reasoning also extends to ICH, where antihypertensive therapy has been the focus of many trials in ICH in the attempt to reduce the risk of hematoma expansion and intraventricular hemorrhage due to elevated BP (74, 397, 464). Many other hypotheses on what would constitute optimal BP management in stroke can be formulated based on assumptions of autoregulation in the affected infarct area, affected hemisphere, or unaffected hemisphere. The setting of optimal BP targets, following ischemic stroke, is also complicated by differences in the extent of the collateral circulation in individual patients, which will play a key role in reperfusion of the penumbra (425, 598). In summary, in both types of stroke, the underlying assumption for many trials has been that autoregulation would be impaired and CBF would then need to be maintained within safe limits by control of BP.

Overall, different strategies for lowering BP, involving different BP target levels, timing of intervention or types of vasodepressor drugs, have shown significant reductions in systolic and

diastolic BP, in comparison with placebo or other controls, but could not demonstrate a difference in favorable clinical outcomes, usually based on mRS <3 (18, 38, 74, 286, 397, 456, 464, 484, 485). On the other hand, most trials have not detected any adverse effects of antihypertensive therapy either. Noteworthy, the *Controlling Hypertension and Hypotension Immediately Post-Stroke* (CHHIPS) trial, comparing the use of labetalol or lisinopril to placebo, reported a reduction in mortality at three months from 20.3% (placebo) to 9.7% in the treatment group (456). A pooled analysis of two previous large RCTs showed that achieving early and stable systolic BP was associated with favorable outcomes in patients with ICH (397).

The lack of impact of BP lowering therapy on the outcome from stroke, as reported by most trials, would suggest that, contrary to the underlying assumptions, autoregulation was intact in the populations studied and the reductions in BP did not influence cerebral perfusion. This interpretation however, needs reconsideration, taking into account three key aspects of the involvement of autoregulation in ischemic and hemorrhagic stroke: i) severity of stroke, ii) extent of BP reduction achieved, and iii) timing of intervention and assessment. The association of stroke severity with impairment of autoregulation would suggest that most large RCT samples would involve a mixture of patients with autoregulation ranging from intact to severely affected, and that the accruing benefits of BP lowering could then be diluted by the prevalence of less severe strokes. As an example, in the pooled analysis of the INTERACT-2 and ATACH-2 trials, the patients showing improved outcomes were mainly those with mild-to-moderate ICH (397). Although most trials demonstrated a significant reduction in BP in the treated group compared to controls, the amplitude of the difference is likely to have an association with outcome. In the RIGHT-2 trial, early application of transdermal glyceryl trinitrate led to a mean reduction in BP of only 5.8 mmHg in comparison with patients receiving a sham patch (38), whilst the trial in ICH, where improvements in outcome were observed, had a sustained mean

systolic BP reduction of 29 mmHg (397). In line with this latter observation, the CHHIPS study, where a difference in mortality was detected, had a systolic BP reduction of 31 mmHg (at two weeks) compared with placebo (456). Although a 'dose-response' relationship remains to be investigated, it is more likely that differences in outcome would be observed with larger BP reductions, as long as the mean BP remains above the lower limit of autoregulation. Following this, positive effects of larger BP reductions may have been obscured in these trials by patients in whom BP was lowered too much, i.e., below the lower limit of autoregulation. Knowledge of a patient's pre-stroke habitual BP is essential to define optimal BP targets post-stroke, but this information is often not known or not taken into account. The most critical aspect of the trials under discussion is the timing of interventions, especially in relation to our current knowledge of the temporal evolution of autoregulation post-stroke. Autoregulation tends to be impaired around two weeks after stroke onset, followed by recovery by three months. Given this time course, it could be expected that maximum benefit would be obtained by achieving BP targets in the most critical period, that is between one and three weeks after onset. This was the case with the CHHIPS trial (456), but in most RCTs, intervention took place less than 36 hours after onset (18, 38, 74, 485) and it was not demonstrated that reduced BP levels were sustained for more than a few days following treatment.

This mismatch between BP control and the time-dependent deterioration of autoregulation post-stroke is likely to have contributed to the absence of significant impact of BP lowering therapy on stroke outcomes (539). An ongoing RCT (CAARBS) will perform multiple observations of BP, following administration of Ca^{2+} channel blockers or angiotensin-converting enzyme inhibitors, that might allow a better assessment of outcome taking into account the timing of BP reduction in comparison with the expected evolution of autoregulation efficacy post-stroke (484).

In summary, the main lessons learned from scrutiny of RCTs aiming to improve outcome by means of BP control, is that inclusion of autoregulation assessment provide the 'missing link' to allow objective interpretation of results that could lead to better informed, individualized treatment of patients with ischemic or hemorrhagic stroke.

D. Autoregulation in cognitive impairment and dementias

i. Vascular dementia

Vascular dementia represents a heterogeneous group of brain disorders in which cognitive impairment is attributable to cerebrovascular abnormalities and is responsible for approximately 20% of all cases of dementia (206). When mixed dementia is taken into consideration (the combination of neurodegeneration and vascular disease), the contribution of vascular changes to all dementias is much more substantial (24, 105, 454, 462, 606, 619). Vascular dementia can present in several ways clinically (36, 206, 365, 496, 564). For brevity, we will divide them broadly into two forms: 1) a typical, easily recognized presentation, and 2) a common, but atypical and less distinct presentation. In the typical presentation and characteristic form, the patient will have a history of clinical stroke followed by the onset of cognitive impairment, or a history of repeated clinical strokes followed by a stepwise deterioration in cognitive function. On examination, these patients have signs of stroke (e.g., hemiparesis), and have characteristic neuropsychological deficits, specifically in executive function and processing speed. Their memory deficits benefit from cues, and typically they function well in a structured environment. In contrast, the common but more atypical presentation of vascular dementia is that of a gradual cognitive decline (more similar to Alzheimer's disease) combined with the identification on MRI of significant vascular brain injury (e.g., diffuse white matter lesions) (206, 496, 564, 606, 619). Often, this vascular brain injury has been clinically silent in the sense that there is no history of transient ischemia attacks

or stroke. Clinically, the vascular lesions may not manifest as hemiparesis, but as a more subtle disorder in balance, reduced motor coordination, vascular Parkinsonism, or loss of urinary control (206). A complicating factor is that there is considerable overlap in cognitive profiles with which patients with vascular dementia or Alzheimer's disease may present. For example, vascular dementia patients can have predominant memory dysfunction, which is a characteristic of Alzheimer's disease, whereas Alzheimer's disease patients can have prominent executive dysfunction, which is characteristic of vascular dementia (372).

In line with coronary and peripheral arterial disease, impaired endothelial function contributes to cerebrovascular disease with its unique features (79, 127, 160, 247, 260, 294, 441, 454, 606). Not surprisingly, a large number of studies, independent of the technique used to examine CBF, have demonstrated that patients with vascular dementia present with lower CBF compared to cognitively healthy peers (266, 597). Two review papers have provided overviews of TCD studies in vascular dementia (compared with Alzheimer's disease and controls), and found that resting CBF is reduced (both in vascular dementia and Alzheimer's disease); and that pulsatility index (a marker of vascular compliance) is increased in both dementias, but more so in vascular dementia. CO_2 reactivity is impaired in both dementias, but again, more so in vascular dementia (297, 495). In vascular dementia, resting CBF seems especially depressed in areas of white matter lesions. Interestingly, cerebral hypoperfusion has also been described in normal appearing white matter (412), suggesting that local blood flow reductions precede and, accordingly, may contribute to damage of white matter and its connectome (http://www.humanconnectomeproject.org). To support this hypothesis, cerebral hypoperfusion and impaired cerebrovascular reactivity to hypercapnia are associated with a larger volume of white matter lesions (35, 596), suggesting that reductions in CBF are present

prior to the onset of dementias, supporting an important role for cerebral hypoperfusion in the pathogenesis of vascular (and potentially other) dementia's.

To date, there have been no studies on autoregulation in vascular dementia to our knowledge, only studies on autoregulation in stroke patients and in patients with small vessel disease described in the sections on autoregulation in stroke and hypertension.

ii. Alzheimer's disease

There is a vast body of literature, mainly preclinical, that describes impairment of cerebrovascular function in Alzheimer's disease (51, 87-89, 193, 264, 277, 405, 442, 487, 550, 588, 619, 655). Changes in both cerebrovascular function and structure appear to be involved in this form of dementia (550). This literature started with the rare genetic forms of Alzheimer's disease and covers animal models mimicking genetic forms in humans, as well as clinical studies addressing genetic causes of human Alzheimer's disease. More recently, evidence of cerebrovascular involvement has also been repeatedly demonstrated in the much more common late onset, sporadic form of Alzheimer's disease (89, 268, 550). Because cerebrovascular disease is commonly present in late onset Alzheimer's disease, it can be difficult to distinguish whether cerebrovascular dysfunction is a consequence of Alzheimer's pathology or vascular disease independent of Alzheimer's pathology (218, 267). Advances in *in vivo* imaging now allow better phenotyping of patients, which helps in differentiating vascular effects caused by Alzheimer's disease from vascular effects that result simply from vascular comorbidities associated with aging (279). Also, ongoing research on rare human genetic forms of Alzheimer's disease may help to shed light on this issue, because cerebrovascular dysfunction can be studied in the early stages of Alzheimer's disease in a population with, because of the young age of onset, limited vascular comorbidities.

Before we discuss what is currently known about autoregulation in Alzheimer's disease, we will first briefly summarize the literature on global changes in CBF, CO_2 reactivity, and NVC in Alzheimer's disease. These aspects of CBF regulation have been studied much more extensively than autoregulation. However, these concepts are sometimes confused, with the result that some studies of NVC or CO_2 reactivity have been reported to reflect changes in autoregulation, which is incorrect.

a. Cerebral blood flow

CBF is essential to support changes in activity of neurons and other brain cells. Disruption of CBF regulation – baseline, temporal, or regional homeostasis - may represent a major factor in the development and progression of Alzheimer's disease and other dementia's. Previous work from animal models found that mild-to-moderate cerebral hypoperfusion impairs neuronal protein synthesis, whilst cerebral ischemia ultimately leads to an increase in local glutamate concentrations and contributes to the accumulation of neurotoxic molecules (e.g., amyloid-β) (655). Reported increases in amyloid-β following ischemia appear to be short-lived however, and it remains debated whether this mechanism can explain the sustained widespread accumulation of amyloid-β in Alzheimer's disease (189). Nonetheless, these vascular-derived insults might contribute to neuronal degeneration in Alzheimer's disease. A reduction in CBF in Alzheimer's disease compared to healthy controls has been observed in multiple studies using different imaging modalities: Xenon-133, SPECT, PET, TCD, extracranial ultrasound, and arterial spin labelling MRI (15, 627). Importantly, reductions in CBF have repeatedly been shown in the preclinical stages of Alzheimer's disease (267, 277). The reduction in CBF shows a regional pattern, and has been proposed as a diagnostic biomarker, comparable to FDG-PET, which is a labeled-glucose imaging modality that can identify regional hypometabolism (15, 636). Such data raises the question if lower levels of CBF in Alzheimer's disease may reflect

synaptic failure (81, 399), resulting in reduced metabolism and reduced demand for CBF. This synaptic failure then continues throughout the course of the disease and is associated with the cognitive decline in the later stages (325). In this scenario, reduced CBF is not a causal factor in neurodegeneration, but a consequence of loss of synaptic function. Support for this notion comes from recent studies, which reported that cerebral global hypoperfusion in the general population is related to accelerated cognitive decline (628, 638) and increased risk for dementia (628). Specifically related to Alzheimer's disease, cross-sectional studies found that lower CBF is present in those with worse cognition (45) and in patients that are rapidly declining (401). In a prospective study, cerebral hypoperfusion, measured using MRI (arterial spin labelling), predicted progression from mild cognitive impairment to Alzheimer's disease (76). Moreover, reduced CBF was also associated with a faster two-year cognitive decline in a cohort of 88 patients with dementia due to Alzheimer's disease (42). After adjusting for subject demographics (e.g., age, sex, and education) and brain structure (e.g., gray matter volume, atrophy, white matter lesions), whole brain and parietal hypoperfusion were associated with accelerated cognitive decline. In another study, these authors confirmed that reduced regional CBF was associated with a decline in global cognitive function, but also executive function (335). These studies may reflect a close matching of CBF to synaptic function, making CBF an early biomarker of disease and a predictor of disease progression.

