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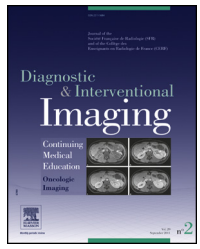

CONTINUING EDUCATION PROGRAM: FOCUS...

Functional imaging of cerebral perfusion

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Abstract The functional imaging of perfusion enables the study of its properties such as the vasoreactivity to circulating gases, the autoregulation and the neurovascular coupling. Downstream from arterial stenosis, this imaging can estimate the vascular reserve and the risk of ischemia in order to adapt the therapeutic strategy. This method reveals the hemodynamic disorders in patients suffering from Alzheimer's disease or with arteriovenous malformations revealed by epilepsy. Functional MRI of the vasoreactivity also helps to better interpret the functional MRI activation in practice and in clinical research.

Reminders about cerebral perfusion

The study of cerebral perfusion provides critical information to understand the functioning of the central nervous system and apprehend its dysfunction, among the main causes of morbidity and mortality in the West. In neurology and psychiatry, the identification of these microvascular pathophysiological disorders may provide information that may help to better characterize a several diseases, or even assess individual vulnerability.

Above all, cerebral perfusion allows for the transfer of appropriate quantities of glucose and oxygen for the functional needs of the brain, while eliminating heat and some catabolites such as CO_2 [1]. Perfusion is a dynamic physiological phenomenon able to respond to changes in the homoeostasis of the vascularized organ and the entire body. Like any biological function, general and local factors are likely to not only modify its state of equilibrium but also its adaptive properties. This adjustment is both passive, due to the

Abbreviations: ASL, arterial spin labeling; BOLD, blood oxygenation level dependent; CBF, cerebral blood flow; CBV, cerebral blood volume; CVR, cerebral vasoreactivity; fMRI, functional MRI; MRA, magnetic resonance angiography; P_aCO_2, arterial pressure in CO_2; P_eCO_2, expiratory pressure in CO_2.

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mechanical characteristics of blood vessels, and active by the arteriolar vasomotricity. The vasomotricity controls the caliber of the arterioles, so as to maintain the blood supply during variations in neuronal activity (neurovascular coupling), cerebral perfusion pressure (autoregulation), capnia, oxygenation and pH (vasoreactivity) [1].

Cerebral perfusion may simply be characterized by the cerebral blood flow (CBF), defined by the volume of blood transiting by the mass of the cerebral parenchyma per unit of time (classically expressed in ml/100 g of cerebral parenchyma/min). Since the density of brain tissue is close to that of water, the mass is often converted into volume, allowing the CBF to be expressed as a percentage of the parenchyma perfused per second (s^{-1}) (Table 1). The direct measurement of this dynamic property is especially difficult. This has given rise to the development of multiple, more or less invasive, methods that can, more or less, be considered in man. Numerous indicators and analytic models, with their advantages and disadvantages, have thereby been proposed [1,2]. The initial methods, such as those developed by Kety and Schmidt with the inhalation of NO_2 [3], measured a global CBF based on the analysis of the concentration of the marker at the entry and exit from the vascular system. In imaging, the CBF is measured on the scale of a cerebral region (rCBF), or even the pixel of a digital image and the voxel with tomography techniques. The success, over the last decades, of the imaging that has been established due to a major reduction in the invasiveness of the procedures and an increase in the temporal and spatial resolutions, has led to assimilate the rCBF with the CBF.

The cerebral blood flow and the cerebral blood volume (CBV) are two physiologically, closely related parameters, since they depend on the variations in arteriolar resistance. The mechanics of the fluids proportionally links variations in the volume with the square root of variations in flow. In the neurosciences, this ratio is estimated by: $([V/Vo] = [F/Fo]^{\alpha})$ Vo and Fo representing the volume and flow at the initial state, and V and F the volume and flow at the final state. With an experimental modulation of the cerebral perfusion by CO_2, α was estimated as being close to 0.40 in the animal [4–6]. In man, values of α between 0.29 and 0.73 have been reported with high regional disparities [7,8]. These heterogeneities are likely to reflect differences between the methods of measurement [9], the regional variability of the capillary density [10,11], the physiological mechanism used to modulate the perfusion [7,12,13], the time interval between the early variations in the CBF that are mainly based on the arteriolar and capillary sectors, and later variations in the CBV that better reflect the venous sector [6,14,15].

Table 1 Basal cerebral perfusion values usually admitted in man [1].

Mean CBF	≅60 ml/100 g/min ≅60 ml/100 ml/min (parenchyma density = 1.04 g/ml) ≅1 ml/100 ml/s ≅0.01/s (or 1% of the parenchyma corresponds to the fresh blood each second)
CBF grey matter	80 ml/100 g/min
CBF white matter	20 ml/100 g/min
Density grey matter / Density white matter	≅1
CBV	4 ml/100 g ≅4% of the parenchyma ≅60 ml of blood for a 1500 g brain
Arterial / capillary / venous CBV [280]	21% / 33% / 46%

Physiological variations in cerebral perfusion

At rest, the cerebral perfusion decreases with age [16] and is significantly higher in women [17]. The cerebral perfusion is closely related to the activity of the brain. It is often measured in the neurosciences and in medicine since it reflects the interaction between the vessels and the neurons through neurovascular coupling. Moreover, the cerebral perfusion is maintained roughly constant in order to deal with variations in the blood pressure and intracranial pressure by autoregulation. The cerebral perfusion is also sensitive to variations in the arterial concentration in CO_2 and O_2 by the vasoreactivity (Fig. 1). All of these physiological functions are based on the vasomotricity that enables, through the dilation and contraction of the vessels, to adjust the cerebral blood flow in order to guarantee the cerebral activity by dealing with the general and local physiological constraints [18].

Innervation of cerebral vascularization

Extrinsic innervation

The extrinsic vascular innervation of the pial arteries arrives from the peripheral nervous system by the upper cervical, sphenopalatine, trigeminal and optical ganglions that relay the information from peripheral baroreceptors. The extrinsic innervation is mainly sympathetic vasoconstrictor (noradrenalin, serotonin, neuropeptide Y) and parasympathetic vasodilator (acetylcholine, nitric oxide, VIP). The arteries progressively divide into arterioles that enter the cerebral parenchyma. They consist of an internal layer of endothelial cells, smooth muscle cells and an outer layer of leptomeningeal cells that form the external tunic. The arteriole is separated from the parenchyma by the Virchow-Robin space that contains the cerebrospinal fluid and is bordered by astrocytes on the outside. As the arterioles enter the parenchyma, the fluid space disappears and the arterioles and then the capillaries are in direct contact with the feet of the astrocytes that form the glia limitans [19–21].

