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Human cerebral circulation: positron emission tomography studies

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We reviewed the literature on human cerebral circulation and oxygen metabolism, as measured by positron emission tomography (PET), with respect to normal values and of regulation of cerebral circulation. A multicenter study in Japan showed that between-center variations in cerebral blood flow (CBF), cerebral blood volume (CBV), cerebral oxygen extraction fraction (OEF) and cerebral metabolic rate of oxygen ($CMRO_2$) values were not considerably larger than the corresponding within-center variations. Overall mean ± SD values in cerebral cortical regions of normal human subjects were as follows: CBF = 44.4 ± 6.5 m*l*/100 m*l*/min; CBV = 3.8 ± 0.7 m*l*/100 m*l*; OEF = 0.44 ± 0.06; $CMRO_2$ = 3.3 ± 0.5 m*l*/100 m*l*/min (11 PET centers, 70 subjects). Intrinsic regulation of cerebral circulation involves several factors. Autoregulation maintains CBF in response to changes in cerebral perfusion pressure; chemical factors such as P_aCO_2 affect cerebral vascular tone and alter CBF; changes in neural activity cause changes in cerebral energy metabolism and CBF; neurogenic control of CBF occurs by sympathetic innervation. Regional differences in vascular response to changes in P_aCO_2 have been reported, indicating regional differences in cerebral vascular tone. Relations between CBF and CBV during changes in P_aCO_2 and during changes in neural activity were in good agreement with Poiseuille's law. The mechanisms of vascular response to neural activation and deactivation were independent on those of responses to P_aCO_2 changes. CBV in a brain region is the sum of three components: arterial, capillary and venous blood volumes. It has been reported that the arterial blood volume fraction is approximately 30% in humans and that changes in human CBV during changes in P_aCO_2 are caused by changes in arterial blood volume without changes in venous blood volume. These findings should be considered in future studies of the pathophysiology of cerebrovascular diseases.

Key words: cerebral circulation, PET, autoregulation, P_aCO_2, neural activity

INTRODUCTION

Measurement of cerebral circulation in humans has been carried out since the 1950s with the use of diffusible inert-gases,[1–3] intravascular X-ray contrast media[4] and intravascular radiotracers.[5] Measurement of cerebral circulation in humans by positron emission tomography (PET)[6–11] and single-photon emission computed tomography (SPECT)[12–14] is currently performed widely in investigating the pathophysiology of various brain diseases, particularly occlusive cerebrovascular disease. Recently, measurement of cerebral circulation by magnetic resonance imaging (MRI) with intravascular contrast media[15,16] has also been attempted. Some indicators of cerebral circulation, including cerebral blood flow (CBF), cerebral vascular mean transit time (MTT), and cerebral blood volume (CBV) can be measured by PET. The relation between these parameters can be expressed as MTT = CBV/CBF.[7,11] CBF and CBV can be measured by PET,[17–21] and MTT and CBV can be measured by MRI with intravascular contrast media.

Parameters of cerebral oxygen metabolism, including

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cerebral oxygen extraction fraction (OEF) and cerebral metabolic rate of oxygen ($CMRO_2$), can also be measured by PET.[18,22] Because energy metabolism in the brain is almost aerobic under normal conditions, cerebral oxygen metabolism can represent cerebral energy metabolism for maintenance of homeostasis and neural activity.

Intrinsic regulation of cerebral circulation involves several factors.[23] Autoregulation maintains CBF in response to changes in cerebral perfusion pressure (CPP). Chemical factors such as P_aCO_2 can affect cerebral vascular tone and alter CBF. Changes in neural activity cause changes in cerebral energy metabolism and CBF. Neurogenic control of CBF by sympathetic innervation has also been observed. In this review, we analyze PET studies of human cerebral circulation and oxygen metabolism with respect to normal values and regulation of cerebral circulation.