Alternatively, reduced CBF may be caused by cerebrovascular dysfunction and contribute to loss of brain function and disease progression through a mismatch of CBF to neuronal demand. Reduced levels of CBF, measured by MRI-arterial spin labelling, represented the earliest sign of late-onset Alzheimer's disease, present even before traditional biomarkers (e.g., cerebrospinal fluid ß-amyloid, cerebral hypometabolism, or brain atrophy) (277). These

findings and others (266, 267) leave open the possibility that cerebral hypoperfusion has a direct causal role in the development of Alzheimer's disease.

b. CO_2 reactivity and NVC

Impaired vascular reactivity to CO_2 may already be present at an early, pre-clinical stage of Alzheimer's disease. Indeed, individuals carrying the *APOE4* gene (223), and those with early stage probable Alzheimer's disease (383), exhibit impaired cerebrovascular responses to hypercapnia measured with TCD, compared to cognitively normal controls. These findings were confirmed in a study in younger, cognitively healthy *APOE4* carriers, that showed reduced responses to hypercapnia using blood O_2 level dependent (BOLD)-fMRI (547). In addition to changes in cerebrovascular reactivity, other studies suggest impaired NVC in Alzheimer's disease, which may also already be present in the pre-clinical stage (193, 265, 267). Using BOLD-fMRI, diminished local CBF responses in brain regions engaged during cognitively demanding tasks in individuals with genetic predisposition for Alzheimer's disease or in early stage Alzheimer's disease have been observed (308). Moreover, fMRI studies indicate disrupted resting-state neural connectivity in brain areas susceptible to atrophy in Alzheimer's disease (e.g., hippocampus, medial prefrontal and cingulate cortex) (308).

c. Autoregulation

Evidence pointing towards progressive impairment in cerebrovascular function and structure in Alzheimer's disease led to the hypothesis that autoregulation is impaired in Alzheimer's disease (96). Clinically, the most relevant consequence of impairment in autoregulation in patients with Alzheimer's disease would be their increased vulnerability to cerebral hypoperfusion following reductions in BP. This increased vulnerability could be a double-edged sword. With impaired autoregulation for a given reduction in BP, the reduction in CBF

would be greater in patients with Alzheimer's disease. Added to this, effects of Alzheimer's pathology and hypoperfusion on neurons, glia, and other cell types could be greater than in healthy brain (206, 267, 550, 642). From a clinical perspective, the most commonly encountered reductions in BP in patients with Alzheimer's disease are those that occur in the context of hypertension, antihypertensive treatment, daily postural changes including orthostatic hypotension, and during peri-operative care.

Studies of autoregulation in Alzheimer's disease

The oldest study of autoregulation in dementia known to us was from 1971 using the methods proposed by Lassen (523). Global and regional CBF was measured using the intra-arterial Xenon-133. Baseline CBF was studied in 24 dementia patients (39-74 years of age), 13 with early onset dementia (<65 years), of whom five had biopsy-confirmed Alzheimer pathology, and nine patients with onset >65 years, including four Korsakoff and three vascular dementia patients. In 15 patients (6 young, 9 old), autoregulation was measured before and after pharmacologically induced BP changes. It is uncertain if any of these 15 patients had Alzheimer's disease. The average reduction in mean arterial BP was 28%, with an associated mean reduction in CBF of 4%. In two cases (young onset dementia), large reductions in BP were obtained (69 and 44%). These changes were associated with reductions in CBF of 25 and 19%, respectively. Increases in BP (in two cases) had no effect on CBF. No control group was included, although the authors could draw from their numerous previous experiments using this technique for comparison. Despite the obvious limitations related to the heterogeneity of the sample (in both age and diagnosis), the authors found no evidence for significant impairment of autoregulation in any of the 15 patients with dementia, regardless of age or underlying diagnosis (523).

The first study of autoregulation in patients with a certain clinical diagnosis of Alzheimer's disease was published in 2009 (91). Nine patients with Alzheimer's disease (three with mild cognitive impairment, CDR 0.5, six with mild dementia, CDR 1, mean age 68 years) and eight age and sex matched controls were studied. The diagnosis was confirmed by neuropsychological evaluation, MRI, and CSF biomarkers. Dynamic autoregulation was evaluated using both spontaneous changes in BP and changes induced by repeated squatting and standing maneuvers (94). These maneuvers induce large (20-30%) changes in BP and mimic the effects of daily life postural changes on BP and CBF (94). CBF velocity, and its changes, were measured using TCD. Alzheimer's disease patients had lower CBF and higher cerebrovascular resistance, while there were no significant differences in total brain volume between patients and controls. Despite these cerebrovascular differences, dynamic autoregulation was equally effective in counteracting BP changes in Alzheimer's patients and controls (94).

Preserved autoregulation was confirmed in a study in 20 Alzheimer's disease patients (no controls), 74.6 years of age, 16 with CDR 0.5, four with CDR 1, 17 with a positive amyloid-PET (640). This study evaluated static autoregulation, where CBF was measured using O^{15}-PET before and after BP lowering induced by intravenous nicardipine. CBF was measured after a reduction in BP that was maintained for 7-10 minutes. While mean BP was reduced on average from 109 to 92 mmHg, global CBF was unaffected (44 versus 43 ml/100g/min). Moreover, there were no regional reductions in CBF, including areas with more white matter lesions, in watershed regions, and in regions with the highest ß-amyloid accumulation (640).

A study of dynamic autoregulation used TCD and evaluated 10 Alzheimer's disease patients (73 years of age) and 17 controls during simple, every day postural challenges - standing up from sitting (583, 585). Standing up from sitting causes transient (<30 s) reductions in BP, between 15 and 20 mmHg in mean arterial BP. When performed as repeated maneuvers, similar

to repeated squat-stand maneuvers, they induce strong oscillations in BP and CBF, with the benefit that sit-stand maneuvers are easier to perform in older patients than squat-stand maneuvers (585). CBF was lower and cerebrovascular resistance was higher in Alzheimer's disease patients compared to controls. Despite these baseline differences, the CBF response to the orthostatic challenges was similar in patients and controls (582, 583). Of note, cortical oxygenation (measured using Near-infrared spectroscopy, NIRS), decreased more in Alzheimer's disease patients, despite similar changes in CBF, which may point towards reduced O_2 supply or increased O_2 extraction in the microcirculation (582). However, the NIRS technique requires further validation.

Other authors confirmed normal dynamic autoregulation in 17 patients with Alzheimer's dementia, 19 with mild cognitive impairment and 20 controls (201). However, the first potentially discrepant observation was made in a study in 12 patients (of whom 10 were also included in (582, 583)). Even though a normal CBF response to a BP reduction following standing was confirmed, the transient increase in BP (20% on average) that followed the return to sitting after standing was associated with a greater increase in CBF in Alzheimer's disease patients versus controls (24 versus 13%). Such a difference was also observed during repeated sit- stand maneuvers, which led to repeated 20% increases and decreases in BP from baseline. In Alzheimer patients, these BP changes led to slightly larger changes in CBF than in controls (27% versus 22%). However, assessment of dynamic autoregulation using TFA again revealed no differences between patients and controls (383).

Thus, after combining these smaller studies, 58 patients with Alzheimer's disease (38 dementia, 20 mild cognitive impairment) were studied with TCD, indicating normal dynamic autoregulation, except for one study with partially conflicting results (383). In addition, 20 patients with mild cognitive impairment were studied using PET and had normal static autoregulation.

Recently, the largest studies on autoregulation in Alzheimer's disease to date were published (122, 125) wherein both dynamic and static autoregulation were investigated. In 53 patients with Alzheimer's dementia (73 years of age), 37 patients with mild cognitive impairment (suspected early stage Alzheimer's disease, 69 years of age) and 47 controls (69 years of age), dynamic autoregulation, measured with TCD, was evaluated during spontaneous changes in BP, and during larger induced changes in BP using repeated sit-to-stand maneuvers (122). These induced changes led to increases and decreases in mean BP of on average 25%. This large study confirmed that dynamic autoregulation was similar in Alzheimer's disease patients (mild cognitive impairment and dementia) and controls. This conclusion was despite clear evidence for other cerebrovascular changes in Alzheimer's disease (reduced CBF, higher cerebrovascular resistance, reduced CO_2 reactivity).

Next, from the 53 patients with Alzheimer's dementia, 44 patients also underwent CBF measurements using MRI-arterial spin labelling with a repeated measurement after six months of BP lowering with nilvadipine versus placebo (125). In 22 patients on nilvadipine, systolic BP was reduced by an average of 11 mmHg, while global and regional CBF were not reduced (125). There was a non-significant trend towards a 10% increase in global CBF following the BP reduction, which is of interest because two other studies of antihypertensive treatment in patients of similar age, but without Alzheimer's disease, found (in larger sample sizes) a significant increase in CBF of 10% following BP lowering treatment (see Section **V**.B.*ii*.).

d. Autoregulation: indirect evidence of normal autoregulation in Alzheimer's disease

There have been several large prospective studies that have measured outcomes that offer indirect evidence suggesting autoregulation is normal, similar to what was discussed in Section **IV**.B. in relation to hypertension and autoregulation. These are outcomes that capture the expected consequences of impaired autoregulation, such as cognitive decline, cerebrovascular

events, and falls or syncope. Regarding falls and particularly regarding syncope, we repeat the caveat that these often represent a failure of BP regulation (296) and not necessarily a failure of autoregulation (Section **VI**.A.).

Recent meta-analyses of antihypertensive treatment show that BP lowering is associated with a lower risk to develop dementia's, including Alzheimer's disease (139). In addition, the SPRINT-MIND study found a lower risk of mild cognitive impairment and possibly dementia when intensive BP lowering treatment (to a systolic BP of 120 mmHg or below) was compared to standard treatment (212). Given the relatively short follow-up times in these studies, and the knowledge that Alzheimer's disease is a slowly progressive disease with an asymptomatic, clinically unrecognized phase that can last 10-20 years, we can assume that many of the participants with an outcome of mild cognitive impairment or dementia due to Alzheimer's disease already had asymptomatic Alzheimer's disease at the time of inclusion. If Alzheimer's disease were associated with impaired autoregulation already in an early stage of the disease - as suggested by animal models (406)- impairment in autoregulation would be predicted to be present at study inclusion in these participants. If so, exposure to BP lowering treatment would have increased the risk for cerebral hypoperfusion, and therefore increased the risk to develop progressive cognitive decline and reach the end-point of mild cognitive impairment or dementia. In reality however, the reverse was found, with a reduced risk (hazard ratio 0.84) to develop dementia (212). Moreover, in the subgroup of older (>80 years old) patients with low cognitive scores on a validated screening test (Montreal Cognitive Assessment), indicating a subgroup that will include many patients with mild cognitive impairment or even unrecognized dementia, there was no increased risk of cognitive deterioration following intensive BP reduction (423).

<u>Contrast with animal models</u>

These findings of preserved autoregulation in patients with late onset Alzheimer's disease are in contrast with observations from an animal model (406). Indications that autoregulation was impaired in Alzheimer's disease came from other studies performed in pre-clinical models [reviewed elsewhere (96)]. For example, impaired static autoregulation was observed at a young age in transgenic mice that overexpress amyloid precursor protein, even before the occurrence of parenchymal amyloid-β deposition (406). Impaired autoregulation in these animals was attributed to vascular dysfunction due to effects of ß-amyloid, impaired contraction of vascular muscle (with increased arterial BP), and altered vascular architecture (96, 308, 406).

There are several potential explanations for the discrepancy between the animal model results and human observations. The animal model for Alzheimer's disease is not a model for late onset Alzheimer's disease, but rather for the rare young onset genetic form. Even there, this represents only a partial model, as they do not involve tau pathology. In addition, animal models sometimes do not develop significant neurodegeneration or cognitive decline. These and other limitations of preclinical models for Alzheimer's disease have been discussed elsewhere (306) and likely contribute to the discrepancies described to date between studies performed in animals and humans. This also highlights the difficulty of translating observations from animals to clinical populations in humans.

e. Summary and clinical interpretation

There is consistent evidence for cerebrovascular changes in Alzheimer's disease, which can be summarized as an increase in vascular resistance, an early reduction in global (and regional) CBF, and impaired NVC and CO_2 reactivity. These changes appear to be somewhat selective, because there is now substantial evidence that autoregulation is preserved in patients with Alzheimer's disease. The available studies were performed under conditions wherein BP was

increased or decreased by approximately 20-25% or less. This was done through BP lowering medication, or by postural challenges to decrease or increase BP. Thus, we can translate these studies to clinical situations such as treatment of mild to moderate hypertension, or to orthostatic hypotension, but not to more extreme conditions such as malignant hypertension (hypertensive crisis), or septic or hypovolemic shock. The clinical implication is that patients with Alzheimer's disease have no increased vulnerability to BP lowering treatment, and therefore do not require higher levels of BP to maintain normal CBF. For example, when a hypertension guideline advices a BP target of <140 mmHg systolic and <90 mmHg diastolic for a hypertensive patient, there is no evidence that if this patient also has Alzheimer's disease, these targets should be raised to a higher levels of BP to preserve CBF. There may of course be other arguments not to follow such guidelines, for example time to benefit, patient preference, severe frailty, and so forth. However, available data indicated that fear of causing cerebral hypoperfusion should no longer be an argument. Of note, but not reviewed here (as it is beyond the current scope), there is also no evidence that Alzheimer's disease patients have increased risk of orthostatic hypotension related to antihypertensive treatment (123, 347, 583, 584).