Intrinsic innervation and the neurovascular unit

The intrinsic innervation of the intra-parenchymatous arterioles by the central nervous system relies on cortical interneurons and the efferences of subcortical neurons

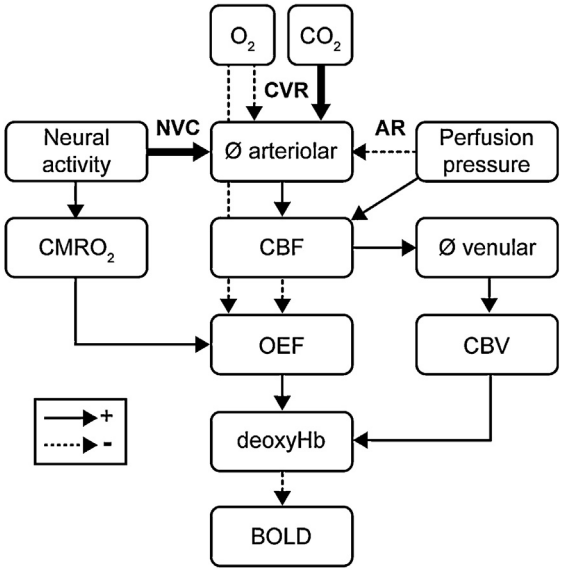

Figure 1. Functional variations in cerebral perfusion and BOLD signal. The full arrows represent a positive relationship and the dotted arrows a negative relationship. The arteriolar caliber is modulated by the neurovascular coupling induced by the neuronal activity, the vasoreactivity to O_2 and, above all, CO_2, the autoregulation of the perfusion pressure (that is, the difference between the mean arterial pressure and the intracranial pressure). The increase in the cerebral blood flow (CBF), higher than the cell needs, reduces the oxygen extraction fraction (OEF) and increases the cerebral blood volume (CBV) which reduces the deoxyhemoglobin content (deoxyHb) in the voxel. Since the deoxyHb is paramagnetic, it shortens the T2. This reduction increases the signal in imaging sensitive to the BOLD effect.

coming from the nucleus basalis of Meynert and the frontobasal region (acetylcholine), the locus coeruleus (noradrenalin) and the raphe nuclei (serotonin). The action of the GABAergic cortical interneurons may contract or dilate the vessels. Whereas GABA is a vasodilator, the activity of these interneurons is modulated by a specific subcortical innervation. The subcortical efferences directly innerve the vascular wall and the astrocytes. Other vasomotor neurotransmitters such as dopamine coming from the ventral tegmental area (black matter) may also act by direct vascular innervation or through the innervation of the astrocytes (Table 2) [22,23].

At the capillary level, the structural association of the pericytes edged by the feet of the astrocytes innervated by cortical interneurons and subcortical neurons form a ''neuron-astrocyte-vasculature tripartite functional unit'', more commonly called ''neurovascular unit'' [19]. The essential role of the astrocytes in the vasodilation induced by neuronal activity has recently been demonstrated [24—26]. In addition, the integrity of the glia limitans is required for arteriolar vasodilation [27].

Neurovascular coupling

Cerebral perfusion is closely related to neuronal activity. This global and local adaptation of cerebral perfusion extensively relies on the perivascular innervation and the neurovascular unit. Therefore, the perfusion is currently measured in the neurosciences and in medicine since it is the direct reflection of the interaction between the vessels and the neurons.

Table 2 Main vasoactive substances [20].

	Vasomotor effect
Ions	
K^+	Dilation
H^+	Dilation
Metabolites	
CO_2	Dilation
O_2	Constriction
Adenosine	Dilation
Neurotransmitters	
Acetylcholine	Dilation
Noradrenalin	Constriction
Serotonin	Constriction
Dopamine	Dilation (D1/D5 receptor) Constriction (D2/D3/D4 receptor)
GABA	Dilation
Other	
NO	Dilation

The increase in perfusion is related to the energy activity of the brain. In man, 75% of the energy intake is consumed by post-synaptic activity, 7% by pre-synaptic activity, 10% by the neuron action potential, 6% by the astrocyte activity and 2% by the transmembrane resting potential [28]. The neuron energy metabolism is based on the use of the oxygen and glucose carried by the blood to the capillaries [29]. The increase in synaptic activity results in a reduction in the oxyhemoglobin (HbO_2) concentration and an increase in that of deoxyhemoglobin (deoxyHb). This initial dip in blood oxygenation before the hemodynamic response may be the most reliable marker of the neuronal activity [30], although its demonstration using BOLD fMRI is unpredictable.

Functional hyperhemia occurs 1 to 2 s after the beginning of the neuronal activity. Although the local increase in CFB is proportional to the glucose consumption [31], the oxygen intake is abnormally high compared with the moderate increase in its capillary extraction. In addition, the hyperhemia covers a wider zone than that of the neuronal activity [32]. The time before the hemodynamic response, the inadequacy between the needs in glucose and the oxygen intake and the early release of lactate have suggested that the glycolysis may initially be anaerobic by the use of the glycogen delivered by the astrocytes, and more quickly useable than the capillary glucose that will be used subsequently. Therefore, the release of glutamate in the synaptic space would lead to an astrocyte recapture that metabolizes it into glutamine by anaerobic glycolysis, then delivered to the neuron. As for the lactate, it would be aerobically metabolized by the neuron to supply the ATP required for ionic re-equilibrium following the neuronal depolarization [29,33].

These elements underline the close anatomo-functional relationship between the neurons, vessels and astrocytes in neurovascular coupling. Its proper operation relies on the structural integrity of the constituents (anatomic,

histological and cellular), an appropriate release and concentration of vasoactive agents, as well as the integrity of their action mechanisms.

From this, the idea progressively emerges that there may be diseases of the neurovascular unit, such as Alzheimer's disease [19,20,34—37].

Autoregulation of cerebral pressure

Autoregulation helps maintain the cerebral pressure significantly constant by adjusting the arteriol dilation according to the variations in the perfusion pressure (PP), defined by the difference between the mean arterial pressure (MAP) and the intracranial pressure (ICP), PP = MAP-ICP. When the perfusion pressure increases due to an increase in arterial pressure, the autoregulation induces a vasoconstriction, in order to avoid the risk of the rupture of the brain-blood barrier (BBB) and tissue edema, or even hemorrhage. When the perfusion pressure decreases due to a drop in the arterial pressure, the autoregulation induces vasodilation in order to avoid the risk of ischemia. When the perfusion pressure decreases due to an increase in the intracranial pressure, the autoregulation induces vasodilation to avoid the risk of ischemia.

The autoregulation that adjusts the arteriolar resistances according to the transmural pressure gradient is maintained by the vascular muscle response to the perfusion pressure by the myotatic reflex and the extrinsic vascular innervation. The limits of the autoregulation may be modified by the sympathetic activity, the arterial pressure in CO_2, chronic arterial hypertension and certain drugs [38—40].

The monitoring of the autoregulation is very important in medicine, in particular in traumatic disorders, since the loss of autoregulation and vasoreactivity to CO_2 are elements pointing to a poor prognosis [38,39,41—45].

Vasoreactivity to circulating gases

Vasoreactivity to CO_2

The effects of CO_2 on cerebral vascularization have been observed for a long time and the inhalation of 5 and 10% volume fraction CO_2 are accompanied by a 50 and 100% increase in CBF, respectively [46]. The CBF variation curve as a function of P_aCO_2 is a sigmoid with an approximately linear portion for the physiological values of the CBF. As of normocapnia (P_aCO_2 = about 40 mmHg), the hypercapnia is accompanied by an increase in the CBF and CBV of 6% and 2%/mmHg de P_aCO_2, respectively, while the hypocapnia is accompanied by a reduction in the CBF and CBV of 3% and 1%/mmHg P_aCO_2 respectively [7,47—49]. The transcranial Doppler measurement of the arterial speed is used to calculate the CO_2 vasoreactivity index, which corresponds to the slope of the curve that describes the mean arterial speed as a function of the expiratory pressure of CO_2. In healthy subjects, this index is close to 1.5 $cm.s^{-1}.mmHg^{-1}$ [50]. This vascular response predominates on the small caliber arterioles — 40—100 μ [51,52] — but all vessels, including the capillaries and venules are involved [51,53].