NORMAL VALUES FOR CEREBRAL CIRCULATION AND METABOLISM AS MEASURED BY PET

CBF, CBV, OEF and $CMRO_2$ are generally measured by PET with ^{15}O-labeled carbon dioxide ($C^{15}O_2$) or ^{15}O-labeled water ($H_2{}^{15}O$) as diffusible tracers, ^{15}O-labeled carbon monoxide ($C^{15}O$) or ^{15}O-labeled oxygen ($^{15}O_2$). Several methods for quantification of CBF, CBV, OEF and $CMRO_2$ by PET have been developed and used.[18–22,24–27] Although the measured values depend on quantification methods and other factors such as the period of radioactive gas inhalation and scanning, which may differ between PET centers, a multicenter study in Japan revealed that between-center variation is not considerably larger than within-center variation and that the overall inter-individual variation in CBF, CBV, OEF and $CMRO_2$ is acceptably small (within 20%).[28] Overall mean ± SD values in cerebral cortical regions of normal human subjects were as follows: CBF = 44.4 ± 6.5 ml/100 ml/min; CBV = 3.8 ± 0.7 ml/100 ml; OEF = 0.44 ± 0.06; $CMRO_2$ = 3.3 ± 0.5 ml/100 ml/min (11 PET centers, 70 subjects). These values were in good agreement with those reported previously from each single PET center.[29–31]

Blood flow of gray matter and white matter was measured in the 1960s by a diffusible tracer, ^{133}Xe.[32–34] Fast and slow components of the clearance slope were considered to reflect the blood flow of gray and white matter, respectively. Reported blood flow of gray and white matter was approximately 80 and 20 ml/100 ml/min, respectively. CBF values of cerebral cortical regions measured by PET have been reported[28–31] and were less than above value for gray matter, indicating a mixture of radioactivity concentration between gray and white matter in a region-of-interest because of limited spatial resolution of PET. It has also been reported that the tissue mixture of gray and white matter may result in underestimation of CBF measured by PET with $C^{15}O_2$ or $H_2{}^{15}O$, because of non-linearity between brain counts and CBF in a compartment model analysis.[19,35,36]

The normal distribution of CBF in humans has been investigated by PET with diffusible tracers ($C^{15}O_2$ and $H_2{}^{15}O$) and by SPECT with accumulative tracers (I-123-labeled *N*-isopropyl-*p*-iodoamphetamine (IMP),[37–39] Tc-99m-labeled hexamethylpropyleneamineoxime (PAO)[40,41] and Tc-99m-labeled ethyl cysteinate dimer (ECD)).[42,43] An anatomic standardization technique that transforms brain images of individual subjects into a standard brain shape and size in three dimensions is used for intersubject averaging of PET and SPECT images.[44] Several methods of anatomic standardization have been developed and used to build a database of normal CBF in humans.[45–48] Investigations of the normal distribution of CBF revealed that blood flow of gray matter is greater than that of white matter; however, regional distributions of CBF differed between tracers.[49,50] For example, CBF in the occipital cortex measured by SPECT was reported to be greater with ECD than with PAO. Age-related changes in the regional distribution of CBF, in which significant decrease in CBF around the Sylvian fissure was observed with age, have also been reported.[51,52] The database of normal CBF and the anatomic standardization techniques have been widely applied to investigate changes in the regional distribution of CBF in neurologic and psychiatric diseases.[53–55]

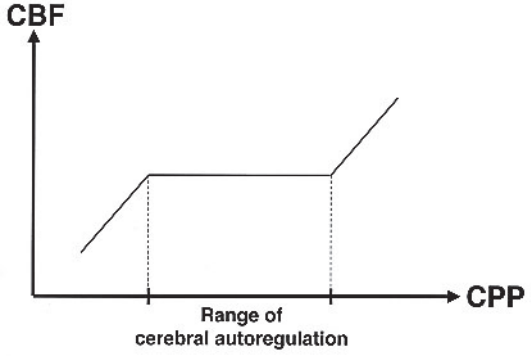

Fig. 1 Cerebral autoregulation.

