Brain perfusion
part 1: regulation mechanisms and measurements of brain perfusion

Hersenperfusie
deel 1: regulatie en bepaling van de hersenperfusie

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ABSTRACT

Diagnostic procedures aimed at *in vivo* evaluation of brain perfusion as an indirect measure of brain function are becoming available for use in small animal medicine, though in contrast with human medicine, these procedures frequently require anesthesia. Besides the direct influence of anesthetics on cerebral perfusion, anesthesia can also cause changes in blood pressure and in arterial carbon dioxide and oxygen tensions. All these parameters have an influence on cerebral perfusion, so it is crucial to understand cerebral blood supply and its regulation when measuring cerebral blood flow.
The requirements of anesthesia when using the different diagnostic techniques, together with the technical properties of these techniques, are highlighted in this paper.

SAMENVATTING

Meer en meer komen diagnostische mogelijkheden ter beschikking voor de *in vivo* meting van de hersenperfusie als maat voor de hersenfunctie bij kleine huisdieren. Een groot verschil met de humane geneeskunde is de nood aan anesthesie tijdens het uitvoeren van deze procedures. Anesthetica hebben niet alleen een directe invloed op de hersenperfusie, maar veroorzaken eveneens veranderingen in de bloeddruk en in de arteriële koolstofdioxide- en zuurstofspanningen. Aangezien al deze parameters de hersenperfusie kunnen beïnvloeden, zijn kennis van de bloedvoorziening van de hersenen en de regulatie ervan van groot belang wanneer men de hersenperfusie wil meten. In dit artikel worden de technische specificaties van de verschillende technieken en de eventuele behoefte aan anesthesie besproken.

INTRODUCTION

Imaging techniques aimed at *in vivo* evaluation of brain perfusion as an indirect measure of brain function are currently becoming available for veterinary application. The most important difference in veterinary medicine is the need for anesthesia for these procedures, which may influence the measurement of cerebral blood flow (CBF). Indeed, CBF changes have been clearly demonstrated after the administration of different anesthetics in man and in different animal species, including dogs, primates and rabbits (Morita *et al.*, 1977; Roald *et al.*, 1986; Yeh *et al.*, 1988; Karlsson *et al.*, 1990; Zornow *et al.*, 1990; Lutz *et al.*, 1991; Van Aken and Van Hemelrijck, 1991; Dormehl *et al.*, 1993; Werner, 1995; McPherson *et al.*, 1997; Ohata *et al.*, 1999; Nagase *et al.*, 2003).

Assessment of these anesthetic-induced changes in CBF, however, requires a high level of understanding of the normal brain physiology, the anatomy of the blood vessels and other factors influencing the CBF. In the present review, the physiological CBF regulation and the different techniques for measuring CBF are highlighted.