Several mechanisms have been proposed to account for the CO_2 vasoreactivity. It seems that the modification in the perivascular pH, induced by the free passage of CO_2 through the BBB and the production of H+ ions ($CO_2 + H_2O \rightarrow H^+ + HCO_3^-$), plays a preponderant role [54,55], since HCO_3^- is used for the clearance of excess lactic acid produced by the neurons and glial cells [54]. The role of NO in the CO_2 vasoreactivity has also been proposed [56]. In physiological conditions, its action is modest [18]. However, in pathological conditions (diabetes, AHT), the endothelial dysfunction and the poor distribution of NO account for the alteration in the CO_2 vasoreactivity of patients. The administration of an ''NO donor'', sodium nitroprussiate, would restore the CO_2 vasoreactivity [50]. The role of the prostaglandins has been demonstrated in certain animal species, but not in man [18].

Physiological variations have been described with a reduced vasoreactivity in women [57], the elderly subject [58] and during the early hours of the day [59,60].

O_2 vasoreactivity

The vascular effects of O_2, as opposed to those of CO_2, have also been known for several decades [61]. Hypoxemia accompanies an increase in the CBF, whether due to hypoxia (by a reduction in the O_2 intake), anoxia (by the inhalation of carbon monoxide (CO) that saturates the Hb in HbCO) or anemia (by a reduction in the functional Hb concentration). However, this effect is observed for pathological values of P_aO_2 under 60 mmHg (threshold of respiratory insufficiency), while the normal P_aO_2 is close to 90 mmHg [18,49,62]. The mechanisms responsible for the cerebral vasodilation with hypoxia are still poorly known. Vascular innervation and the peripheral baro or chemoreceptors are not involved. However, the ventrolateral region of the bulb is sensitive to hypoxia and its destruction alters the vasodilation at hypoxia without modifying the CO_2 vasoreactivity [63]. Another analogous, more caudal region has also been described. Adenosine may be the mediator of this vasodilation during mild hypoxia while the H^+ and K^+ ions may play a role in case of severe hypoxia [18,64,65]. Finally, chronic hypoxia provokes structural modifications in the microvascular walls and angiogenesis that reduces the intercapillary distance [66]. In a recent experimental study carried out in adults exposed to prolonged hypoxia by residing at 4400 m, we observed an increase in the cerebral perfusion associated with an alteration in the vasoreactivity [67].

Normobaric hyperoxia, obtained by the inhalation of 85 to 100% O_2, induces a vasoconstriction responsible for a 7 to 31% reduction in the CBF [61,64,68—71], or even an increase in the CBF [72]. The effects of hyperoxia on cerebral perfusion are significant for a P_aO_2 superior to 300 mmHg [61]. The reduction in the P_aCO_2 concomitant with the inhalation of O_2 may increase the reduction in CBF. The vascular effects of hyperoxia would be due to the inactivation of the NO-dependent vasodilation by an increase in the O_2- free radicals [73].

Functional imaging of cerebral perfusion

The functional imaging of cerebral perfusion may be defined as the study in imaging of the functional variations in cerebral perfusion induced by vasomotor stimuli. We have seen that the perfusion was physiologically modified by the neuronal activity (neurovascular coupling), the intracranial

perfusion pressure (autoregulation), the CO_2 level in the blood and, to a lesser extent, the O_2 level (vasoreactivity) (Fig. 1). According to the temporal resolution of the techniques, we have measurements at the state of equilibrium, or of the hemodynamic response to the vasomotor stimulus over time.

Influence of the initial conditions

The functional variations of cerebral perfusion may be influenced by the initial conditions. Insofar as the basal cerebral perfusion reflects the initial dilation of the arterioles and, as long as the structural and functional integrity of the arteriolar system is preserved, we can intuitively think that the variation in perfusion induced by a vasomotor stimulus is inversely proportional to the initial perfusion. This functional aspect of the perfusion was above all studied with neurovascular coupling. The polemics that opposes the proportional model [74—79] with the additive model that defends the independence of the variations in perfusion of the initial conditions [80—85] has not been solved [72,86]. Increases in the BOLD signal and the CBF tend towards maximum values. The extreme experimental conditions required to reach them are far from the physiological conditions. This does not guarantee the validity of the physiological models usually used in such conditions [72]. Even pharmacological challenge using neuromediator (e.g., L-DOPA a regional vasodilator) failed to demonstrate significant change of the hemodynamic response to hypercapnic stimuli using BOLD contrast [87].

Although, the relationship between the basal conditions of perfusion and the hemodynamic response to the CO_2 vasoreactivity has not been studied as extensively as that of the neurovascular coupling, it seems necessary to have a good assessment of the basal cerebral perfusion. Ideally quantitative, this measurement may be semi-quantitative in patients with anatomic hypotheses.

Imaging of the neurovascular coupling

Imaging of neurovascular coupling is one of the main methods in functional neuroimaging. Among other techniques, BOLD fMRI contrast is based on the modifications in cerebral oxygenation following that of the synaptic activity and, above all, that of the perfusion that is induced by the neurovascular coupling (Fig. 1). This approach privileges the control of the neuronal activity that determines the regressor of an observed vascular signal. The changes in the hemodynamic response are therefore interpreted as the consequence of those of the neuronal activity. The close relationship between the synaptic activity and BOLD signal, demonstrated in the animal, its non-invasive nature and reproducibility, have made the fMRI become, within several years, the most used technique in functional neuroimaging [88,89].

The neuronal activity associated with a cognitive task is accompanied by an arteriolar vasodilation and an increase in the regional cerebral blood flow (rCBF), leading to vasodilation of the venules and veins due to their elasticity (balloon model) [90,91]. In addition, the exaggerated increase in oxygen intake in the blood flow induces hyperoxygenation of the venous blood, reflected by an increase in the oxyhemoglobin concentration and a reduction in the deoxyhemoglobin concentration. Now, deoxyhemoglobin is paramagnetic. By altering the homogeneity of the intra and perivascular magnetic field, the deoxyhemoglobin decreases the intensity of the free induction decay observed in T_2*-weighted gradient echo that is a true endogenous contrast agent. Thereby, in response to neuronal activity, the reduction in the deoxyhemoglobin concentration is accompanied by an increase of several percentages in the T_2*-weighted signal (Fig. 1) [89,92].

The estimate of the neuronal activity from the analysis of the BOLD signal is based on the hypothesis that their relationship is approximately linear, which does not exclude complex non-linear relationships and interactions between the different elements in this relationship. This hypothesis was backed up by several experiments coupling fMRI with different electrophysiological methods [88].

In spite of many approximations, the location of the neuronal activity by BOLD fMRI was experimentally validated in the animal [88] and in clinical practice by the comparison with the evoked potentials [93], the magnetoencephalography [94], the pre- and per-surgical stimulations [95—97] and lesion studies [98—100].

However, the relationship between the neuronal activity and the BOLD signal is very indirect and is influenced by multiple, often interdependent, physiological factors [101,102]. The BOLD signal has been shown to be sensitive to the quality and intensity of the neuronal response to the stimulus [103,104], to the basal conditions of perfusion [74—76,80,85], to the blood oxygenation [105—107], to the capnia [108], to the vasoreactivity [109—112]... In addition, it is advisable to add variations in the general factors to these sources, that may influence them such as age [58,75,113—115], sex [17], the consumption of substances such as caffeine [116—118], alcohol [119], neuroleptics [120,121], apomorphine in patients with Parkinson's disease s [122], anesthetic products [123,124] or products modulating the activity of neurotransmitters [125].