The impairment in NVC or CO_2 reactivity that are associated with Alzheimer's disease are not directly related to autoregulation. Higher levels of BP may not translate into better NVC, nor will lower levels (within the ranges described) further impair NVC. In contrast, longstanding untreated hypertension can promote cerebrovascular disease and thereby further impairment in NVC or CO_2 reactivity. Some studies even suggest that it is not BP *per se*, but factors associated with hypertension, that cause impairment in NVC. For example, elevated levels of tissue or circulating angiotensin II (194, 441) may directly affect endothelial function, which could then contribute to impairment in NVC, independent of changes in BP. The clinical relevance of this discussion is that hypertension and Alzheimer's disease often co-exist. Around 40% of

Alzheimer's disease patients also have hypertension (124). *Vice versa*, the prevalence of hypertension increases to 60% with aging. Because aging is the strongest risk factor for Alzheimer's disease (355), many older hypertensive patients may develop Alzheimer's disease.

E. Autoregulation in neurocritical care

We have explained the strong capacity of the cerebrovasculature and dynamic autoregulation to protect against significant increases in CBF (hyperperfusion) during acute increases in BP, or hypertensive emergencies. Clinical conditions that can cause such increases in BP include drug abuse (i.e., cocaine, amphetamines), anxiety or panic disorders, stroke, traumatic brain injury, aortic dissection, and hypertensive disorders of pregnancy (448). End-organ damage to brain (and the retina) can result if autoregulatory capacity is exceeded, resulting in marked increases in CBF, endothelial dysfunction, increased microvascular pressure, loss of blood-brain barrier integrity, and edema (448).

Neuro-intensive care is a field where protection of the brain against effects of either reduced or increased perfusion pressure is critical (107, 108, 352, 448, 482). In the majority of this review, we have discussed autoregulation and diseases related to autoregulation, generally in the context of conditions where ICP is normal and relatively stable. In neurocritical care, this situation can be very different. For example, in ICH or in traumatic brain injury, brain damage can result from elevated ICP. Under these conditions, monitoring and treatment is therefore not only focused on maintaining adequate CBF to supply O_2 and glucose, but also on adapting BP to changes in ICP. The importance of ICP monitoring and the availability of long-term measurements of ICP in the neuro-ICU, has led to monitoring of autoregulation based on the relationship between BP and ICP, as well as the relationship between BP and CBF (107, 108, 352, 482). This field of clinical research is unique in that it has provided long-term (hours)

monitoring, where changes in autoregulation over time can be linked to clinical prognosis (52, 108, 110, 112, 113, 307, 359, 482). In this setting, additional factors come into play in relation to autoregulation (e.g., brain swelling and edema, CSF circulation, vascular or neuroinflammation, or changes in the meninges or choroid plexus – key sites of immune cell trafficking), making BP and ICP regulation, versus CBF regulation, topics that would require a review of its own. Fortunately, several excellent recent reviews on this topic are available (20, 108, 482).

F. **Direct control of the brain on blood pressure?**

Recently, the idea has resurfaced that the brain may directly control BP to preserve its function. This was the idea formulated by Hill and Bayliss around 1890 (40, 249), who were convinced that there was no active autoregulation to maintain CBF, and therefore (paraphrased) the rest of the body functioned as a slave to the brain, increasing BP if the brain needed more CBF. Indeed, in more recent times, common examples such as the increase in BP following stroke has been interpreted as direct control of the brain on BP in response to the failing CBF. In a similar vein, the higher BP that is associated with aging has been considered to be caused by the brain in response to the waning CBF with aging (379). This idea was recently reframed (120 years after Hill) as the 'selfish brain' hypothesis (note that the 'selfish brain' term has also been used for very different hypotheses for mood disorders, addiction, etc.) (379).

A recent study provided evidence for a direct effect of the brain on BP, following a change in ICP and cerebral hemodynamics (368). This study identified astrocytes that lie adjacent to brain autonomic centers as potential modifiers of BP to maintain brain function. There are however several methodological caveats to this study. First, the results are presented as if it is a reduction in CBF that triggered the astrocytes' response (368). However, the reduction in CBF was

brought about by an increase in ICP, raising the question of whether the astrocytic response was due to increased ICP or to reduced CBF (368). Raising ICP to lower CBF was perhaps the only reasonable design, because other options to reduce CBF (i.e., lowering BP) would have triggered baroreflex responses (296). Activation of the classic baroreflex response would have confounded the results, as the authors wished to test if astrocytes functioned as a 'brain baroreflex'. The increase in ICP (and subsequent reduction in CBF) led to an increase in BP with a delay of about 30 seconds, and persisting for about 30 minutes – the time scale of these changes clearly differs from the faster changes associated with the classic' baroreflex. Interpretation of this work is further complicated by the fact that the somewhat moderate increased in ICP (10-15 mmHg) was associated with a 40% reduction in CBF, suggesting autoregulation in this model was rather ineffective. In contrast, multiple other studies have reported that CBF is maintained quite effectively during increases in ICP of this magnitude or more. These issues aside, this study of astrocytes is of potential interest, perhaps applicable to the neuro-intensive care unit setting, where elevated ICP is frequently observed (see Section **V.**E.). Second, with regard to the discussion above, most other instances where CBF is reduced (e.g., following BP lowering, antihypertensive treatment, postural changes, hypovolemic or septic shock), ICP *decreases* in parallel with CBF (332, 625). Therefore, it remains uncertain if a reduction in CBF - without an increase in ICP - would trigger a 'brain-initiated' increase in BP, mediated through the autonomic nervous system.

G. **Anesthesia and autoregulation**

From a clinical perspective, the topic of anesthesia and autoregulation involves not only the use of anesthetic drugs, but also control of respiration and respiratory gases, BP, combined with the potential hemodynamic effects of surgery. The relevance of taking autoregulation into account to prevent cerebral ischemia during surgery has recently been reviewed (653) and is

also explained in our call-out text box for clinicians. A discussion of complex cardiovascular or cardiothoracic surgery, with extracorporeal circulation and anterograde selective cerebral perfusion (538) is beyond the scope of this review. This also applies to the use of anesthesia in traumatic brain injury, where a recent review identified important knowledge gaps (182). For the effects of changes in concentration of respiratory gases (O_2 and CO_2) on CBF we refer to sections I. C. and III. B. of this review. Here we briefly discuss the effects of anesthetic agents on CBF and autoregulation, and refer to a recent review for further reading (525).

Anaesthetic agents affect brain metabolism (188, 525). For most agents, the suppression of consciousness reduces metabolism and hence demand for O_2 consumption. If, as under normal conditions, the tight coupling between metabolism and CBF is maintained (Section I B), this reduction in the cerebral metabolic rate of O_2 ($CMRO_2$) will equally reduce CBF. However, some anethetic agents cause an uncoupling of metabolism and blood flow (188, 525). In some cases, there may also be direct effects of anesthetics on the cerebral vasculature, changing vascular tone and thus cerebrovascular resistance. The net outcome of such changes on CBF during anesthesia depends on whether metabolism and blood flow remain coupled, and on interaction with changes in respiratory gases. Although anaesthetics affect CBF, most agents do not impair autoregulation, with the exception of volatile anaesthetics (the fluranes) (525). The effects of commonly used anaesthetic agents on CBF, metabolism ($CMRO_2$), and autoregulation are briefly summarised below.

Isoflurane, desflurane, and sevoflurane (volatile agents) have a direct vasodilatory effect on cerebral blood vessels, and this effect is independent of the dose or depth of anaesthesia (373). The effects on autoregulation however are dose-dependent, with normal autoregulation at lower dose for isoflurane or desflurane (1 MCA; minimum alveolar concentration), but impaired autoregulation above 1.5 MAC. For sevoflurane, autoregulation is already impaired at a dose above 1 MCA (390, 525).

Effects of fluranes or anaethetics are modified by CO_2, where hypercapnia lowers the threshold for impairment in autoregulation, and hypocapnia increases it. These anaesthetics all lower brain metabolism ($CMRO_2$), and because they also induce vasodilation, cause uncoupling between metabolism and CBF (i.e., CBF is higher than metabolism would demand) (525). Nitrous oxide, when used as a single agent (which is no longer in practice), increases CBF while $CMRO_2$ remains stable; however when used in combination with other anaesthetics, results are inconclusive. There is no information on its effects on autoregulation (390, 525). Propofol reduces brain metabolism, which in turn leads to a reduction in CBF. Direct *in vitro* vascular application of propofol causes vasodilation. Autoregulation remains intact unless doses of propofol exceed 200 µgram/kg/min (390, 525). Ketamine increases CBF through direct vasodilation, but here is no evidence for effects on autoregulation (390, 525). Etomidate reduces $CMRO_2$ and thereby CBF. This agent has a potential direct vasoconstrictor effect, but there are no known effects on autoregulation. Unique among anesthetics, etomidate does not lower BP (525). Dexmedetomidine reduces CBF, potentially by activation of post-synaptic alpha2-adrenergic receptors that induce vasoconstriction, and in addition reduce $CMRO_2$ (525). Benzodiazepines (e.g. midazolam), non-benzodiazepine agents that target GABA (e.g. zolpidem), and opioids (e.g. fentanyl) reduce $CRMO_2$ and thereby CBF, but do not affect autoregulation (390, 525).

Because of their effects on cerebral metabolism and on cerebrovascular tone, anesthetic agents can also affect NVC. From a research perspective, this has implications for the interpretation of studies on NVC in preclinical models, which are most commonly performed under anesthesia (188). Anesthesia may also affect NVC in humans (508, 630). New approaches that allow studies in awake animals have been proposed to address this potential limitation (188).

VI. IMPACT OF DAILY LIFE CHALLENGES ON CEREBRAL BLOOD FLOW

A. Postural challenges

i. *Orthostatic hypotension*

Whenever we stand up from a lying or sitting position, the combination of our upright posture and Earth's gravity causes large shifts in circulatory volume (300-500 ml) from the central body and head to the lower abdomen and legs (220). These fluid shifts lead to reductions in venous return to the heart, reducing cardiac output and BP. Actively standing up also causes reflex arterial vasodilation (to support muscle perfusion) that contributes to the reduction in BP. Maximum decreases in BP after standing are reached within 15 seconds, and can easily be as large as 15-25% (220). The baroreflex usually restores BP within 30-40 seconds (296). Failure to normalize BP after 60 seconds is termed orthostatic hypotension, defined as a sustained reduction in systolic BP of 20 mmHg or more.

Even without orthostatic hypotension, normal BP responses pose daily challenges for autoregulation. Their speed of onset limits the potential for autoregulation to buffer these BP changes. This explains the common subtle symptoms we all may experience upon standing up. In orthostatic hypotension however, sustained reductions in systolic BP can be as large as 60 mmHg and exceed the lower limits of autoregulation, causing cerebral hypoperfusion, dizziness, falls, or syncope.

The longer we lie or sit, the stronger is this transient decrease in BP. Other postural challenges may also cause large reductions in BP. For example, getting up after squatting leads to strong reductions in BP (94). Combining standing with a Valsalva maneuver (e.g., singing, blowing a horn) may also elicit a strong fall in BP. Bending forward may cause abdominal vascular compression, more so in pregnant women or in obesity, and provoke hypotension (220).

These challenges occur on a daily basis and are an important reminder that BP is not a stable entity *per se*. Steady-state BP, measured sitting after 5 minutes of rest, should indeed be more

or less constant in a healthy person if repeated with an interval of days or weeks. However, when measured over shorter time intervals throughout a day, BP constantly varies with postural changes. The strong impact of postural changes on both BP and CBF can easily be learned from studies using repeated sit-stand or squat-stand maneuvers (94, 583) (Figure 4).

ii. Syncope

Syncope (or fainting) is defined as a brief loss of consciousness caused by a transient reduction in CBF (221, 548, 556). This definition clearly sets syncope apart from the two other most common causes of transient loss of consciousness - seizures (epilepsy) and psychogenic syncope. The definition of syncope may have contributed to a common misconception that syncope is caused by a disorder in autoregulation. Syncope is however primarily caused by a failure to maintain stable and adequate BP (221, 548, 556). Theoretically, for the same reduction in BP, a person with impaired autoregulation could experience (pre)syncope earlier than someone with normal autoregulation. However, the influence of BP regulation in syncope outweighs that of autoregulation (510).