CEREBRAL BLOOD SUPPLY

The blood supply to the brain originates from two major sources: the internal carotid arteries (*a. carotis interna*), which form the anterior cerebral circulation, and the vertebral arteries (*a. vertebralis*), which merge into the basilar artery (*a. basilaris*) and supply the posterior cerebral circulation (Jenkins, 1972). The bilateral sources of the blood supply are joined at the base
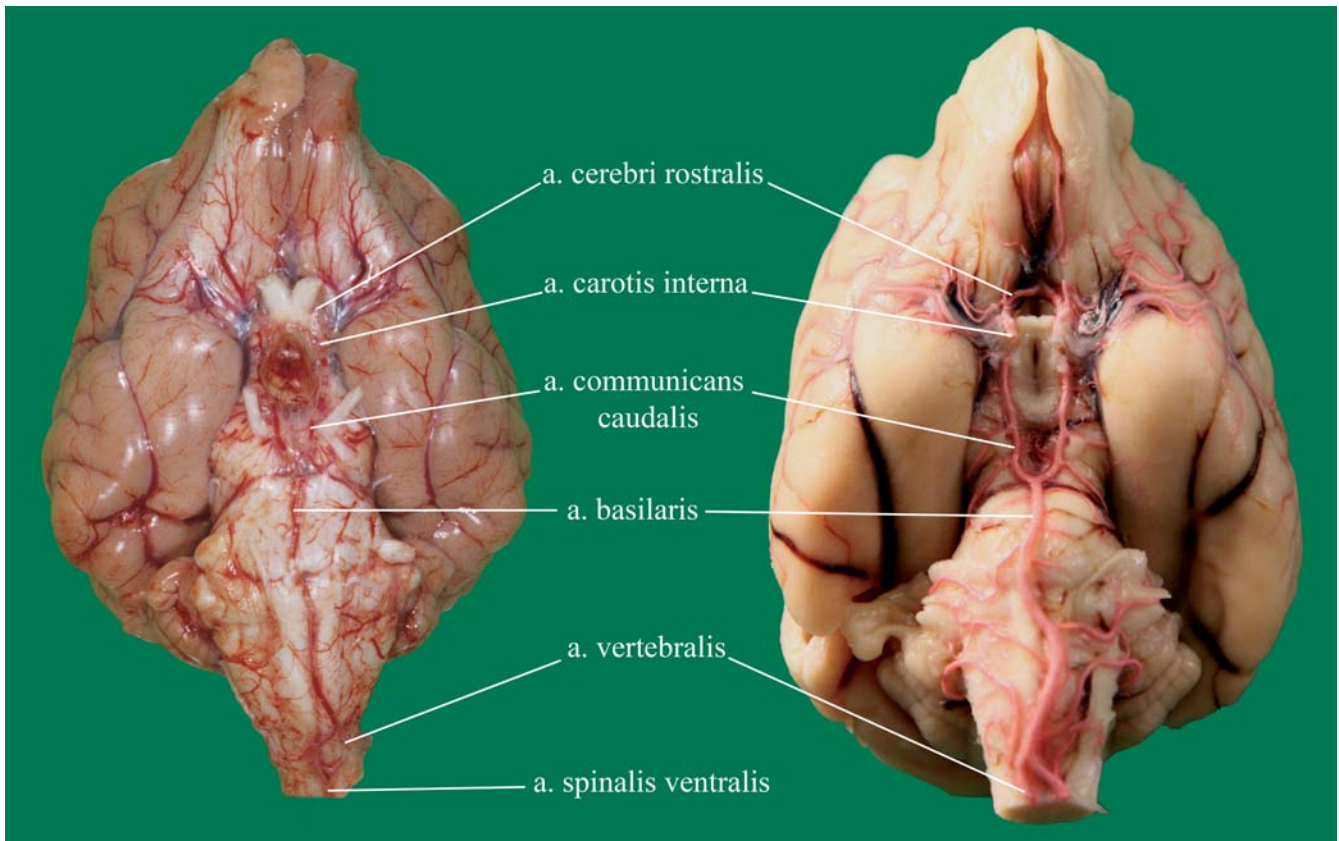
Figure 1. Topography of the circulus arteriosus cerebri (circle of Willis) and its supplying arteries on the ventral surface of the canine brain. Left: non-fixated brain; right: brain fixated in 3.5% formaldehyde after arteries were injected with latex.

of the brain by the *circulus arteriosus cerebri*, the so-called circle of Willis, which is typical for mammals (Figure 1). Overall, there are four potential arterial channels to this cerebral arterial circle in mammals: the internal carotid arteries, the basilar artery, the maxillary arteries (with anastomosing branches to the internal carotid arteries, forming a *rete mirabile* in the cat), and the vertebral arteries. The left and right vertebral arteries merge with the ventral spinal artery (*a. spinalis ventralis*) to supply the basilar artery. The internal carotid arteries consist of an extracranial and an intracranial part. The basilar and the intracranial part of the internal carotid arteries together form the circle of Willis (Jenkins, 1972; Simoens *et al.*, 1979; King, 1987). The general anatomic pattern of these afferent vessels is similar in all mammals, although the details of the vessels and the extent of their anastomoses can differ. In some species, for example, the maxillary arteries are more developed than the internal carotid arteries, whereas in other species the internal carotid arteries are more developed (King, 1987). In cats, the lumen of the proximal two-thirds of the internal carotid artery is obliterated in the first weeks or months after birth and the intracranial part of the internal carotid artery is supplied by anastomosing branches between the maxillary arteries and the internal carotid arteries forming a *rete mirabile*. Consequently, a significant part of the brain is supplied by maxillary blood, whereas in dogs, on the other hand, the anastomosing branch of the maxillary artery is quite slender (King,

1987). Compared to humans, the vertebral arteries in dogs are of more importance for the total blood supply to the brain. Furthermore, an adequate blood supply to the canine brain is ensured by anastomoses between the two internal carotid arteries, between the latter and the maxillary arteries, and between the vertebral, occipital and deep cervical arteries. These differences might explain why cerebrovascular diseases are less common in dogs than in humans (Garosi and McConnell, 2005). Functionally, the arterial circle of the brain provides anastomotic channels for the distribution of blood required for different physiologic demands and serves as a stabilizer for the maintenance of constant blood pressure in the terminal arteries that arise from the circle (Jenkins, 1972).