In pathological conditions, a modification in the BOLD signal was observed in the presence of transient arterial hypertension [126,127], arterial stenosis [111,128—130], micro-angiopathy [110,128], migraine [131], multiple sclerosis [132], Alzheimer's disease [75,133] and near a macroscopic lesion such as a stroke [109,110,134], tumor [112,135—140], arteriovenous malformation [137,141,142]. The pathophysiology of these BOLD signal variations is highly varied, insofar as these disorders may have an overall or locoregional influence on the basal CBF, neurovascular coupling and vasomotricity.

Several alternatives have been proposed for a better estimate of the neuronal activity in MRI. However, they are based on the measurement of the vascular effects of the neuronal activity. Perfusion imaging by arterial spin labeling allows for the dynamic and repeated measurement of the variations in perfusion induced by cognitive activity, with an excellent topographic characterization. However, the signal-noise ratio remains low [143—145]. The quantitative BOLD fMRI allows for the calculation of the oxygen consumption by the neurons, by associating the conventional BOLD fMRI with a conventional and simultaneous measurement of the BOLD and CBF signals modulated by a vasodilation test using CO_2 inhalation [81,146,147].

Therefore, to interpret the BOLD fMRI of the neurovascular coupling, it's important to have an estimate of the basal value and the functional variations in the cerebral perfusion (Fig. 2). This aspect becomes especially essential in EEG-fMRI. In fact, the modifications in the hemodynamic response to abnormal neuronal activity in epileptogenic zones should be taken into account in order to identify these regions. Without these adjustments, the risk of localization error would be too high to consider the clinical use of the EEG-fMRI [148].

Imaging of autoregulation

The autoregulation of perfusion pressure is an important function to monitor when there is intracranial hypertension, in particular during a serious traumatic brain injury. Taking into account the risks related to the transport of heavily equipped subjects outside of intensive care, the autoregulation may be assessed with the transcranial Doppler [38,41,45,149]. To experimentally modulate the perfusion pressure, compression cuffs may be used on the thighs. A systemic hypotension is provoked by suddenly releasing the pressure. The autoregulation then induces vasodilatation in reaction to the drop in perfusion pressure [150].

However, studies on the imaging of autoregulation are rare and remain experimental [126].

Imaging of vasoreactivity

The imaging of cerebral vasoreactivity is another approach for the functional imaging of cerebral perfusion. As opposed to the imaging of neurovascular coupling that privileges the study of the neuronal activity, the imaging of the cerebral

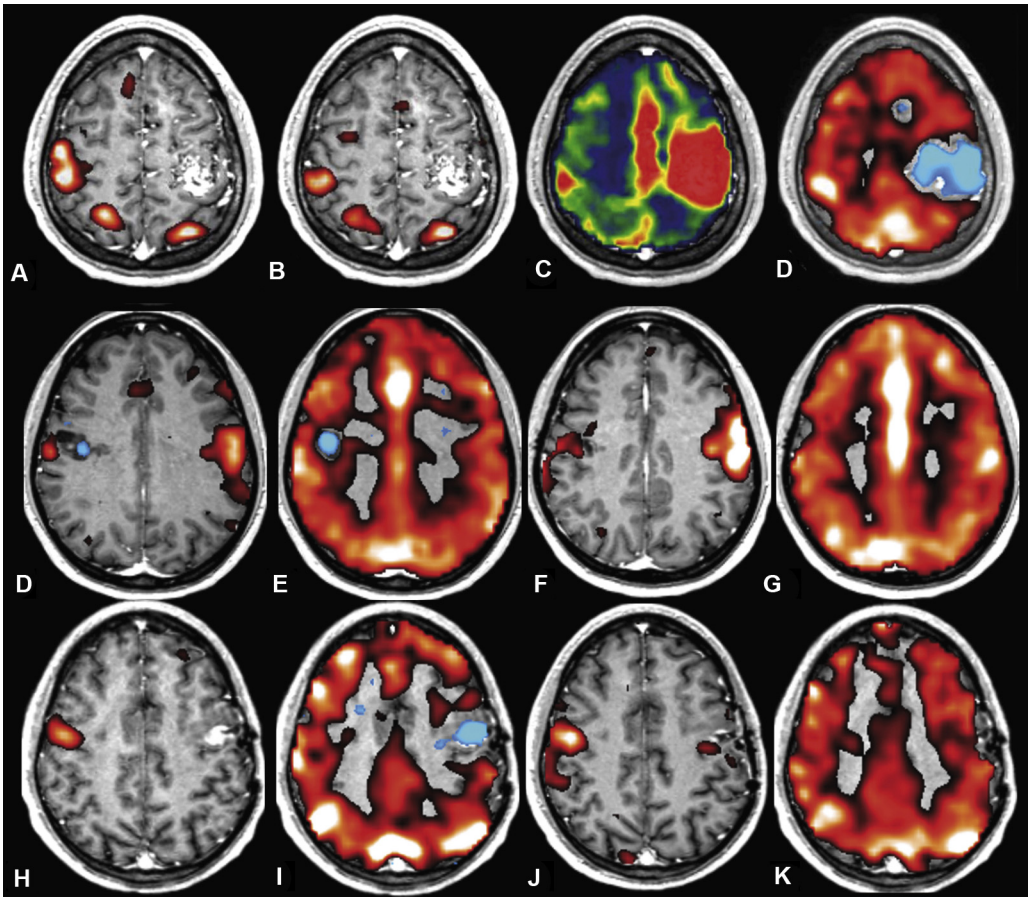

Figure 2. False negatives in fMRI activation induced by modifications in perfusion. In fMRI, an increase in the BOLD contrast is expected near the functional cortex. If absent, an alteration in the perfusion and its functional properties may be the cause and lead to negative results. A—D. Patient with a left precentral arteriovenous malformation. The movements of the left hand are accompanied by a right primary sensorimotor activation (A), while the movements of the right hand are not accompanied by a left primary sensorimotor activation (B). The mapping of the cerebral blood volume reveals locoregional hyperperfusion due to the lesion (C), with inverted vasoreactivity in projection of the precentral cortex (D). E—H. Patient with a ganglioglioma of the right precentral gyrus without facial palsy. Before surgery (E, F), inverted activation is detected in projection from the primary motor cortex next to the tumor (E), related to an inversion of the vasoreactivity (F). After the surgery, there is a pseudo-recovery of the activation (G), with normalization of the vasoreactivity (H). I—L. Patient with a recurrence of xanthoastrocytoma of the left precentral gyrus, manifested by seizures of the right hemiface. No pre-surgical facial palsy. Before surgery (I, J), the movements of the lips did not allow the activation of the ispitumoral primary sensorimotor cortex, as opposed to the healthy hemisphere (I). The mapping of the vasoreactivity to hypercapnia shows an extensive positive vascular response in red, with an inverted response around the lesion in blue, masking the functional cortex (J). The post-surgical fMRI shows pseudo-recovery of the ipsitumoral primary sensorimotor activation (K), associated with normalization of the vasoreactivity (L) [139].

vasoreactivity privileges the study of a non-neuronal vasomotor stimulus, such as CO_2 or acetazolamide.