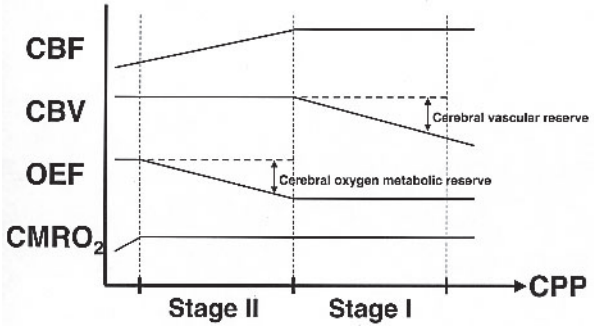

Fig. 2 Hemodynamic changes to decrease in CPP.

REGULATION OF CEREBRAL CIRCULATION

Intrinsic regulation of cerebral circulation involves several factors[23]: autoregulation in response to changes in CPP; chemical control of CBF, e.g., by P_aCO_2; metabolic regulation in response to changes in neural activity; and neurogenic control of CBF by sympathetic innervation. Here, we discuss these four factors.

CBF autoregulation

CBF autoregulation is the mechanism by which CBF is maintained during changes in CPP of cerebral arterioles (Fig. 1). CBF is maintained by autoregulatory vasoconstriction and vasodilatation of arterioles when CPP is increased or decreased, respectively.[56] When CPP increases beyond the upper limit of autoregulation, CBF increases.[57,58] This can cause hypertensive encephalopathy, which is characterized by cerebral vasodilatation and breakdown of the blood-brain barrier.[59–61] When CPP decreases below the lower limit of autoregulation, CBF decreases.[62] Decreased CPP due to major cerebral arterial occlusive disease causes autoregulatory vasodilatation to maintain CBF (stage I hemodynamic change) (Fig. 2).[7] Decreased CPP below the lower limit of autoregulation causes decreased CBF with increased OEF to maintain $CMRO_2$ (stage II hemodynamic change) (Fig. 2).[7] To assess stage I hemodynamic compromise as an indicator of cerebral vascular reserve, the CBF response to acetazolamide, a cerebral vasodilator, is measured by PET and SPECT. Reduced vasodilatory capacity is a major predictor of stroke recurrence.[13,14]

Chemical control (P_aCO_2)

Chemical factors, including P_aCO_2, can affect cerebral vascular tone and alter CBF. Hypercapnia produces cerebral vasodilatation[63–66] and increases CBF.[63,67] CO_2 diffuses through the blood-brain barrier and induces extracellular acidosis, which relaxes vascular smooth muscle.[66,68,69] Hypercapnia-induced cerebral vasodilatation is a direct effect of H^+ on vascular smooth muscle[70–73]; the blood-brain barrier itself is impermeable to H^+. Conversely, hypocapnia decreases CBF.[63,67,74] Thus, the extracellular pH of vascular smooth muscle is affected by P_aCO_2.[74] It has been reported that hypercapnia increases CBF by approximately 6% per mm Hg change in P_aCO_2, and hypocapnia decreases CBF by approximately 3% per mm Hg change in P_aCO_2.[67,75] Because responsiveness to vasodilating substances with insufficient CPP is reduced by autoregulatory vasodilatation,[10,76] hypercapnia can be used to estimate cerebral perfusion reserve in occlusive cerebrovascular disease.[77–79]

Recently, regional differences in vascular response to changes in P_aCO_2 have been investigated with the use of an anatomic standardization technique.[67] A large capacity for vasodilatation was observed in the pons, cerebellum, thalamus and putamen, whereas a large capacity for vasoconstriction was observed in the temporal, temporooccipital and occipital cortices. In the assessment of cerebral perfusion reserve, these regional differences should be considered. Vascular responses to changes in P_aCO_2 have been reported to be decreased significantly with normal aging in humans, indicating progression of sclerotic changes in the cerebral perforating and medullary arteries.[80,81] Decreased vascular response to hypercapnia with age has also been observed in rats.[82,83] Because cerebral vascular responsiveness to changes in P_aCO_2 reflects the range of cerebral autoregulation, this range may narrow with aging.