REGULATION OF CEREBRAL BLOOD FLOW

The net pressure gradient causing blood flow to the brain is called the cerebral perfusion pressure (CPP). Since CPP is closely related to CBF, maintenance of cerebral blood flow depends on a balance between the pressure within the skull (intra cranial pressure, ICP) and the mean arterial blood pressure (MAP) (CPP = MAP – ICP). However, when the central venous pressure (CVP) is higher than the ICP, CPP becomes the difference between MAP and CVP (Morgan *et al.*, 2006). In humans, at normothermia and at rest in the awake subject the mean perfusion pressure generally exceeds 70 mmHg (Harrington *et al.*, 2007). Total
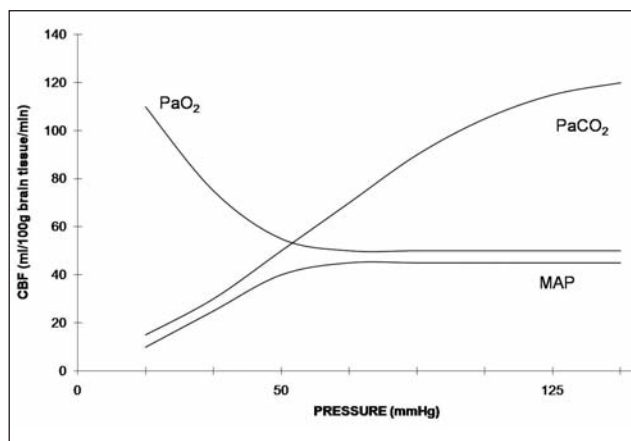
Figure 2. Cerebral blood flow alterations. Alterations in cerebral blood flow (CBF) caused by changes in the partial arterial oxygen pressure (PaO_2), the partial arterial carbon dioxide pressure ($PaCO_2$) and the mean arterial blood pressure (MAP). (after Shapiro, 1975)

CBF averages 50 ml/100 g brain tissue/minute; however, differences exist between gray and white matter. Blood flow in the gray matter is about 80 ml/100g/minute, whereas flow in the white matter is 20 ml/100g/minute (Morgan *et al.*, 2006). In the awake normal canine brain, normal EEG function is expected with a CBF of 50 ml/100g brain tissue/minute (Thurmon *et al.*, 1996).

In healthy awake animals, blood supply to the brain is controlled by autoregulatory mechanisms, which keep CBF constant in the face of perfusion pressure changes. However, alterations in CBF can occur as a result of changes in metabolic rate, arterial oxygenation, arterial carbon dioxide tension, mean arterial pressure and venous outflow (Figure 2). As already mentioned, sedatives and anasthetics can also cause changes in CBF (Prielipp *et al.*, 2002; Harvey *et al.*, 2007).

Autoregulation of cerebral blood flow

Autoregulation, also called pressure-flow reactivity, is the intrinsic ability of an organ or a vascular bed to maintain constant perfusion in the face of arterial blood pressure changes (Gao *et al.*, 1998). In the brain, an abrupt change in blood pressure is followed immediately by parallel changes in CBF; it takes about 5 to10 seconds for the autoregulation to return the flow back to baseline (Tiecks *et al.*, 1995). The original concept of cerebral blood flow pressure autoregulation stipulates that CBF maintains a plateau, sometimes with a slight slope, between mean cerebral perfusion pressures (CPP) of 50 to 140 mmHg (Figure 2) (Lassen, 1959; Powers, 1991). It was confirmed that autoregulation of cerebral blood flow is indeed very effective in this pressure range (Harvey *et al.*, 1996). However, animal experiments and human observations give varying values for normal CBF, but also for the lower and upper limits of autoregulation. This discrepancy can be attributed to species differences, CBF me-

thodology and the use of anesthetic agents (Gao *et al.*, 1998).