In normal conditions, the vasoreactivity is influenced by sex [151], age [58,152], arterial pressure [153], basal perfusion conditions [106,152,154,155], anesthetic [106,156], modulation of the action of vasomotor neuromediators, such as that shown for acetylcholine [157,158], but not for noradrenalin [159] or dopamine [87].

The vasoreactivity is greater in the grey matter than in the white matter [9,84,108,160—166]. Within the grey matter, there are regional variations that may be under the influence of variations in the microvascular density [10,11] and the heterogeneous distribution of vasomotor neuromediators [101]. However, the published results often differ and do not provide an exact idea about these regional variations. Therefore, the vasoreactivity of the cerebral cortex is greater than that of the cerebellum [163,164] or inversely [7], than that of the basal ganglia [163,164,167] except for the thalamus [166] or inversely [168]... Differences have also been reported within the cerebral cortex, with a more marked vasoreactivity in the occipital and frontal lobes [163,164] although this is not constant [166,169].

In pathological conditions, global alterations in the hemodynamic response have been observed with chronic arterial hypertension [50,170], diabetes [50,171—173], sepsis [174], the administration of certain antihypertensive drugs [175], opioid agonists [176], in the presence of diffuse intracerebral factors such as microangiopathy [128,177—179], transient global amnesia [154], CADASIL [180,181], normal pressure hydrocephalus [182], traumatic brain injury [38,39,41—45,183,184], Alzheimer's disease [185—189]... Locoregional variations are also observed downstream from arterial stenosis [111,128,129,190—198], in focal epilepsy [199—201] and near a macroscopic lesion, such as a stroke [109,110,202], an arteriovenous malformation (Fig. 2) [141,203] or a tumor [112,139,140].

Value of the measurement of the cerebral vasoreactivity

Value of neurovascular coupling for functional imaging

The different functional imaging techniques for cognition, such as BOLD fMRI, are mainly based on neurovascular coupling. However, in spite of obvious modifications in the BOLD signal in patients, almost all of the studies do not take into account possible intra- and inter-individual variations in the physiological mechanism at the origin of the measured signal. During the interpretation of the BOLD signal, it is therefore impossible to distinguish the specific effects of the variations in neuronal activity from variations in the hemodynamic response or a possible interaction between these two factors. This represents an obvious limit to the technique that has to be overcome in order to better interpret fMRI results [101,109,112,139,140].

The evaluation of the hemodynamic response is obtained by the test of vasoreactivity to CO_2, even though the mechanisms involved differ. In spite of this physiological approximation, the normalization of the neurovascular BOLD signal by a hypercapnia test is at the base of the quantitative fMRI [76,162,204]. This approach consists of simultaneously measuring the BOLD signal and the cerebral blood flow. These parameters provide, by hypercapnia calibration of a biophysical model of the BOLD signal, the relative quantification of the consumption of oxygen by the cerebral parenchyma [81,146,147,205]. From then, this method, in the cognitive neurosciences, allows for comparison of the intra- and inter-individual data to better estimate the modifications induced by aging, neurodegenerative disease, disabling focal cerebral lesions (epilepsy, tumor and removal, ischemic stroke...).

In clinical practice, this approach would allow for a better interpretation of the functional mapping, in particular in patients before surgery, by taking into account alterations in the vasoreactivity near the lesions (Fig. 2) [112,139,140].

Prognostic value in steno-occlusive disease

In patients monitored for steno-occlusive disease of the cervical arteries, the measurement of the vascular reserve in the territory of the damaged artery is used to assess the risk of an ischemic stroke (CVA) or a transient ischemic attack (TIA). Downstream from an occlusion or severe stenosis, the reduction in perfusion pressure is compensated by the autoregulation and vasodilation that help maintain the constant perfusion. The absence of additional vasodilation attests to the absence of vascular reserve to deal with an increase in perfusion required to compensate the reduction in the blood supply (increase in the stenosis, reduction in the cardiac output or the arterial blood pressure), thereby exposing the patient to arterial ischemia [190,206—215]. Therefore, the study of the vascular reserve offers a functional evaluation of the functionality of the vascular network downstream from the stenosis and the available collaterality [216,217].

The clinical value of this imaging may be determinant in patients with tight intracranial arterial stenosis in which the treatment is highly debated. In fact, following an initial ischemic episode, the risk of recurrence under medical treatment may attain 30 to 40% after 2 years, or even 60% when there are clinical signs of hemodynamic disorders [218]. Currently, endovascular treatment by stent is considered only following a new ischemic episode. This being so, the morbidity related to this treatment has called its justification into question [219]. Thereby, the imaging of the vascular reserve may better characterize the nature of a CVA/TIA in these patients. A reserve maintained downstream from a stenosis would be in favor of a thromboembolic CVA/TIA, while an altered reserve may more reveal a CVA/TIA of hemorrhagic origin [214]. In patients with tight intracranial arterial stenosis, this imaging may identify patients at risk of a failure of a well carried out medical treatment and help better select patients likely to benefit from endovascular treatment (Figs. 3 and 4) [198].

The imaging of cerebral vasoreactivity shows an improvement, or even normalization, of the vascular reserve after the surgical treatment of a carotid stenosis [197,220,221], moyamoya disease [195,222—226] or tight intracranial arterial stenosis (Fig. 4).