Syncope is caused by a failure to maintain BP at a level that is required to maintain sufficient CBF (183, 592). Autoregulation operates within two boundaries: the magnitude (static) and the speed (dynamic) of BP changes. The magnitude refers to the limits of static autoregulation. When BP falls below the lower limit of autoregulation (e.g., below a systolic BP of 70-80 mmHg), CBF will fall progressively with further reductions in BP. The speed refers to limitations in response time of dynamic autoregulation. Slow changes in BP are much more efficiently buffered than fast changes, and very fast changes (e.g., those occurring within 1-5 seconds) cannot be buffered at all.

BP is determined by cardiac output and total peripheral resistance (62, 183, 278, 337, 651). Cardiac output is in turn determined by stroke volume and heart rate, whereas peripheral vascular resistance is determined by vascular structure, vascular mechanics, and vascular tone of the systemic circulation (62, 183, 278, 337, 651). The baroreflex system plays an important role in short-term BP regulation, as it controls heart rate and peripheral vascular resistance through the parasympathetic (mainly vagus nerve) and sympathetic arms of the autonomic nervous system (296).

Even if baroreflex function is normal, syncope can occur when certain challenges exceed baroreflex capacity (41, 199, 296, 558). Examples are severe hypovolemia (bleeding, excessive fluid loss due to diarrhea, vomiting, exercise, or hot environments), or large volume shifts (when standing up after prolonged squatting, e.g., during gardening). This leads to a fast and large reduction in BP, that due to its speed of onset, cannot be buffered by autoregulation and leads to hypoperfusion. Many cases of syncope occur during temporary baroreflex dysfunction (296). Called neurally-mediated reflex, or vasovagal syncope (296), such disorders can cause the baroreflex to initiate bradycardia and peripheral vasodilation, leading to prolonged reductions in BP below the lower limit of autoregulation, and loss of consciousness. These circumstances include pain, fear, strong emotion, sustained orthostatic stress (standing still for long periods), amongst others. Baroreflex failure associated with disease is seen in autonomic failure (e.g., diabetes, Parkinson's disease, primary autonomic failure, or spinal cord lesions (296). Finally, cardiac disorders (structural or rhythm) can cause syncope through their effects on BP.

B. Physical activity

The spectrum of physical activity encompasses the areas of low-, moderate- and vigorous-intensity physical activity, but also the lower end of the spectrum including sedentary behavior (e.g., sitting and lying). The interest in understanding the impact of exercise-like physical activity on health (394), including the regulation of CBF (324) and its impact on brain health, dates back to the middle of the previous century. During the most recent decade, studies have started to acknowledge the importance of examining the impact of lifestyle or behavior, driven by the observation that increasing sedentary behavior, independent of exercise performance, is related to all-cause mortality and morbidity (154, 587). More recent work also suggested the potential of sedentary behavior to affect cardiovascular and cerebrovascular health, and thus brain health (68, 159, 613).

i. Sedentary behavior

In studies designed to better understand the immediate impact of prolonged sedentary behavior in healthy individuals, Carter *et al.* examined the impact of four- and six-hour periods of prolonged, uninterrupted sitting on CBF (69). Using TCD, prolonged, uninterrupted sitting led to a small (1.4-3.4 cm/s, equivalent to 2-5%), but significant decline in middle cerebral artery CBF velocity in healthy volunteers. Because there was a small (0.9 mmHg) reduction in end-tidal CO_2, which may be the result of changes in pulmonary ventilation during prolonged sitting, it remains uncertain if a change in $PaCO_2$ could have contributed to the reduction in CBF (69). In this range, even small changes in $PaCO_2$ (e.g., 1 mmHg) can cause significant changes in CBF (3-8%) (93, 388). The effect of sitting on CBF has also been explored in groups at increased risk for cerebrovascular disease. A study in 12 older adults (70 years of age) found a small reduction in CBF (614), however, $PaCO_2$ or end-tidal CO_2 was not measured in that study. In 22 older adults (78 years of age, nine women), there was no reduction in CBF after three hours sitting (364). CO_2 was measured in that study and remained stable. Of note, there

was an increase in BP with sitting. In 25 middle-aged workers with prehypertension (449), sitting, but not sitting alternated with periods of standing, was associated with a decline in CBF over the day (without measurements of $PaCO_2$ or end-tidal CO_2). Finally, a recent cross-sectional study found in 52 healthy older adults that greater sedentary time was significantly associated with lower CBF in lateral and medial frontal regions (654).

Some of these studies have also investigated if sedentary behavior may affect autoregulation or CO_2 reactivity. While cerebrovascular responses to hypercapnia were preserved, changes in autoregulation during sit-to-stand maneuvers were found in one study (69). Prolonged uninterrupted sitting for four hours resulted in a decrease in phase in the very low frequency range (69). The subsequent study that adopted a six hours uninterrupted sitting protocol found an increase in normalized gain in the very low frequency range (69). The differential impairment in autoregulatory parameters between both studies may relate to a time-dependent, progressive impact of sitting on autoregulation. It is hypothesized that impairment in autoregulation may first affect phase (i.e., the latency of response), before affecting gain (i.e., the efficiency of the response) (629). However, a series of studies from our laboratory in an older population with or without increased cardiometabolic risk found no impact of prolonged, uninterrupted sitting on autoregulation, despite a significant decrease in CBF (236, 364). Therefore, it is unlikely that a change in autoregulation is responsible for the reductions in CBF during prolonged sitting that were found in some studies. One should also consider the potential impact of sitting on alternative interacting pathways or mechanisms, including baroreflex sensitivity, cerebral metabolism, endothelial function, or NVC.

Population (239) and laboratory-based studies (143) aimed at better understanding the impact of prolonged sitting on health outcomes, highlight the relative importance of breaking up

sedentary behavior, independent of the duration and intensity of this physical activity break. For this purpose, studies have interrupted prolonged sitting and found that breaking up sitting prevents the decline in CBF in healthy volunteers (69). Interestingly, this is not a universal finding across all populations, since a recent study found that effects of 3 hours sitting on CBF were not prevented by physical activity breaks in subjects with pre-diabetes (236) or older individuals (364). Possibly, in subjects with *a priori* increased risk for cerebrovascular disease, low-intensity physical activity breaks are insufficient. Some support for this hypothesis is provided by a recent study that found that 30-minutes of moderate-intensity walking exercise prevented the decline in CBF associated with prolonged sitting (614). However, this study did not measure and control for changes in $PaCO_2$.

Taken together, recent studies suggest that prolonged sitting is associated with a stimulus-dependent decrease in CBF, but with no consistent effect on dynamic autoregulation. The exact mechanisms underlying these changes in CBF are unclear, but appear to result from the prolonged period of physical inactivity, since regularly interrupting sitting with short bouts of low-intensity physical activity or moderate-intensity walking exercise prevents these effects. However, changes in $PaCO_2$ due to changes in ventilation and lung perfusion are expected with prolonged sitting, and can be altered by the bouts of physical activity, and these changes alone may explain the effects on CBF. $PaCO_2$ was not always measured and accounted for in these studies. Further work is required to better understand the impact of sedentary behavior at different levels of the cerebrovasculature, including the blood-brain barrier, or more chronic changes such as vascular remodeling or changes in vascular mechanics. Whether effects of sitting are distinct in populations with impaired cerebrovascular health and hypoperfusion, and translate to detrimental long-term effects is unclear at this time and requires further examination.

ii. Exercise: role of intensity

Exercise can be regarded as an ultimate, integrative stimulus for the brain to regulate CBF, especially since exercise is known to evoke large changes in key stimuli that affect CBF – O_2 consumption, BP, cardiac output, blood gases (especially $PaCO_2$), activity of sympathetic nerves, and brain activity. All these variables change with exercise, often with different magnitudes and patterns, constantly challenging the sufficient delivery of CBF to meet metabolic demand (but also to prevent hyperperfusion) (55, 529). Changes in CBF in response to incremental levels of exercise are typically described as biphasic. There is a progressive increase in CBF in response to whole-body exercise, up to an exercise intensity of ~60% of maximal O_2 consumption, followed by a plateau in CBF and a decrease towards resting levels when reaching maximal intensity exercise [see review (55)]. Our understanding of regulatory mechanisms that contribute to the biphasic CBF response to incremental levels of exercise is limited by the complexity and redundancy in processes that regulate blood flow to the brain. Below, we have summarized what are thought to be the most important factors contributing to the biphasic CBF response.

Early hypotheses assumed there was a key role for exercise-induced changes in blood gases - especially $PaCO_2$ - contributing to changes in CBF with exercise. This idea was supported by the sensitivity of the cerebrovasculature to changes in $PaCO_2$, but also the observation that incremental levels of exercise first caused an increase in $PaCO_2$, followed by a (hyperventilation-induced) decline in $PaCO_2$ towards (near) maximal exercise intensity. Indeed, CBF was increased with increasing $PaCO_2$ levels at baseline (520) or when mitigating the drop in $PaCO_2$ during near maximal exercise (420). During submaximal exercise however, increases in CBF seem less dependent on changes in $PaCO_2$, although this stimulus may still contribute to the regional distribution of CBF (54). In addition to $PaCO_2$, PaO_2 may also play

a role in regulating CBF during exercise, especially when exercise is performed during acute or chronic hypoxia. For example, exercise during acute hypoxia elevates the CBF response, possibly as a compensatory response to a lower PaO_2 and maintenance of O_2 delivery. In contrast, lower CBF responses to exercise are observed during chronic hypoxia. At a minimum, these studies highlight the importance of measuring both $PaCO_2$ and PaO_2 when attempting to understand the regulation of CBF during exercise.

During exercise, marked increases in BP (30% or more), cardiac output (300-600%) and neural activity may support appropriate regional distribution of blood flow of the peripheral circulation and the brain. These factors all show a clear temporal linearity with increases in activity level, suggesting that BP, cardiac output, or neural activity alone are unlikely to dictate the biphasic CBF response during exercise. Moreover, any increases in BP should be buffered by autoregulation. Regarding cardiac output, studies have examined whether altered cardiac output during exercise, either within individuals [e.g., manipulation (414)] or between subjects [e.g., heart transplantation (526)], is followed by comparable changes in CBF. Despite increases in cardiac output with exercise, CBF remains largely unaffected, suggesting a relatively modest role for cardiac output in contributing to CBF changes with exercise. In addition, studies aimed at better understanding neurogenic mechanisms, (e.g., by blocking activity or effects of parasympathetic nerves), provide somewhat conflicting results that may relate to methodological issues pertaining to these experiments (e.g., effectiveness of blockade). There is currently limited evidence supporting a key role for neurogenic mechanisms in mediating CBF changes during exercise (529).

A final factor for regulation of CBF relates to cerebral metabolism. Whilst various techniques, exercise protocols and methodological designs have been used, the general consensus is that exercise leads to a gradual, dose-dependent increase in cerebral O_2 uptake, reflective of elevated cerebral metabolism (529). Accordingly, increases in cerebral

metabolism may contribute to the increased CBF at low- to moderate-intensity exercise. However, the lower CBF at near maximal exercise was not reflected by a decrease in cerebral metabolism (530). Possibly, a compensatory increase in O_2 extraction and/or cerebral delivery of O_2 may contribute to a further increase in cerebral metabolism with higher-intensity exercise. Alternatively, studies have suggested changes in substrate utilization may occur during exercise. More specifically, cerebral metabolism normally (under resting conditions) is thought to mainly depend on O_2 and glucose. However, during exercise, there is an increased uptake of lactate, accompanied by a reduced uptake of O_2 and glucose, which may suggest that the brain uses lactate as fuel, thus being less dependent on the consumption of glucose and O_2 (463).

Since older age is an important risk factor for cerebrovascular pathology, several studies have explored the impact of aging on CBF during exercise. Studies examining these responses have previously been reviewed in detail (55), and suggest the presence of a similar biphasic CBF response to incremental levels of exercise as observed in healthy young individuals. However, CBF is markedly lower in older individuals compared to healthy young subjects, both at rest and during exercise (170, 171, 174). Despite these differences in absolute CBF between both groups, the magnitude of change in cerebral metabolism, including the dependency on the various metabolic substrates at different levels of exercise, are comparable between younger and older subjects. Similarly, comparable responses are found between younger and older individuals in central hemodynamics (e.g., BP, cardiac output) and neural activity. One potential factor, partly contributing to the age-related differences, may involve a lower $PaCO_2$ in older individuals (174). Other factors, such as brain atrophy or altered vasodilator mechanisms, may also contribute to these age-related differences in CBF during exercise.