The main compensatory response depends on the ability of precapillary resistance vessels to react to changes in regional cerebral perfusion pressure (rCPP). To maintain this rCBF, pial arterioles contract when rCPP increases and dilate when rCPP decreases (Greisen, 2005). If rCPP continues to decrease (between 60 and 30 mmHg), the capacity for compensatory vasodilation can be exceeded, which leads to autoregulation failure, which in turn causes (r)CBF to decrease (Catafau, 2001). In dogs, CBF remains unchanged when CPP is reduced down to 60% of the control value due to a compensatory decrease in cerebral vascular resistance (CVR). However, a further decrease of CPP to 50% or 40% is not compensated, and this causes a sharp fall of CBF (Artru *et al.*, 1989).

Interestingly, significant variations were observed in the cerebral autoregulation in hypotensive rats, which challenges to some extent the classic and accepted description. Two phenomena were reported: hyperautoregulation, in which the vasodilation was greater than that required to maintain blood flow, and a lack of vasodilation in rats with CPP between 30 and 90 mm Hg (Jones *et al.*, 2002).

Partial arterial carbon dioxide pressure ($PaCO_2$) and cerebral blood flow

Together with autoregulation, the cerebrovascular response to changes in CO_2 is an important mechanism in maintaining adequate blood flow to the brain (Kety and Schmidt, 1948; Grubb *et al.*, 1974). Normal ranges of the $PaCO_2$ are 35 to 45 mmHg (4.6-6 kPa) (Akca, 2006). The golden standard for the determination of $PaCO_2$ is an arterial blood gas analysis. $PaCO_2$ can be estimated indirectly by measuring the CO_2 in a gas sample at the end of an exhalation (end-tidal PCO_2 or $ETCO_2$). In healthy humans and dogs, where more or less normal ventilation/perfusion conditions in the lungs exist, changes in $ETCO_2$ were shown to correlate well with changes in $PaCO_2$ (Young *et al.*, 1991; Haskins, 2007). This is not the case in anesthetized and critically ill patients, where the relationship between $ETCO_2$ and $PaCO_2$ is variable due to changes in breathing pattern, but also due to the occurrence of atelectasis (Hoffman *et al.*, 1989; Russell and Graybeal, 1992).

In the range of $PaCO_2$ from 20 to 80 mmHg, the cerebral blood flow increases by about 2 ml/min/100g of brain tissue for every 1 mmHg increase in $PaCO_2$. This increase of CBF is the result of cerebral vasodilation, mainly mediated through changes in extracellular pH (Dormehl *et al.*, 1993; Golding *et al.*, 1999; Giardino *et al.*, 2007). Rat studies have shown that the relationship between $PaCO_2$ and CBF can be represented in a sigmoid graph with two plateaus, one below 25 mmHg and another above 75 mmHg. Within this range, the CBF increases linearly from 100 ml/min/100g to 200 ml/min/100g (Figure 2). Therefore, even small changes in respiration that alter $PaCO_2$

can produce significant changes in global CBF (Duong *et al.*, 2001). However, the degree to which CBF is altered by changes in $PaCO_2$ decreases progressively with age and during periods of hypotension, and it is also brain region dependent (Giardino *et al.*, 2007). Indeed, a significant hyperperfusion of pons, cerebellum and thalamus was observed during periods of hypercapnia, suggesting a larger capacity for vasodilation compared with anterior and occipital cortices (Ito *et al.*, 2000).

As blood pressure and $PaCO_2$ can change simultaneously, mutual interference has to be considered. Cerebral vasodilation induced by hypotension, for example, abolishes partially hypocapnia-induced cerebral vasoconstriction in dogs (Artru *et al.*, 1989). When the cerebral autoregulation is intact, and in the absence of cerebrovascular disease, hypocapnia does not reduce global CBF to a level likely to produce ischemia. A decrease in $PaCO_2$ is still accepted as a useful tool to decrease CBF, as long as CPP remains above the lower limit of autoregulation (Artru *et al.*, 1989).

Partial arterial oxygen pressure and CBF

Whereas the relationship between $PaCO_2$ and CBF is linear (between 25 and 75 mmHg), changes in CBF in response to a decrease in PaO_2 only occur at very low arterial oxygen tensions (Figure 2). When PaO_2 decreases below 50 mmHg, vascular resistance decreases in order to increase CBF and maintain the essential cerebral oxygen delivery (Kety and Schmidt, 1948; Shapiro, 1975; Quint *et al.*, 1980).

Other factors that cause vasodilation or vasoconstriction of cerebral vessels can alter the degree of compensation or *vice versa*. Hence the responsiveness of the cerebral vasculature to hypercarbia during hypoxia depends on the level of hypoxia.