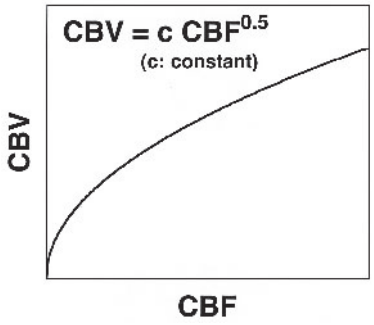

Fig. 3 Poiseuille's law describing the relation between CBF and CBV.

An increase in CBF during hypercapnia with no change in the density of perfused capillaries has been observed at the microvascular level in animals.[84] Change in capillary diameter during hypercapnia and hypocapnia has also been observed in animals.[85] The relation between CBF and CBV (including arterial, capillary and venous blood volume) during changes in P_aCO_2 has been investigated in animals[86–89] and humans.[90] Results showed that the increase in CBV during hypercapnia is less than that in CBF and that the degree of decrease in CBV during hypocapnia is less than that in CBF. The relation between CBF and CBV during changes in P_aCO_2 was determined in humans as follows: $CBV = 1.09CBF^{0.29}$.[90] According to Poiseuille's law, vascular resistance decreases by a power of 4 of the vessel diameter. Blood volume increases proportionally to the square of the diameter, yielding the relation: $CBV = c\ CBF^{0.5}$ (c: constant) (Fig. 3), which is in good agreement with the relation during changes in P_aCO_2.

Metabolic regulation due to neural activity

Neural activation increases regional cerebral energy metabolism and CBF. PET studies in humans have shown that regional CBF and $CMRO_2$ increase during neural activation. The increase in CBF is greater than that in $CMRO_2$ and results in a decrease in OEF, which corresponds to the ratio of $CMRO_2$ and CBF.[91–94] This discrepancy between increases in CBF and $CMRO_2$ during neural activation causes an increase in venous blood oxygenation and, therefore, a decrease in venous blood paramagnetic deoxyhemoglobin concentration. This

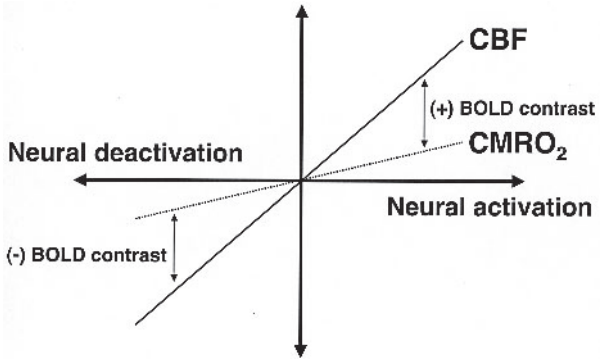

Fig. 4 Changes in CBF and $CMRO_2$ during changes in neural activity and changes in BOLD signal.

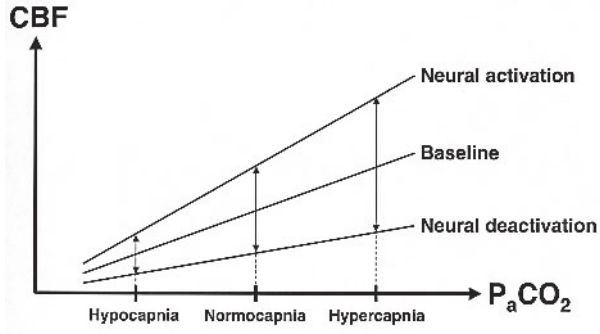

Fig. 5 Changes in CBF during changes in P_aCO_2 under activation, baseline and deactivation conditions.