Taken together, the biphasic pattern of CBF during exercise seems to relate to multiple physiological mechanisms that have a complex integration, synergism and redundancy to

prevent impairment of CBF during exercise. Based on current evidence, the balance between cerebral metabolism and $PaCO_2$ seem to contribute most to the biphasic pattern of CBF during incremental levels of exercise, which can be present in healthy young as well as in older populations. Nonetheless, a lower CBF in older individuals may be present at rest and during exercise, which in part may relate to a lower $PaCO_2$. Better insight into these responses of acute exercise may help to understand, but also to guide and optimize, the effectiveness of exercise training strategies to improve cerebrovascular and brain health.

iii. Exercise training

Several studies have examined the potential clinical impact of exercise training and/or physical activity in primary and secondary prevention of cerebrovascular diseases, and have largely provided convincing evidence for a role of regular exercise in the clinical management of these diseases. Since this is beyond the scope of this review, we refer to excellent reviews in the literature that have covered this topic (144, 158). Here we discuss the impact of regular exercise training on CBF and autoregulation, but also whether these effects depend on the population examined.

In contrast to a relatively large number of studies examining the acute effects of exercise on CBF, few have thoroughly examined the impact of regular exercise training on regional or global CBF. A recent study in healthy older men examined the impact of eight-weeks of exercise training and examined global and regional CBF using MRI (311). Interestingly, this study found improved regional CBF in the frontal lobe, particularly the subcallosal and anterior cingulate gyrus, whereas a significant decrease was found in the temporal fusiform gyrus. These regional differences may explain the absence of an effect on global CBF in this study (311). Others also found regular exercise training to improve local CBF (336), including elevated bilateral blood flow to the hippocampus (77). When exercise training is causally

linked to increases in local CBF, one may expect that cessation of exercise training would decrease CBF. Indeed, a study of 10-days cessation of exercise training in older master athletes found reductions in CBF in the hippocampus and grey matter (13). These results suggest that exercise training increases local CBF, specifically in regions that are linked to cognitive function.

In line with studies performed in healthy individuals, exercise training also seems to improve local CBF in clinical populations. For example, exercise training for six-months in stroke survivors improved CBF to grey matter and perfusion in the parietal lobe (483). However, increased local CBF is not a universal finding. For example, Alfini and coworkers found increased CBF in the left insula in subjects with mild cognitive impairment, whilst 12 weeks of endurance exercise training decreased CBF in the left insula and improved cognitive function (14). In subjects with cognitive impairment, changes in local CBF should be interpreted with caution, especially when examining brain regions that may be related to impaired cognitive function. Previous work has linked decreased regional CBF to the pathophysiology of cognitive impairment (628, 638). Future studies are warranted, preferably adopting a longitudinal design and concomitant assessment of cognitive function, to better understand the impact of exercise training on regional CBF and the impact of these regional changes in CBF for clinical populations.

Related to the central topic of this review, one may question whether regular exercise training impacts autoregulation. Aengevaeren *et al.* was among the first to examine this question and compared autoregulation between older master athletes and age-matched sedentary controls. In this cross-sectional comparison, no differences in autoregulation were found between groups (7). Subsequent cross-sectional studies also found no significant differences in autoregulation between highly trained *versus* sedentary individuals (271, 345, 450). It is important to highlight that some recent studies suggest that changes in autoregulation may be present after high-

intensity exercise (142). Such changes consisted of very small reductions in TFA phase at 0.1 Hz. Another study found no effects of high intensity training on autoregulation (572). Whilst work on exercise and autoregulation, largely coming from cross-sectional comparisons, suggests that regular exercise training has little impact on autoregulation in healthy individuals, one may question whether this conclusion can be extrapolated to clinical populations. In one study, patients with chronic obstructive pulmonary disease exhibited preserved autoregulation compared with healthy controls, and eight-weeks of exercise training did not alter autoregulation in either group (339).

Taken together, exercise training seems to have no major impact on autoregulation. However, regular exercise training is a potent stimulus for changes in global and regional CBF, in both healthy individuals as well as in those with cerebrovascular disease. Specifically, regular exercise training is associated with increased regional CBF, such as in the hippocampus and grey matter (i.e., regions that match with cognitive abilities like memory and attention). ~~The exact mechanisms for these regional changes in CBF are unclear, but may be related in part to brain or regional atrophy, neuronal activity, and/or regional brain volumes. Within this respect, previous studies have linked cellular biological factors, e.g., brain-derived neurotrophic factor and myokines, to contribute to (hippocampal) neuroplasticity (304).~~

Although aerobic exercise is known to have beneficial effects on the cerebral vasculature, brain health, and cognitive function, mechanisms that underlie these changes are still relatively poorly understood (49, 541). Several mechanisms are likely to be involved. Part of the benefit of exercise may be hemodynamic, including effects of shear stress on phosphorylation and activity of eNOS, reductions in oxidative stress, angiogenesis, and increased CBF (49, 541). Another mechanism may relate to effects of neurotrophic factors including brain-derived neurotrophic factor (BDNF). Exercise increases expression of BDNF, known to have positive effects on neuronal plasticity, neurogenesis, synaptogenesis, hippocampal and cognitive

function (49, 541). Other data suggest that BDNF signalling may be dependent on activity of eNOS and production of NO by endothelial cells (49, 541). Considering the importance of the topic for brain health, further research is warranted to better define pathways explaining and facilitating optimization of exercise training to improve brain health.

VII. SUMMARY AND CONCLUSION

The brain is a richly perfused organ with a dense vascular supply, characterized by relatively high blood flow and low vascular resistance. Its high metabolic demand, roughly one fifth of the total body metabolism, in an organ that represents less than 2% of total body weight, depends on autoregulation to maintain adequate blood flow. A second important characteristic is that the brain is enclosed in the skull, which requires a much tighter control of tissue pressure (ICP) compared to other organs that have more room to expand. Autoregulation also plays an important role in the homeostasis of ICP, because an increase in cerebral blood volume will increase ICP and vice versa.

Autoregulation is the mechanism that safeguards blood flow to the brain in the context of changes in BP, the most important determinant of CBF. In this review, we have discussed physiological and pathophysiological examples where changes in BP occur. These include everyday changes in body position including effects of gravity on hemodynamics, physical activity, hypertension, and antihypertensive treatment. Autoregulation operates by regulating cerebrovascular resistance to counteract changes in BP. In relation to acute adjustments, these changes are thought to mainly occur due to actions of pressure-sensitive vascular muscle that alter vascular resistance through vasodilation or vasoconstriction (Figure 8).

The time frame over which changes in BP occur determines the effectiveness and stabilization of CBF by autoregulation. The effect of relatively slow changes in BP on CBF are best described by the model of *static* autoregulation, where it has been shown that CBF is held stable (within a margin of about ± 10%) across a wide range of BP levels (≈ 50 – 150 mmHg in MAP). The effects of faster changes in BP on CBF are captured in the model of *dynamic* autoregulation, where progressively faster changes in BP lead to larger changes in CBF. A consequence of dynamic autoregulation is that even with optimally functioning autoregulatory mechanisms, there can still be variability in CBF caused by changes in BP.

In contrast to what is often stated, autoregulation is a robust mechanism that is not generally affected by aging or hypertension. Evolving research suggests it also remains relatively intact in Alzheimer's disease. However, autoregulation does not function in isolation. We have described that CBF is affected and controlled by multiple factors, such as blood gases, neurovascular innervation, endothelial function, ICP, metabolism, and NVC. Conditions such as hypertension and Alzheimer's disease can therefore affect CBF, even if they do not impair autoregulation. As an example, endothelial dysfunction associated with hypertension may lead to a chronic reduction in CBF, while autoregulation (which is independent from endothelial function) is still intact, and therefore, when BP is lowered by antihypertensive treatment, there is no risk of hypoperfusion, despite the lower baseline CBF. Thus, a reduction in CBF or impairment in NVC, as has been observed in hypertension and in Alzheimer's disease, should not be interpreted as evidence of failed autoregulation, and should not justify attempts to raise BP levels to restore CBF or NVC. *Vice versa*, a finding of normal autoregulation in a clinical population (e.g., stroke, hypertension, Alzheimer's disease) should not be interpreted as a guarantee that global or regional CBF, or NVC, will be normal. Instead, we proposed an integrative approach to study the regulation of CBF, hoping to stimulate research and clinical efforts to disentangle autoregulation from the multiple other mechanisms that influence CBF.

Call-out text boxes for clinicians

1. *Three common misconceptions about cerebral autoregulation with implications for clinical research and care.*

There are three important misconceptions about autoregulation that appear commonly in the literature, both in clinical medicine and science, including physiology. These will be discussed below.

One of the most important misunderstandings is that autoregulation means that CBF is always constant over a range of values for arterial BP (perfusion pressure). This concept is common in the literature, as many studies of autoregulation include a statement that can be paraphrased as 'cerebral autoregulation is the mechanism that maintains a stable CBF in the face of changes in BP'. This view may have resulted from a misinterpretation of Lassen's classic autoregulation curve. His publication showed a perfectly flat plateau phase where CBF was constant between a very wide range of mean arterial BP from 50 mmHg to 150 mmHg. As we explain in this review, we suggest a different, more comprehensive, definition of autoregulation: "Cerebral autoregulation is the combination of mechanisms that reduce the impact of changes in BP on CBF, in duration and in magnitude." This review also explains the differences between static and dynamic autoregulation. We propose the following definitions: "In static autoregulation, for gradual changes in BP over a wide pressure range (the autoregulatory range), CBF is maintained within 10-20% of baseline values. In dynamic autoregulation, more rapid changes in BP lead to transient larger deviations in CBF. Here, autoregulation reduces the duration of these changes, by restoring CBF towards baseline before full recovery of BP."

A second common misunderstanding relates to the interpretation of the rightward shift of the autoregulation curve with chronic hypertension and aging, including an upward shift of the

lower limits of autoregulation. To counteract chronically high levels of BP, autoregulation has to maintain increased cerebrovascular resistance through vasoconstriction, or other mechanisms, in order to prevent what can be referred to as 'breakthrough of autoregulation' and hyperperfusion. This cerebrovascular adaptation could become irreversible, for example through inward vascular remodelling leading to narrowing of the vessel lumen, a common structural change seen in resistance vessels during chronic hypertension. This has led to a widespread concept that older people or people with longstanding hypertension have become dependent on higher BP levels to maintain adequate CBF. In other words, hypertension is thought to serve the purpose of overcoming this irreversibly high resistance of the cerebral circulation. Treating hypertension by lowering BP would have adverse effects through cerebral hypoperfusion and ischemia. Studies performed in the last 30 years suggest this concept needs to be revised. This is discussed in detail in this review.

A third misunderstanding is that autoregulation, CO_2 reactivity, and NVC are sometimes confused or used interchangeably. For example, a study that finds impairment in NVC may be interpreted or even reported as showing impaired autoregulation. However, impaired NVC or CO_2 reactivity do not automatically translate into impairment in how CBF responds to changes in BP (i.e., autoregulation). To address this misunderstanding, we briefly discussed CO_2 reactivity and NVC in this review.

2. Implications of misconceptions of autoregulation for clinical medicine

Misconceptions of autoregulation can have serious consequences because they can lead to erroneous medical judgement. The first misconception, that CBF is always perfectly stable, can lead clinicians to rely too much on the brain's capacity to maintain a relatively constant CBF. For example, during surgery, the effects of hypotensive or hypertensive episodes on CBF may be underestimated, leading to cerebrovascular injury. Pohl and Cullen presented a case series

of four patients undergoing a specific surgical procedure in a chair, wherein they argue that low BP, although still within the 'normal autoregulatory range', combined with an upright (seated) position, led to brain ischemia (see review for references and discussion). That publication has had clinical impact in that it has led to guidelines that require closer monitoring of BP during these procedures, however, there has been no translation to other procedures.

The second misconception, that older hypertensive people require higher BP levels to maintain CBF, is likely to have led to undertreatment of hypertension in older adults for many decades, and continuing to date. This may have been done out of the fear that lowering BP too much would lead to reduced CBF. However, as we describe in this review, evidence that has accumulated over the last 30 years suggests the opposite, i.e., that untreated hypertension reduces CBF, whereas CBF remains stable or even slightly increases with treatment of hypertension, also in older people with (cerebro)vascular disease or cognitive impairment.