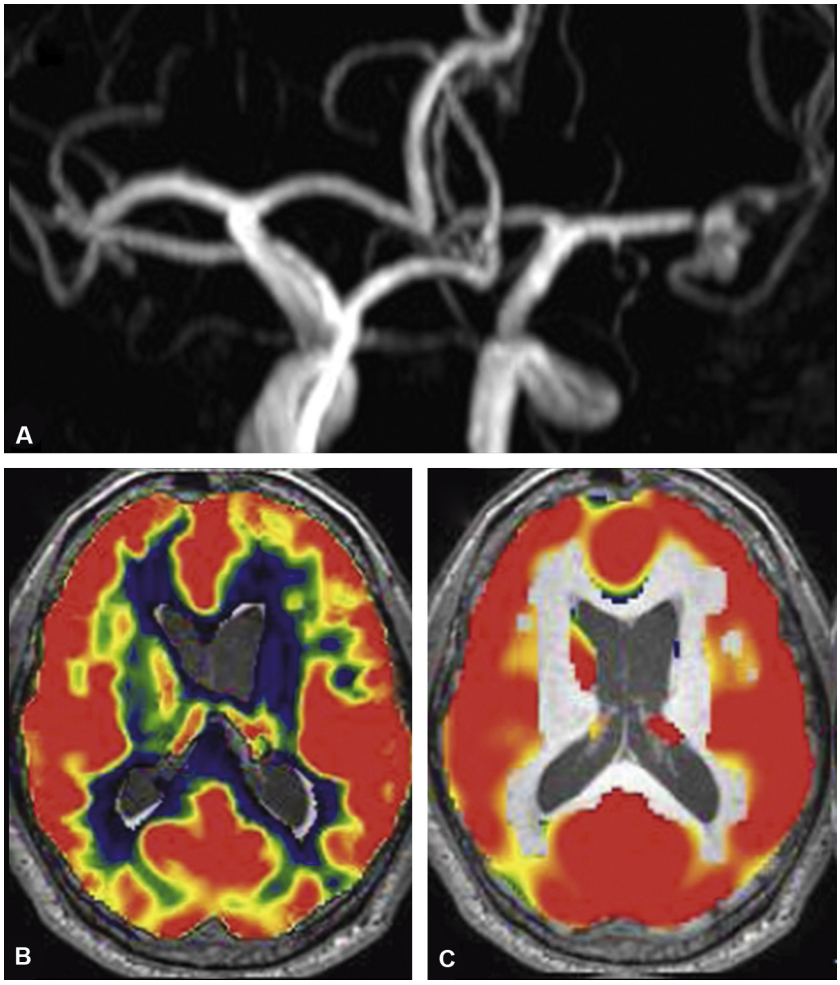

Figure 3. Tight intracranial arterial stenosis without reduction of the vascular reserve. A. A 44-year-old man treated for left capsulolenticular infarction revealing tight stenosis of the termination of the first portion of the left middle cerebral artery, accompanied by a post-stenotic aneurism. B. The basal perfusion is normal. C. The vasoreactivity does not show an alteration in the vascular reserve in the territory downstream from the stenosis. Most likely, it consists of a thromboembolic ischemia. A deficiency recurrence was not noted under well carried out anti-platelet therapy. The aneurism was surgically treated.

Towards imaging of the vasoreactivity for diagnostic purposes

The global and regional variations in the cerebral vasoreactivity observed in patients may reveal modifications in the basal cerebral perfusion [5,8,74], mechanical vascular properties [180,227], concentration of vasomotor substances in the perivascular environment, relations between the vessels, astrocytes and neighboring neurons [101]. However, a great many cerebral and cerebrovascular disorders are likely to be accompanied by global and locoregional alterations in vasoreactivity, as shown in patients [82,109,111,112,128,177,186,192,228] and experimental animal models [27,158,180,229—233].

The potential fields for the application of the imaging of the vasoreactivity for diagnostic purposes are extremely vast. However, the imaging of the vasoreactivity is only used in case of occlusive arterial disease, in order to assess the vascular reserve of the cerebral parenchyma and the risk of ischemic stroke. The cerebral imaging of the vasoreactivity may be used to search, in the entire brain, infracentimetric spatial anomalies of the functional modulation of the cerebral perfusion. It would be possible to estimate the sensitivity and specificity of these anomalies by comparing the results with those obtained in controls. For diagnostic purposes, this imaging of the microvascular function and its interactions with the metabolic, neuronal and glial perivascular environments may offer a better phenotypic characterization of neurological and psychiatric diseases, or even an estimate of the individual vulnerability to these disorders even before the appearance of clinical signs or macroscopically identifiable lesions in imaging. In the same way that the injection of contrast product offers a functional contrast, the imaging of the vasoreactivity may offer a functional contrast that should be put to use for medical purposes.

In neurodegenerative disease, three recent studies have shown alterations in the vasoreactivity in Alzheimer's disease and patients at risk [186,188,189], by underlining the importance of microvascular disorders in the physiopathology of the disease, as suggested by the data in the animal [234—237]. On the other hand, in an analogous study carried

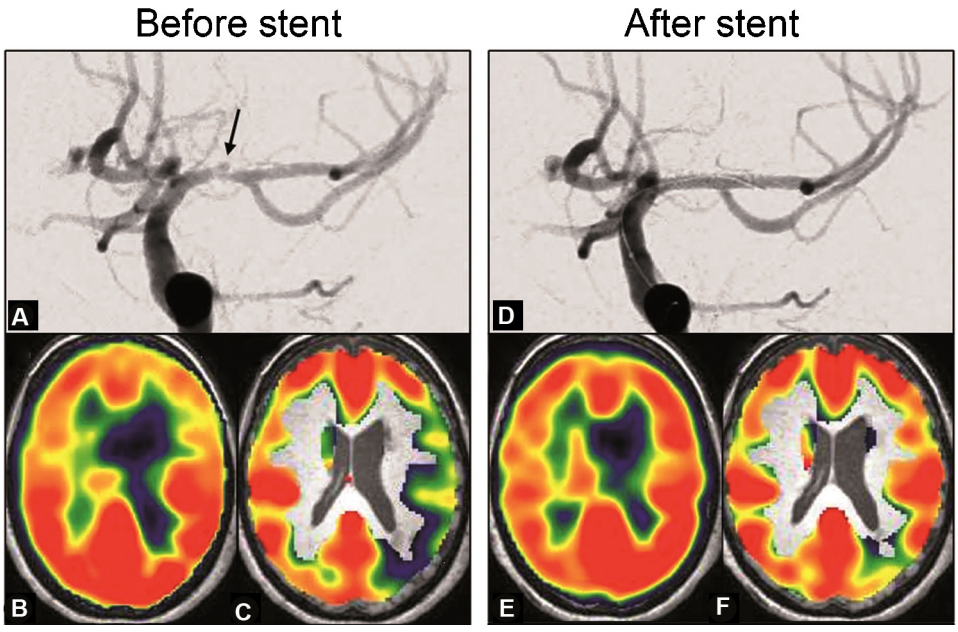

Figure 4. Tight intracranial arterial stenosis with reduction of the vascular reserve [198]. A. A 63-year-old woman treated for tight stenosis of the M1 portion of the left middle cerebral artery (arrow), revealed by a deep ischemic stroke. A—C. Pre-surgical examinations. D—F. Post-surgical examinations. A and D. The angiography shows tight stenosis before (A) and after dilation by stenting (D). B and E. Basal perfusion MRI measured by arterial spin labeling. The basal perfusion is normal and globally symmetrical, both after and before the intervention. C and F. BOLD-fMRI of the vasoreactivity to hypercapnia. The fMRI of the vasoreactivity to CO_2 shows a major alteration in the vascular reserve in the territory of the arterial stenosis (C). It obviously is a hemodynamic ischemia. Except for the posterior junctional territory, the intervention normalized the vascular reserve (F).

out in patients monitored for idiopathic Parkinson's disease, we did not find a significant alteration in the cerebral vasoreactivity (Fig. 5) [87]. In this context, the normality of this examination may be a diagnostic criterion to distinguish it from vascular parkinsonism.

In epileptology, perfusion anomalies have been described outside of seizures, both in the irritative cortical zones and in the non-epileptic zones [200,238]. In focal epilepsy, interictal basal hypoperfusion has been reported with a cortico-thalamic diaschisis [239]. More surprisingly, an increase in the perfusion of the epileptogenic cortex and hypoperfusion of the healthy cortex has been identified up to 10 min before the occurrence of a seizure [240,241]. Beside these basal perfusion anomalies, a reduction in the perinidal vasoreactivity has been detected in patients with arteriovenous malformations and epilepsy whereas the vasoreactivity was normal in the absence of epilepsy (Fig. 6) [242].

In neuro-oncology, the BOLD MRI, sensitive to variations in tissue perfusion and blood oxygenation, illustrate the considerable inter-individual and intra-tumoral variability [243—246]. Therefore, the perfusion imaging can show functional differences in microvascularization according to the type of tumor. The crude angiogenesis of certain tumors is without vasoreactivity, while the angiogenesis of others is closer to normal cerebral vascularization and have vasoreactivity [247].