decrease can be detected by blood oxygenation level-dependent (BOLD) contrast by means of functional magnetic resonance imaging (fMRI),[95,96] which is used widely to study brain activation.[97] A significant negative correlation between changes in OEF and BOLD signal during neural activation has been reported in human PET studies.[94] This supports the assumption on which BOLD contrast studies are based: that the discrepancy between increases in CBF and $CMRO_2$ during neural activation causes an increase in venous blood oxygenation (Fig. 4).[98]

PET studies of the hemodynamics of crossed cerebellar diaschisis (CCD), which is caused by contralateral supratentorial lesions, have shown a reduction in CBF and $CMRO_2$.[99–103] Because no differences in vascular response to hypercapnia, hypocapnia or acetazolamide stress were observed between the CCD side and the unaffected side of the cerebellum,[103–105] the mechanism of CCD can be considered secondary hypoperfusion due to neural deactivation. The degree of difference between $CMRO_2$ values on the CCD side and the unaffected side was less than that between the CBF values, resulting in significantly higher OEF on the CCD side (Fig. 4).[102,103] Increased OEF with decreased CBV in the CCD side indicates that neural deactivation primarily causes vasoconstriction rather than a reduction in oxygen metabolism.[103]

The relation between CBF and CBV during changes in neural activity has been investigated in animals and humans. The hemodynamic mechanism of increased CBF during neural activation has been investigated in animals at the microvascular level by laser-Doppler flowmetry.[106–108] Two hypotheses exist to explain the mechanism of hemodynamic regulation.[109] One is that change in capillary blood volume changes CBF, and the other is that change in capillary flow velocity changes CBF. One animal study showed that the increase in CBF was greater than the increase in pial arteriolar diameter during neural activation.[106] Early blood volume increase during neural activation, indicating active neurovascular regulation of blood volume in the capillary bed, has also been observed in animals.[107] Mandeville et al. observed a mismatch between the responses of relative CBV measured by MRI with a paramagnetic contrast agent and relative CBF measured by laser-Doppler flowmetry in rats during somatosensory stimulation.[110] In humans, PET and MRI studies of cerebral hemodynamics indicate that CBF and CBV increase during neural activation.[111–114] A PET study showed that the increase in CBF was greater than that in CBV during visual stimulation of 8-Hz photic flickers, resulting in a decrease in cerebral vascular MTT, although the increases in CBF and CBV were almost identical during visual stimulation of 2-Hz flickers.[114] This indicates that when the increase in CBF is great, it is caused primarily by an increase in vascular blood velocity rather than an increase in CBV. The relation between CBF and CBV during neural activation was $CBV = 0.88CBF^{0.30}$, in good agreement with Poiseuille's law.[114] As mentioned above, CCD can be considered to represent neural deactivation. The degree of difference between CBF values on the CCD and unaffected sides of the cerebellum has been reported to be similar to that between CBV values on the two sides; this suggests that MTT, i.e., vascular blood velocity, does not change during neural deactivation.[103] The relation between CBF and CBV of the CCD and unaffected sides was expressed as $CBV = 0.29CBF^{0.56}$, which is also in good agreement with Poiseuille's law.[103]

It has been reported that tissues with increased CBF due to neural activation show the same vascular response to changes in P_aCO_2 as that seen for resting CBF.[75] Inao et al. reported that, despite a decreased vascular response to acetazolamide stress because of a steno-occlusive lesion of a major cerebral artery, normal CBF response to neural activation was observed.[115] These findings indicate that the mechanism of vascular response to neural activation is independent of that to either P_aCO_2 change or acetazolamide stress (Fig. 5). No differences in vascular response to hypercapnia, hypocapnia or acetazolamide stress were observed between the CCD side and the unaffected side of the cerebellum,[103–105] indicating that the mechanism of vascular response to neural deactivation is also independent of that to either P_aCO_2 change or acetazolamide stress (Fig. 5).