3. General overview of dementia

For readers outside the field of dementia, a brief introduction might be useful. The rapidly expanding scientific literature on dementia contains many apparently contradicting views, which can easily confuse those outside the field, but sometimes even those who work in the field. One example is the relationship between vascular disease and Alzheimer's disease. Vascular dementia and Alzheimer's disease have been presented as two separate and distinct disorders. This has occurred historically and continues today, with separate scientific communities and conferences, such Vascog (www.Vas-cog.com) for vascular cognitive impairment and dementia, and AAIC (www.alz.org/aaic) for Alzheimer's disease. Therefore, studies that link vascular disease and cerebral hemodynamics to Alzheimer's disease, as done in this review, may seem counterintuitive.

Historically, around 1900 when Alzheimer's disease was first reported, vascular dementia and dementia due to syphilis (lues) were believed to be the most common causes of dementia. Alzheimer's disease was identified as a rare cause of dementia, that was clinically and pathologically different from these common causes of dementia. The distinct pathological features were extracellular (extraneuronal) plaques, much later (1980s) found to consist of ß-amyloid and intracellular tangles that were found to contain tau. In the decades following its discovery, Alzheimer's disease received little attention as it was thought to represent a rare dementia limited to younger age, with an onset well before age 60. All this changed around 1980, when realisation came that the rapidly growing number of older people with dementia warranted a strong research effort. Robert Butler, then director of the National Institute of Aging, was instrumental in putting Alzheimer's disease on the map as a common, and not a rare, cause of dementia. The identification of Alzheimer pathology in a substantial number of older people who had died from what was then often named 'senile dementia', led Butler to label all late onset dementia under the umbrella term of 'Alzheimer's disease'. The idea was, correctly, that a single disease would better succeed in a coordinated research effort and in raising the required funding for this effort. It is important to realise that at that time, many considered 'senile dementia' not to be a disease, but a normal consequence of aging. Until recently, pathological confirmation of the underlying cause of dementia was only possible after death. Autopsy studies confirmed a high prevalence of ß-amyloid and tau pathology in people who had died from or with late onset dementia, up to approximately 70% of cases. However, these studies also found considerable other pathologies to be present, either as an alternative cause of dementia, or as a pathology contributing to dementia. A common finding is the co-existence of cerebrovascular pathology. In approximately 30-70% of patients clinically diagnosed with Alzheimer's disease, there is cerebrovascular pathology that is thought to have contributed to the dementia together with Alzheimer pathology. In addition, some patients

clinically diagnosed as Alzheimer's disease only have cerebrovascular pathology. A consequence of all this is that some epidemiological studies that have linked vascular risk factors to clinical Alzheimer's disease may in fact be driven by links between vascular factors and cerebrovascular pathology. With the arrival of PET-ligands that can image ß-amyloid pathology and more recently tau pathology during life, it is now possible to phenotype patients with dementia in clinical studies. This has led to a movement to redefine Alzheimer's disease, moving back from a broader umbrella term to cover (almost) all late onset dementia, to a more pathology-specific definition based on the presence of ß-amyloid and tau pathology (NIAA research framework). This will help to disentangle the complex interactions between vascular disease, Alzheimer's disease pathology and late onset dementia. It is also very possible that better *in vivo* phenotyping will lead to a further 'unmasking' of the contribution of vascular pathology to late onset dementia.

ACKNOWLEDGMENTS

None

GRANTS

During the preparation of this manuscript, FMF was supported by the National Institutes of Health (NS-096465 and NS-108409) and JC by Alzheimer Nederland (WE.03-2015-15040).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

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Figure Legends

Figure 1. Overview of cerebral autoregulation.

General overview of autoregulation and key summary points for this review. Panel A shows two graphs illustrating the concepts of static and dynamic autoregulation. Panel B provides a summary of modifiers or factors that have a direct influence on CBF or on the relationship between BP and CBF (i.e., autoregulation). Examples include hemodynamics (including the rate of rise or temporal profile of changes in BP) and behavior (sedentary versus exercise). Panel C summarizes the impact of normally functioning autoregulation, while panel D summarizes consequences of impairment in autoregulation in relation to brain health. See text for further details.

Figure 2. Static autoregulation: summary of animal models.

Data for a range of experimental models, replotted from the original publications, illustrating the relationship between CBF and mean arterial pressure (MAP). Many studies either examined the low end or the high end of the autoregulatory curve, but a few quantified both ends of the curve within a single publication. For all species, there was a substantial range of MAP where CBF was relatively stable (118, 167, 233, 242, 251, 287, 367, 543, 573). For clarity, we have not plotted all studies of this type, but for reference cite some additional examples (78, 497, 574). For the panels with data from dogs, cats, baboons, and rats (filled circles), CBF is expressed in ml/min/100g. For panels with data from rabbits, mice, and rats (open circles), CBF is expressed as percent change with the control value set at 100.

Figure 3. Effect of the time scale of BP changes on autoregulation of CBF.

Schematic representation explaining how the time period in which changes in BP occur affects autoregulation of CBF. Slower changes (e.g., weeks, such as with chronic hypertension or

treatment of hypertension) have minimal effects on CBF, whereas with more rapid changes, the effects on CBF can increase such that there is essentially no effective autoregulation with very fast BP changes occurring within seconds. This presentation represents a hypothetical model of the transition from static autoregulation (slow changes in BP) to dynamic autoregulation (faster changes in BP).

Figure 4. Oscillations in BP and CBF induced by repeated sit to stand maneuvers.

An example of repeated sit-to-stand maneuvers to induce strong oscillations in BP and CBF, from a patient in a study on autoregulation in Alzheimer's disease (122). Starting with a baseline recording while seated, the patient was asked to stand up for 10 s, then to sit down for 10 s, followed by standing up for 10 s, and so on [using methods proposed previously (585)]. With a cycle duration of 20 s, large oscillations in BP and CBF (blood velocity in the left and right middle cerebral artery) are induced at 0.05 Hz, a frequency where dynamic autoregulation is active (see text for details). Changes in systolic BP, which had a seated baseline value of ≈ 150 mmHg, oscillated between ≈ 110 to ≈ 190 mmHg and CBF velocity, which had a seated baseline value of ≈ 50 cm/s, oscillated between 40 and 70 cm/s). SBP, systolic blood pressure recorded using Finapres; CBFV, blood velocity in the left (L) and right (R) middle cerebral arteries, measured using TCD.

Figure 5. Dynamic autoregulation phase shift and gain.

Using a zoomed-in section of the data presented in Figure 4, this graph illustrates the relationship between changes in BP (black line) and CBF (blue line) induced by the repeated sit-to-stand maneuvers at 0.05 Hz, see details in the legend for Figure 4. The timing of these

sit-stand maneuvers is schematically illustrated at the bottom of the graph. Note that the BP and CBF graphs are not fully synchronous; this is an effect of autoregulation. The leftward shift of CBF (here, represented by the left middle cerebral artery blood velocity signal recorded with TCD) compared to BP (systolic BP measured using Finapres) is referred to as phase shift. Phase shift is one of the parameters that follows from transfer function analysis. The inserted graph in the top of the Figure is a schematic explanation of phase shift. If we consider the repeated changes in BP and CBF as an oscillatory signal, resembling a sinusoid with a period of 360 degrees, the leftward shift of CBF can be quantified in degrees (or converted to radians), in this example approximately 40-50 degrees, which, in this frequency (0.05 Hz, the very low frequency range) indicates normal dynamic autoregulation. The parameter gain is also illustrated, representing damping, where effective dynamic autoregulation will result in relatively smaller changes in CBF compared to BP. Because BP and CBF have different physical units, gain is not necessarily below 1.

Figure 6. Comparison of hemodynamic traces from one of Bayliss's 1895 animal experiments with those from a human experiment performed in 2009.

Panel A shows the original Figure from Bayliss and Hill (40). The transient increase in carotid arterial BP appears to be passively followed by the trace labelled CVP, which represents cerebral venous pressure, which was used in this experiment as a proxy for CBF; Systemic venous pressure (SVP)was recorded simultaneously and remained stable (to indicate that the cerebrovascular changes were not secondary to systemic changes). Panel B shows tracings from a human experiment from Claassen et al. (94). The transient increase in BP (evoked by a squat-stand maneuver) also appears to be passively followed by CBFV (see also the legends for Figure 4 and 5), a proxy for CBF. Closer inspection and analysis, as described in Figures 4

and 5, are required to appreciate effects of autoregulation. BP, blood pressure; SVP, systemic venous pressure; CVP, cerebral venous pressure; CBFV, blood velocity recorded in the middle cerebral artery.

Figure 7. Effects of antihypertensive treatment on CBF in hypertensive patients.

Summary of studies that measured effects of antihypertensive treatment on blood pressure (BP) and cerebral blood flow (CBF), using different techniques to measure CBF: TCD (A), MRI arterial spin labeling (B) and Xenon-133 CT (C). Panel A: data from a study investigating antihypertensive treatment in patients with mild or moderate hypertension, after 2-3 weeks and after 3 months of treatment (647). Panel B: summary from three studies. Two of these studies [Label 1: (104), Label 3: (569)] investigated effects of standard versus intensive BP lowering treatment. One study [label 2: (180)] investigated effects of stopping antihypertensive treatment (causing BP to increase). Panel C: this study compared different ß-blocking agents to lower BP (211). See text for details on all these studies.

Figure 8. Mechanisms that contribute to myogenic responses and the impact of these mechanisms on regulation of vascular tone, the distribution of intravascular pressure in brain, and autoregulation of CBF.

Several mechanisms have been implicated in regulation of myogenic responses. Vascular diameter is highly sensitive to changes in the cellular membrane potential (A). Membrane potential is determined by the integrated effects of mechanisms that produce depolarization or hyperpolarization of the cell membrane (A). Two key regulators in the context of pressure-induced changes in vascular tone are voltage-dependent calcium channels (e.g., $Ca_V2.1$) and

large conductance potassium channels (BK_{Ca})(A). Several molecular mechanotransducers have been proposed to function as sensors for changes in pressure and initiators of depolarization of vascular muscle, resulting in increased intracellular Ca^{2+} (B). Increases in intracellular Ca^{2+} can also occur due to Ca^{2+} release from the sarcoplasmic reticulum (SR)(local Ca^{2+} signals) resulting in activation of contractile proteins (myosin light chain kinase, MLCK), phosphorylation of myosin (MLC), contraction of vascular muscle, and a reduction in diameter of resistance vessels (B). Local release of Ca^{2+} sparks from the SR can activate BK_{Ca}, producing local hyperpolarization and feedback that limits the degree of vasoconstriction. In addition to activating $Ca_V2.1$, mechanotransduction activates guanine nucleotide exchange factors that activate RhoA (RhoGEF) and a RhoA target, Rho kinase (ROCK). ROCK exerts inhibitory effects on myosin light chain phosphatase (MLCP). As discussed in the main text, there are several candidate sensors (or mechanotransducers) for pressure changes (C) as well as modulators of autoregulation (D). Integrated changes in myogenic responses and thus vascular tone influence the distribution of intravascular pressure that normally occurs along the vascular tree in brain (E) as well as the efficacy of autoregulation of CBF (F). See text for further details.