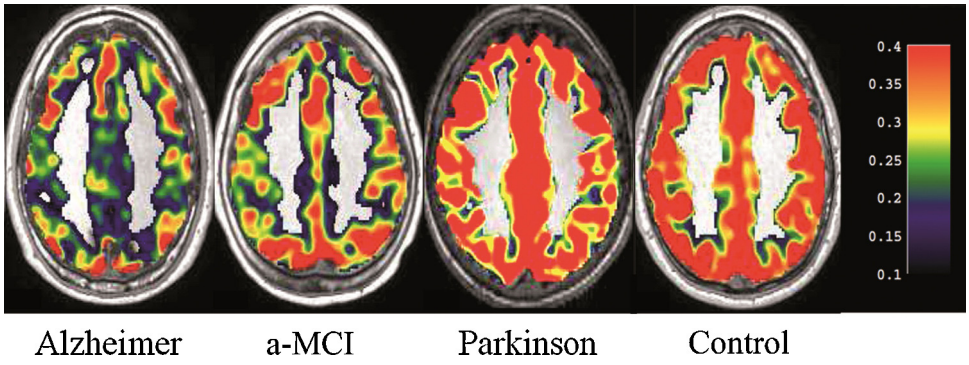

Figure 5. Vasoreactivity and neurodegenerative diseases. These illustrative cases of subjects about 70 years old, without microangiopathy, demonstrate that the study of cerebral vasoreactivity to CO_2 using BOLD fMRI detects diffuse abnormalities in a patient treated for beginning Alzheimer's disease and in a subject at risk with amnestic mild cognitive impairment (a-MCI) [186], while the vasoreactivity is normal in patients with Parkinson's disease when compared with a healthy subject [87].

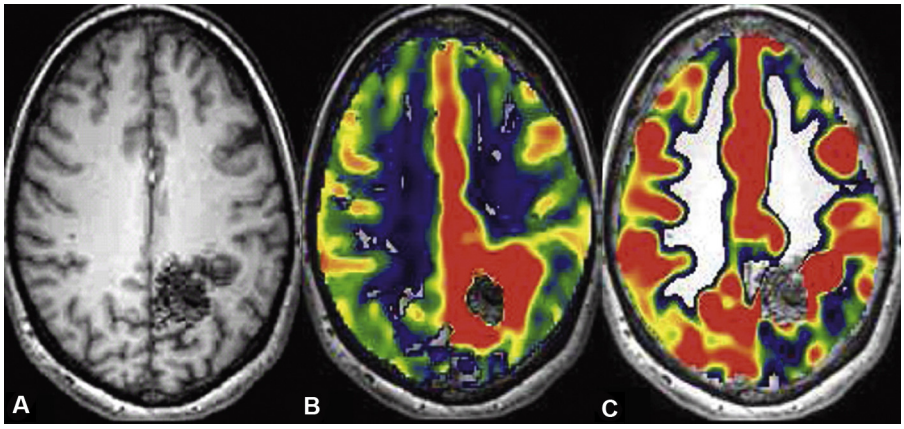

Figure 6. Alteration in the vasoreactivity in a patient with an arteriovenous malformation revealed by an epileptic seizure. A. Left parietal internal arteriovenous malformation (AVM). B. Local hyperperfusion that spares the parietal cortex. C. However, the BOLD-fMRI of the vasoreactivity to CO_2 reveals an alteration in the inferior perinidal parietal cortex (C). This presentation is described in patients with AMV revealed by epilepsy, while the perilesional vasoreactivity in patients without epilepsy was normal [203].

In traumatology, the monitoring of functional perfusion disorders is very important since their occurrence is a poor prognostic factor [38,39,41—45,183,184]. Several rare experimental trials have been carried out by perfusion CT-scan with Xenon 133 [43,248] or by positron emission tomography [249]. However, it is legitimate to wonder about the pertinence of having cerebral mapping when the expected anomalies are usually diffuse. This is why these barely ambulatory patients are usually explored in bed by transcranial Doppler during a modulation of the capnia. Nevertheless, several difficult cases may be solved by the regional anomalies detected by perfusion MRI or perfusion CT-scan during a short hypercapnia test.

Techniques to measure cerebral vasoreactivity

Choice of imaging method

Initially studied in transcranial echo Doppler, then in nuclear medicine (PET, SPECT), the imaging of the vasoreactivity appeared in MRI several years ago, with the development of rapid acquisition sequences. Perfusion tomodensitometry has also been proposed [250].

Compared with other imaging techniques, MRI is available and non-invasive while providing an image with an infra-centimetric spatial resolution and a temporal resolution of about one second, which make clinical use conceivable. In addition, cerebral MRI is currently used in neurology, neurosurgery and psychiatry, providing directly superimposable functional and morphological data during the same examination.

Several MRI methods have been proposed: BOLD contrast [109,161,225,228,251,252], ASL [170,195,215, 216,253—255], susceptibility contrast by the injection of gadolinium [9,256,257], magnetic resonance angiography [217,258].

In addition to their availability, the multiplicity of methods attests to the limits of each of them. Excluding macrovascular imaging (Doppler, MRA), the calculation of the CVR is based on the same principle with, for variations in the capnia:

$CVR = \Delta signal\ (\%) / \Delta P_eCO_2\ (mmHg)^*$.

Theoretically, ASL is the best method since it allows the cerebral blood flow to be quantified and the variation in its signal may be expressed as a flow variation. Nevertheless, ASL requires careful methodological rigor with a correction of the T1 effects, the choice of post-saturation times and a 3T MRI to have a sufficient signal-noise ratio to detect a variation of several percent of this already very low signal [259]. Moreover, ASL with a fixed inversion time is sensitive to major variations in the arterial transit time of the labeled blood bolus, distorting the quality of the measurement in steno-occlusive disease. The current temporal resolution of multi-T1 ASL sequences does not allow for dynamic ASL. This being the case, the acquisitions with pseudo-continuous labeling cover the entire brain with a resolution under 10 s, allowing for the study of the dynamic variations in perfusion [67,216]. Now and in the absence of steno-occlusive disease, ASL seems to be the choice method to study healthy subjects in physiology [67] and the cognitive neurosciences, patients presenting a neurodegenerative disease or even children. However and in spite of these theoretical advantages, the use of ASL in this context remains very marginal compared with the increasing number of BOLD contrast studies.

Although, the BOLD signal is influenced by a great many parameters (Fig. 1), this reproducible method is correlated with variations in the cerebral blood flow [57,260]. We have already seen that variations in the signal were sensitive to the basal perfusion conditions. As a result, a measurement of basal perfusion either by ASL or susceptibility contrast is required to make sure that the differences in the BOLD signal variations are really due to modifications in the cerebral vasoreactivity and not simply the consequence of a modification in the basal perfusion [112,186,189].

Perfusion imaging by susceptibility contrast during the first pass of a gadolinium bolus may also be proposed. The main limit is the need to inject two boluses of contrast product, one before the vasomotor stimulus and the other after. In addition, the quantification of the results is still difficult, in particular in the presence of a rupture of the

brain-blood barrier. It also lacks the measurement of hemodynamic changes that might be relevant [112] because such imaging approach is performed at two different steady-states.

The perfusion CT-scan is also based on the study of the transit of a bolus of contrast product. The limits for this approach are the need to carry out two examinations, one before the vasomotor stimulus and the other after, thereby doubling the irradiation and the quantity of iodine injected [2,250]. The cover volume may also be limited, although it increases with the optimization of the detectors. The quantification of the perfusion, easier than with MRI, and its great availability may be determining elements if, in the future, the clinical applications of the imaging of the vasoreactivity becomes necessary.