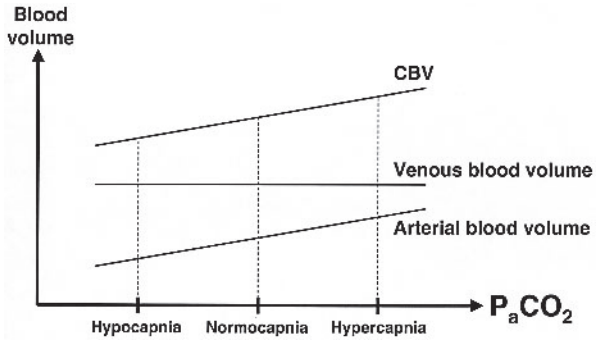

Fig. 6 Changes in CBV, arterial blood volume and venous blood volume during changes in P_aCO_2.

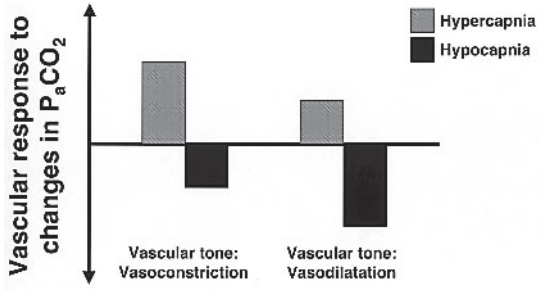

Fig. 7 Assumed relation between cerebral vascular tone and vascular responses to changes in P_aCO_2.

Neurogenic control of CBF by sympathetic innervation
Sympathetic innervation of the intracranial arteries contributes to the regulation of cerebral perfusion.[116,117] Sympathetic stimulation has been reported to reduce CBF in cats[118] and dogs,[119] whereas no change has been observed in baboons.[120] Parasympathetic stimulation has been reported to increase CBF in cats.[121] Increased CBF after stellate ganglion block has also been observed in humans by SPECT with ^{99m}Tc-labeled PAO.[122] Previously, we measured changes in CBF and myocardial blood flow (MBF) in relation to mental stress in humans by dual-PET.[123] MBF, blood pressure, heart rate and plasma concentrations of adrenaline and noradrenaline increased significantly during mental stress. Although these sympathetic responses were observed, no significant change in global CBF was observed. In general, neurogenically induced changes in CBF due to sympathetic innervation are considered to be very small.[23]

CEREBRAL VASCULAR COMPONENT

The CBV in a brain region is the sum of three components: arterial, capillary and venous blood volumes.[22,124,125] The arterial blood volume fraction for systemic circulation is reported to be 20–30%.[126] The radioactivity concentration in arterial blood can be differentiated on a regional time-activity curve of $H_2{}^{15}O$ by kinetic analysis. Therefore, the arterial blood volume in the brain can be determined.[125] A PET study showed the arterial blood volume fraction to be approximately 30% in humans.[127] The capillary blood volume is considered to be negligibly small[22]; however, capillary blood volume in the living human brain is unknown. The fraction of capillary blood volume per total volume of brain tissue was reported to be approximately 2% in cats.[128]

Changes in arterial blood volume and CBV during hypercapnia and hypocapnia were investigated by PET and MRI. Results by PET showed that changes in human CBV during hypercapnia and hypocapnia are induced by changes in arterial blood volume without changes in venous blood volume (Fig. 6).[129] Increases in blood volume and vessel diameter in arteries but not veins during hypercapnia have also been observed in the rat brain by ^{19}F nuclear magnetic resonance.[89] CO_2 diffuses through the blood-brain barrier and induces a change in extracellular pH.[66,68,69] Changes in extracellular pH then induce changes in the diameter of arterioles as a direct effect of H^+ on vascular smooth muscle.[70–73] Because arterial blood volume measured by PET and MRI includes the blood volume of cerebral arterioles, the findings obtained from PET and MRI studies correspond well with physiologic observations. In addition, increased arterial blood volume during acetazolamide stress has also been observed in the human brain.[130]