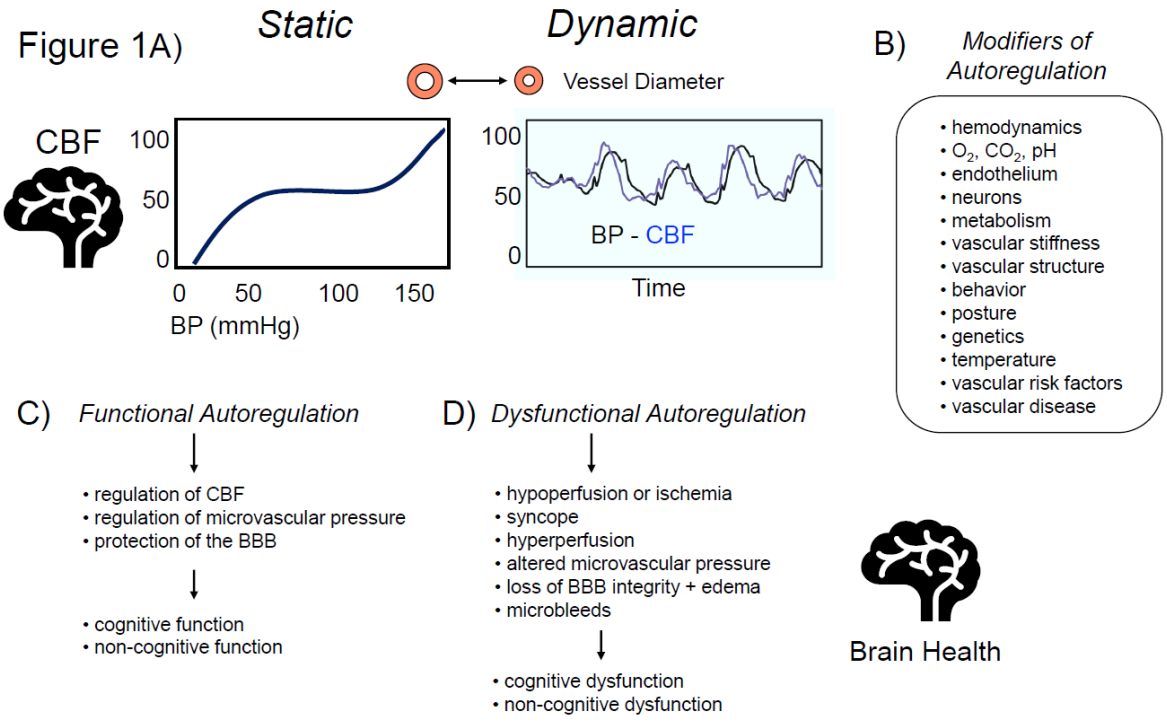


Figure 1A)
Static
Dynamic
Vessel Diameter
CBF
100
50
0
0 50 100 150
BP (mmHg)
100
50
0
BP - CBF
Time
B) Modifiers of Autoregulation
• hemodynamics
• O2, CO2, pH
• endothelium
• neurons
• metabolism
• vascular stiffness
• vascular structure
• behavior
• posture
• genetics
• temperature
• vascular risk factors
• vascular disease
C) Functional Autoregulation
• regulation of CBF
• regulation of microvascular pressure
• protection of the BBB
• cognitive function
• non-cognitive function
D) Dysfunctional Autoregulation
• hypoperfusion or ischemia
• syncope
• hyperperfusion
• altered microvascular pressure
• loss of BBB integrity + edema
• microbleeds
• cognitive dysfunction
• non-cognitive dysfunction
Brain Health

Figure 2

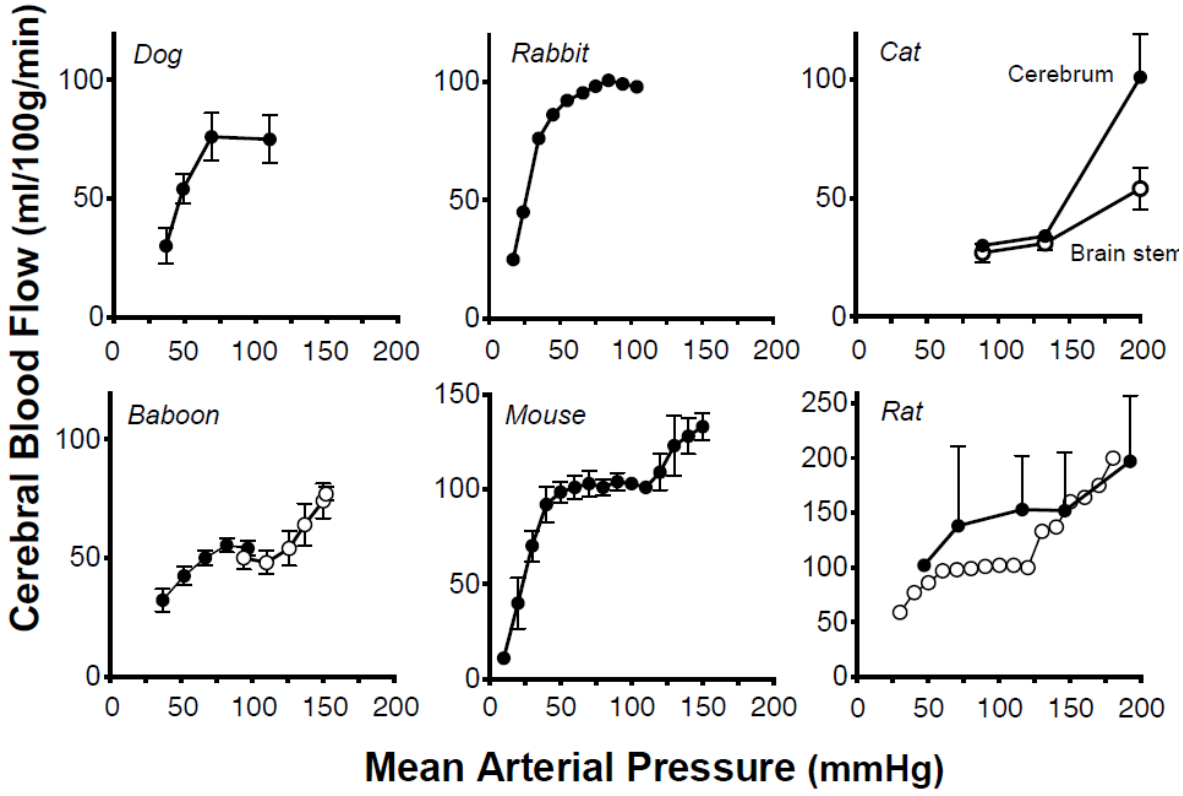

Cerebral Blood Flow (ml/100g/min)
Dog
Rabbit
Cat
Cerebrum
Brain stem
Baboon
Mouse
Rat
0 50 100 150 200
Mean Arterial Pressure (mmHg)

Figure 3

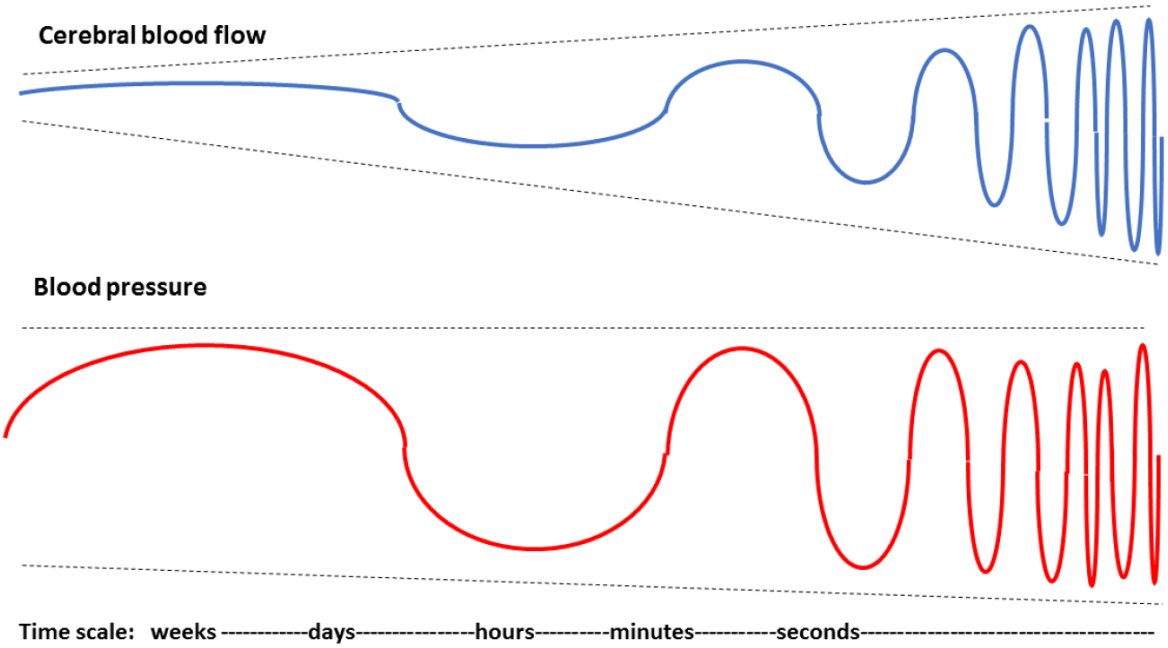

Cerebral blood flow
Blood pressure
Time scale: weeks ----------days----------hours---------minutes----------seconds----------

Figure 4

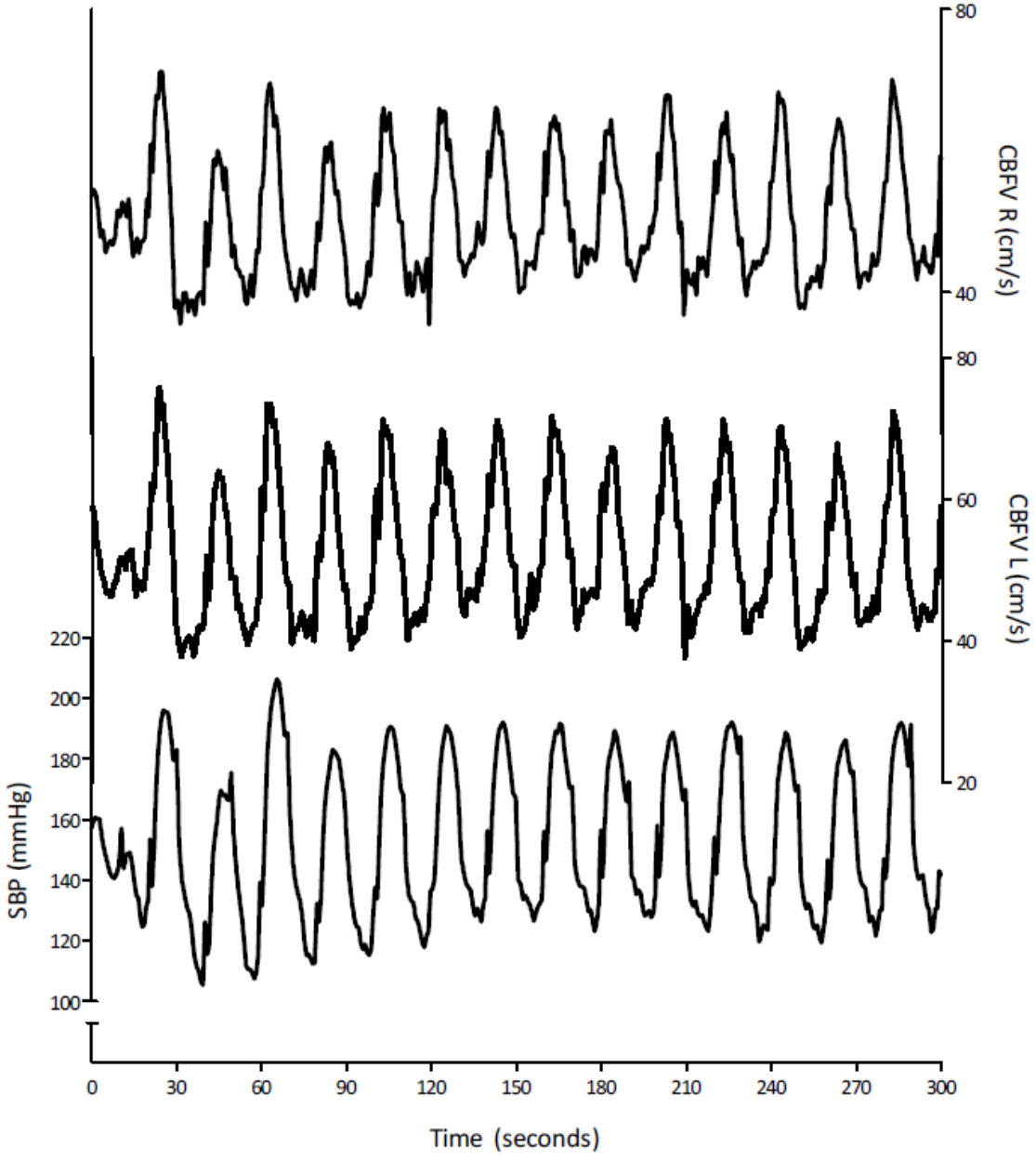

80
CBFV R (cm/s)
40
80
60
CBFV L (cm/s)
40
20
220
200
180
160
140
120
100
SBP (mmHg)
0
30
60
90
120
150
180
210
240
270
300
Time (seconds)