Choice of vasomotor stimulus

In clinical practice, MRI of the vasoreactivity is above all obtained by modulating the capnia either by hyperventilation, apnea, inhalation of CO_2 or injection of acetazolamide. The study of the vasoreactivity with oxygen is much less developed since the vasomotor effects of oxygen are very low (see above) [64,68—71].

Acetazolamide (Diamox®) is a carbonic anhydrase inhibitor that converts CO_2 into bicarbonates. It provokes hypercapnia and acidosis responsible for a vasodilation and an increase in the CBF of about 20 to 30% [9,80,261]. In imaging, 15 mg/kg of the product is administered by intravenous route with a maximum of 1200 mg. The onset of action is after several minutes. Its efficacy lasts for several hours before a return to the initial state. This product has several contraindications (kidney failure, liver failure, allergy...) and many secondary effects (hydro-electrolytic disorders, diabetes, nephritic colic...). The pharmacokinetics and the adverse effects of acetazolamide limit its use in imaging and in particular in fMRI [80]. This stimulus requires two imaging examinations, one before the injection and the other at least 20 minutes after the injection. The intravenous administration of the product and its contraindications limits its use in healthy volunteers.

The sustained hyperventilation for at least 1 min induces hypocapnia with a P_eCO_2 under 30 mmHg, that is a reduction of 10 mmHg or more [8,50,74,82,109,164]. The hyperventilation is accompanied by a vasoconstriction responsible for a 25% reduction in the CBF [8,262] and a 1 to 5% drop in the BOLD signal [74,82,109,164]. Moreover, the hyperventilation is responsible for tachycardia without a change in the arterial pressure [50].

On the contrary, an apnea of at least 20 s is required to observe an increase in the CBF, which may attain 60% and a 1 to 5% increase in the BOLD signal [168,251,263—266]. The 20s apnea allows for a 7 mmHg rise in the P_eCO_2 de 7 mmHg and a 45% increase in the arterial velocity, but it also provokes an increase in blood pressure, secondary hyperventilation and transient hypocapnia. The return to equilibrium takes 45 s. However, the hypoxia does not seem to affect the increase in perfusion [267].

The hyperventilation and apnea are easy and reliable tasks. However, they induce movements of the head and are highly dependent on the sometimes-altered performances of the subjects and, a fortiori of the patients [109]. Moreover, except for sensory stimulations (visual for example), it's very difficult to carry out an additional cognitive task to study neurovascular coupling in the functional regions of motor skills or language.

The vasodilatation induced by the inhalation of 5 to 10% CO_2 for 2 to 3 min is accompanied by an increase in the cerebral blood flow (CBF) of 2 to 11%, 6% per mmHg, and the cerebral blood volume of 1.8% per mmHg [7]. Similar MRI results have been observed with ASL [254]. In BOLD fMRI, the increase in cerebral perfusion is accompanied by an increase in signal ranging from 0.2 to 0.3% per mmHg or 2—4% for an increase in expiratory pressure in CO_2 close to 10—15 mmHg [87,112,161,186,251,252,268]. The signal progressively varies to reach a plateau after 30—60 s. A return to the state of equilibrium also requires 30—60 s [58,76,162,166,167,251]. The amplitude of the variation in signal induced by the inhalation of CO_2 is roughly superior that induced by the neurovascular coupling that is about 0.5 to 3%. This difference is not due to a sudden increase in neuronal activity for a moderate hypercapnia test [46,269].

Among the disadvantages of the inhalation of CO_2, several minor adverse and rapidly reversible effects should be noted. They have been reported during respiratory function tests and include mild headache, shortage of air, anxiety or fatigue [270—272]. The anxiogenic effects of the inhalation of CO_2 are experimentally used to provoke anxiety disorders, or even panic attacks, although the appearance of such effects requires much longer inhalation protocols (15—20 min) or the use of mixtures more concentrated in CO_2 (20—35% CO_2) [273,274]. The mean arterial pressure and the pulse are stable for several minutes of inhalation [50], whereas an increase in these parameters may be observed with an inhalation of over 10 min [275].

The inhalation of carbogen a 7/93% mixture of CO_2/O_2, is an potential alternative, since there are no reported contraindications or adverse effects. This aspect is readily used in a clinical context in brain-damaged subjects [50,111,182,246]. Carbogen is currently used in clinical practice, in cardiorespiratory fitness tests and to test the hyperventilation reflex to hypercapnia. In spite of the high oxygen content, the inhalation of carbogen with over 3% CO_2 provokes a vasodilation that in turn induces an increase in the arterial speed of about 1.5 $cm.s^{-1}.mmHg\ P_eCO_2^{-1}$ [50]. The increase in the BOLD signal is 2 to 6% in the grey matter [87,112,161,186,252]. With its high oxygen content, carbogen also induces tissue hyperoxia. This hyperoxia may provoke an increase in the BOLD signal of up to 3% in the grey matter [69,246], in spite of a potential reduction of several percent in the CBF [70]. This effect is accounted for by the intake of freely diffusible O_2 that is directly used by the neurons without having to extract the O_2 carried by the hemoglobin. This results in a reduction in the oxygen extraction factor and the deoxyhemoglobin concentration. This increase in oxygenation has to be taken into account now that the effects of carbogen are studied in BOLD imaging since, as with the interpretation of neurovascular coupling, it's difficult to distinguish the increase in perfusion from the local increase in oxygenation (Fig. 1). Moreover, the properties of carbogen have been used in neuro-oncology to increase the oxygenation of brain tumors and their radiosensitivity [245,246,276—278]. In spite of the encouraging experimental results [279], the evaluation of

the effects of radiosensitization by carbogen and nicotinamide have been disappointing [276,277]. However, we can debate the possibility of a better selection of patients, in particular on the basis of imaging of the tumor response to radiosensitizing agents [276].

Conclusion

To conclude, the functional imaging of cerebral perfusion is used for the mapping of the three main properties of brain microvascularization: neurovascular coupling, vasoreactivity to circulating gases and autoregulation of the perfusion pressure. BOLD fMRI of the cerebral vasoreactivity to CO_2 is increasingly used. fMRI of the cerebral vasoreactivity may be used to estimate the vascular reserve and risk of a stroke in steno-occlusive disease in order to improve the treatment. fMRI of cerebral vasoreactivity detects early alterations in Alzheimer's disease and the subjects at risk. fMRI of cerebral vasoreactivity may be used to better interpret the results in fMRI activation, in particular before neurosurgery.

Therefore, it's only a question of time, access and propagation of techniques. Most likely, the coming decade will confirm the development of the clinical applications of the functional imaging of perfusion for brain and heart diseases, as well as for other organs.

TAKE-HOME MESSAGES

- Functional imaging of cerebral perfusion is used in the mapping of the 3 main properties of brain microvascularization: neurovascular coupling, vasoreactivity to circulating gases and autoregulation of the perfusion pressure.
- BOLD fMRI of cerebral vasoreactivity to CO_2 is increasingly used.
- fMRI of cerebral vasoreactivity may be used to estimate the vascular reserve and the risk of stroke in steno-occlusive disease in order to improve the treatment.
- fMRI of cerebral vasoreactivity detects early alterations in Alzheimer's disease and subjects at risk.
- fMRI of cerebral vasoreactivity may be used to better interpret the results in fMRI activation, in particular before neurosurgery.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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