CEREBRAL VASCULAR TONE

Normal human CBF under resting conditions has been investigated by PET,[29–31] and its coefficient of variation has been reported to be approximately 20%. Interindividual variation of cerebral vascular tone may contribute such interindividual variation in CBF. Several determinants of cerebral vascular tone, including sympathetic innervation of intracranial arterioles,[131] nitric oxide (NO)[132] and potassium (K^+) channels,[133] have been proposed.

We have investigated regional differences in cerebral vascular tone by assessing vascular responses to changes in P_aCO_2 by PET.[67] In the temporal, temporooccipital and occipital cortices, little capacity for vasodilatation and a large capacity for vasoconstriction were observed, which suggests that the cerebral vascular tone at rest tends toward vasodilatation in these regions (Fig. 7). The capacity for neocortical vasodilatation in hypercapnia was greatest in the frontal cortex, suggesting that cerebral vascular tone tends toward vasoconstriction in this neocortical region (Fig. 7). Such regional differences in cerebral vascular tone were also related to regional differences in cerebral vascular MTT; MTT of neocortical regions was shortest in the frontal cortex and longest in the temporooccipital and occipital cortices.[134] Regional heterogeneity of sympathetic innervation of intracranial arterioles has been reported. For example, the occipital lobe shows less sympathetic innervation than other brain regions show.[131] Less sympathetic innervation in the

occipital lobe may be related to the tendency of the cerebral vascular tone at rest toward vasodilatation. In addition, it has been reported that sympathetic innervation of intracranial arterioles acts to protect against acute arterial hypertension.[135] Less sympathetic innervation in the occipital lobe may also be related to hypertensive encephalopathy, which is characterized by cerebral vasodilatation and breakdown of the blood-brain barrier and is often seen as brain edema in the occipital and/or temporooccipital cortices.[60,61]

MTT in the cerebellum, thalamus and putamen was shorter than that in all other regions,[134] indicating that CPP was greatest in these regions because MTT is inversely proportional to CPP.[6,11] It has been reported that these regions have a large capacity for vasodilatation in response to hypercapnia, suggesting that cerebral vascular tone in these regions tends toward vasoconstriction.[67] This tendency may also be related to high CPP in these regions. In addition, the cerebellum, thalamus and putamen are common sites of hypertensive intracerebral hemorrhage.[136] The cause of the regional differences in CPP is unknown but may be related to anatomical variations in cerebral vasculature.

CONCLUSION

We reviewed the literature on human cerebral circulation and oxygen metabolism measured by PET with respect to normal values and regulation of cerebral circulation. A multicenter study in Japan revealed normal values of CBF, CBV, OEF and $CMRO_2$ with acceptably small inter-individual variation overall. Several factors are involved in intrinsic regulation of cerebral circulation: autoregulation in response to changes in CPP; chemical control of CBF, e.g., P_aCO_2; metabolic regulation due to changes in neural activity; and neurogenic control of CBF by sympathetic innervation. Regional differences in vascular response to changes in P_aCO_2 have been reported, thus indicating regional differences in cerebral vascular tone. Relations between CBF and CBV during changes in P_aCO_2 and during changes in neural activity were in good agreement with Poiseuille's law. The mechanisms of vascular response to neural activation and deactivation were independent of those of responses to P_aCO_2 changes. CBV in a brain region is the sum of three components: arterial, capillary and venous blood volumes. It has been reported that the arterial blood volume fraction is approximately 30% in humans and that changes in human CBV during changes in P_aCO_2 are caused by changes in arterial blood volume without changes in venous blood volume. These findings should be considered in future studies the pathophysiology of cerebrovascular diseases.

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