Figure 5

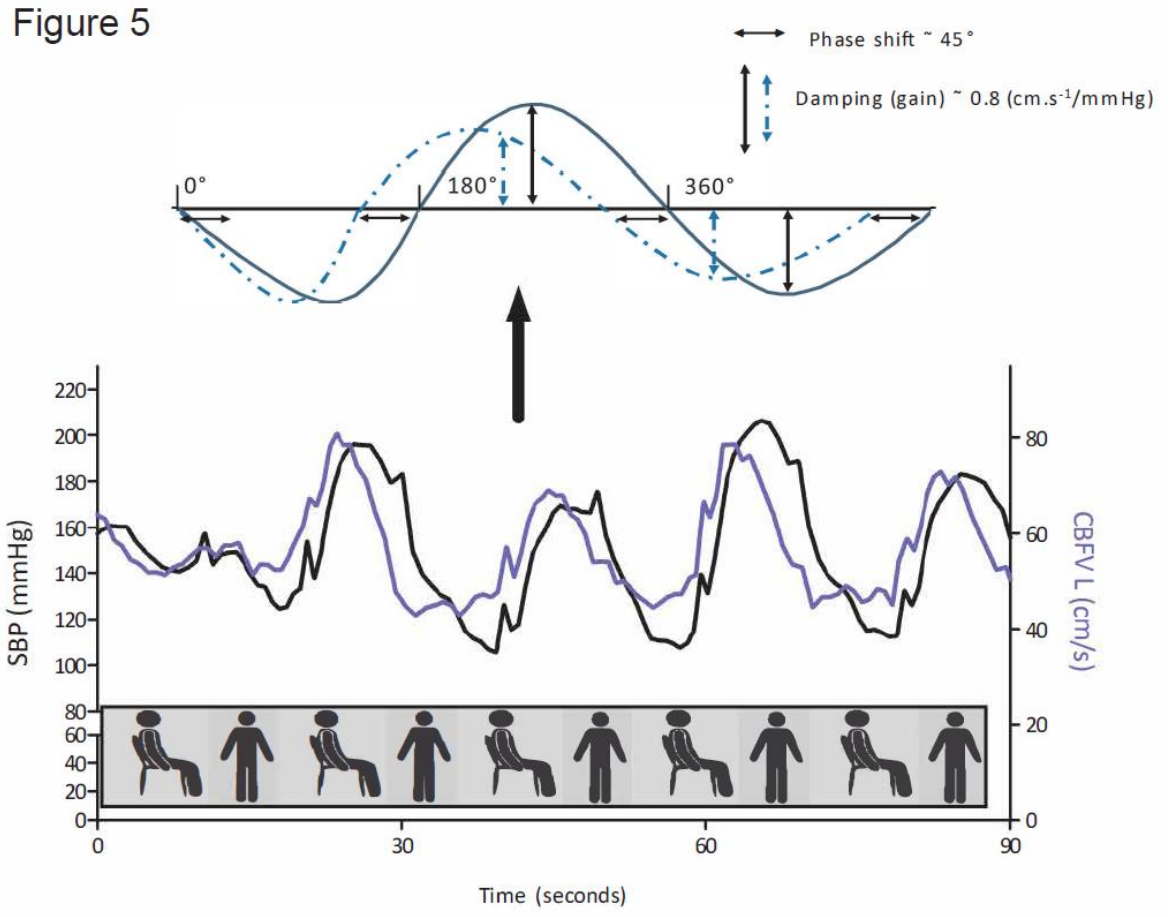
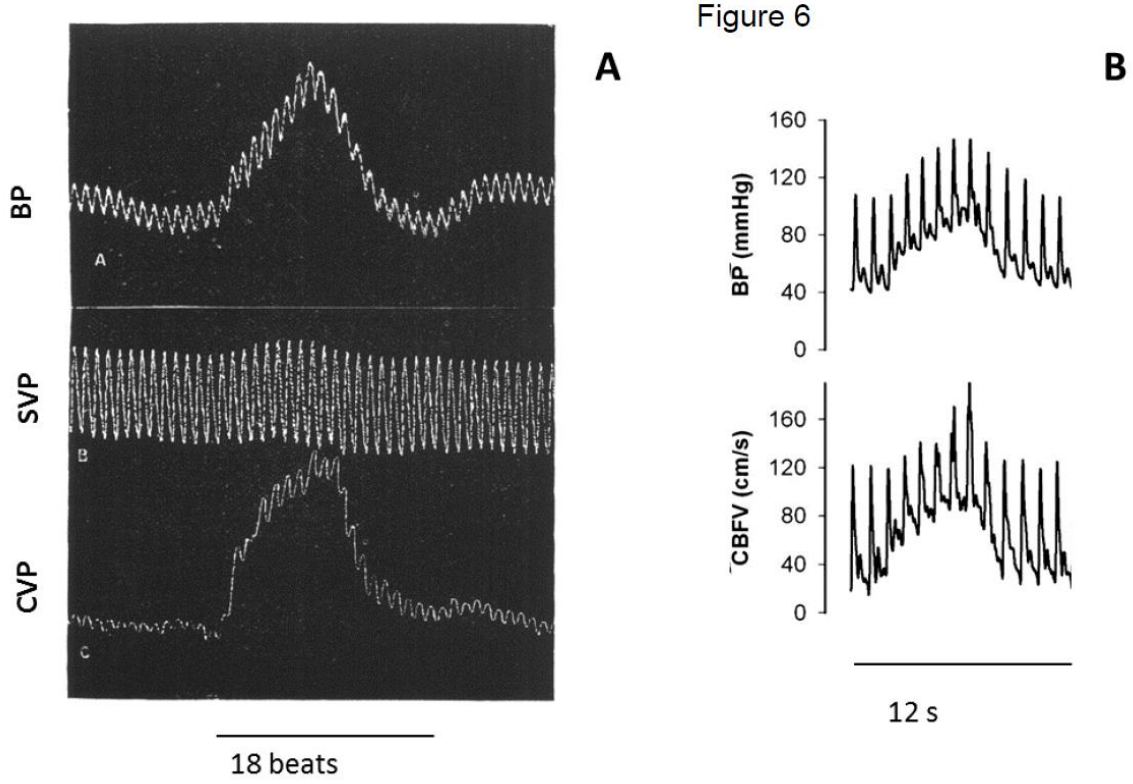


Figure 6



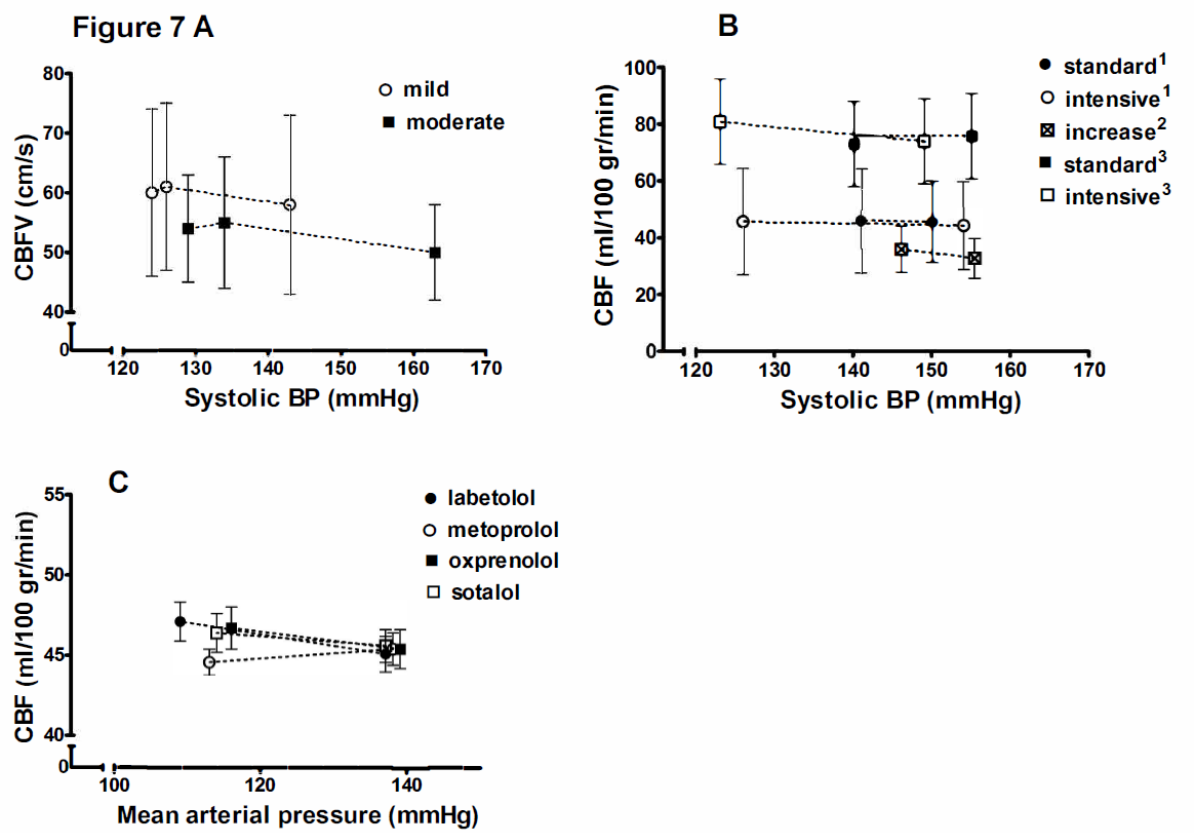


Figure 7 A
CBFV (cm/s)
Systolic BP (mmHg)
mild
moderate
B
CBF (ml/100 gr/min)
Systolic BP (mmHg)
standard1
intensive1
increase2
standard3
intensive3
C
CBF (ml/100 gr/min)
Mean arterial pressure (mmHg)
labetolol
metoprolol
oxprenolol
sotalol

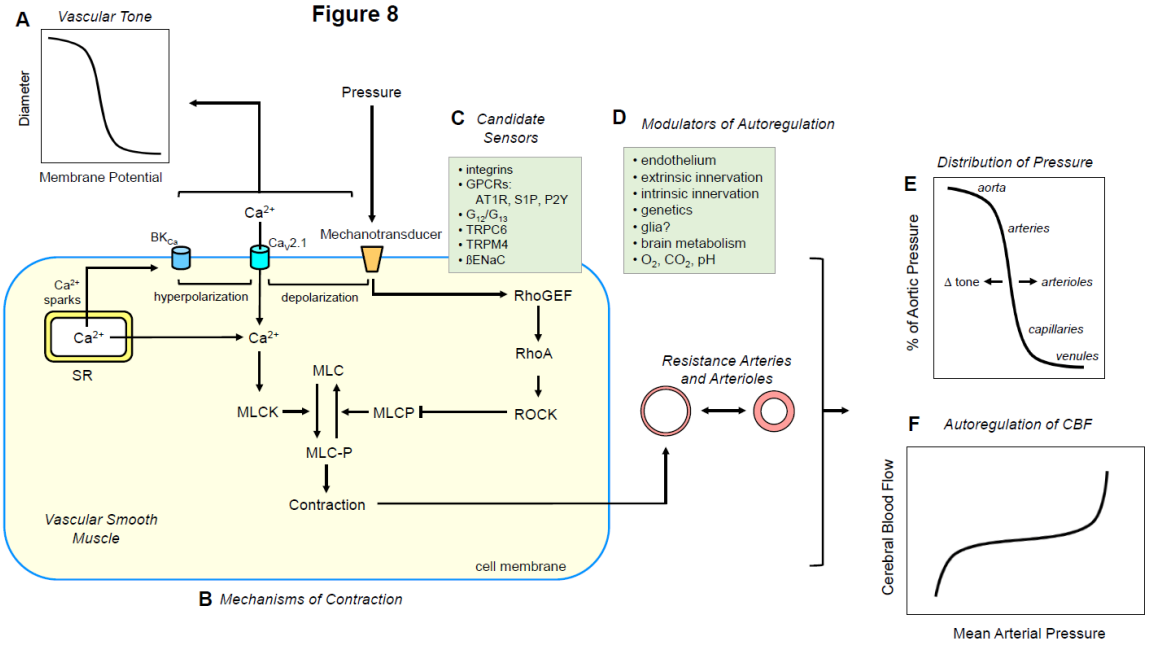


Figure 8
A Vascular Tone
Diameter
Membrane Potential
Pressure
C Candidate Sensors
• integrins
• GPCRs: AT1R, S1P, P2Y
• G12/G13
• TRPC6
• TRPM4
• βENaC
D Modulators of Autoregulation
• endothelium
• extrinsic innervation
• intrinsic innervation
• genetics
• glia?
• brain metabolism
• O2, CO2, pH
Ca2+
BKCa
CaV2.1
Mechanotransducer
Ca2+ sparks
hyperpolarization
depolarization
RhoGEF
RhoA
ROCK
Ca2+
SR
MLC
MLCK
MLCP
MLC-P
Contraction
Vascular Smooth Muscle
cell membrane
B Mechanisms of Contraction
Resistance Arteries and Arterioles
E Distribution of Pressure
% of Aortic Pressure
aorta
arteries
Δ tone
arterioles
capillaries
venules
F Autoregulation of CBF
Cerebral Blood Flow
Mean Arterial Pressure