MEASURING CEREBRAL BLOOD FLOW (CBF)

An ideal imaging technique would enable continuous non-invasive measurement of blood flow and metabolism across the whole brain. Unfortunately, none of the imaging techniques currently available fulfils this ideal (Coles, 2006). Moreover it would be interesting for veterinary medicine to perform measurements without the need for sedation or even general anesthesia, as both alter cerebral perfusion and metabolism. However, most techniques require general anesthesia in small animal patients under clinical circumstances.

Several methods can be used for determining CBF. There is a major difference between the quantification of global and regional CBF, absolute and relative quantification and, last but not least, the clinical and experimental situations.

Absolute quantification of global cerebral blood flow in dogs can be obtained using a venous outflow technique (Zornow, *et al.*, 1990). This method consists of catheterization of the sagittal sinus after craniotomy, isolation of the cerebral venous drainage from extracranial sources and the determination of the weight of the brains after euthanasia. With this technique, absolute quantification is possible and the CBF is expressed in ml per 100g brain tissue per minute. The use of a closed cranial window, where catheterization of the sagittal sinus is combined with the measurement of pial arterioles and venules using a videomicrometer attached to a microscope, has also been described in rabbits and dogs (Ohata *et al.*, 1999; Nagase *et al.*, 2003). The advantage of this technique is that the reaction of the pial vessels can be studied. The major disadvantage of both methods is the highly invasive and very complicated procedure, for which reason they are strictly reserved for experimental conditions.

The measurement of regional brain activity can be performed with the help of functional brain imaging modalities. These imaging modalities measure changes in regional cerebral blood flow (rCBF) or metabolism. Regions of interest are analyzed over different brain areas and the values obtained can be compared with a normal database. By comparing regional brain activity during experimental conditions with regional brain activity during control conditions, functional activations can be analyzed (Jueptner and Weiller, 1995).

In most (clinical) circumstances, the methods for relative quantification of regional or global blood flow changes are just as useful as the absolute quantification of CBF.

FUNCTIONAL IMAGING MODALITIES BASED ON THE USE OF RADIONUCLIDES

Positron emission tomography

Positron emission tomography (PET) is a non-invasive diagnostic tool that uses positron emitting radionuclides. PET provides tomographic images of quantitative parameters, including regional cerebral blood flow (rCBF), regional cerebral blood volume (rCBV), regional oxygen extraction fraction (rOEF), regional cerebral metabolic rate of oxygen and glucose ($rCMRO_2$ and rCMRGl), etc. (Wintermark *et al.*, 2005). These measurements can only be done sequentially because different radiopharmaceuticals are needed to investigate different parameters. When sampling of arterial blood is possible, PET also allows accurate *in vivo* quantification with good regional resolution in humans (Kaisti *et al.*, 2003).

A PET-based imaging technique using [^{15}O] H_2O has been described in rats to quantify CBF. To avoid invasive arterial blood sampling, dynamically acquired PET images of the heart were used (Iida *et al.*, 1992; Yee *et al.*, 2005).

Due to inherent resolution limits and partial volume effects, CBF is difficult to measure accurately in small areas of low activity surrounded by areas of high radioactivity (Prielipp *et al.*, 2002). Other limitations are the very short half-life of the tracers and the fact that the tracers must be generated by a cyclotron, which has to be in the immediate vicinity of the camera (Pe-

remans *et al.*, 2003). The fact that some of the tracers ($^{15}O_2$, $C^{15}O_2$, $C^{15}O$) need to be inhaled, together with the high cost of this technique, is a major disadvantage, especially in veterinary medicine (Coles, 2006). On the other hand, the main advantages of the PET technique are its non-invasiveness and its sufficient quantitative accuracy (Wintermark *et al.*, 2005).

Single Photon Emission (Computed) Tomography

To quantify rCBF by means of brain perfusion, Single Photon Emission (Computed) Tomography (SPE(C)T) with inhalation of the diffusible gas ^{133}Xe is still used as a "gold standard" in many human hospitals where PET is not available. However, because of the short acquisition time and the low γ-ray energy of ^{133}Xe, this isotope is less than optimal to obtain good-quality SPECT images. Secondly, because ^{133}Xe inhalation requires active cooperation, patients with respiratory impairment cannot be studied adequately (Catafau, 2001).

Because of these disadvantages, retention tracers such as ^{99m}Tc-HMPAO (hexamethylpropyleneamine oxime) and ^{99m}Tc-ECD (ethyl cysteinate dimer) were developed and are now more commonly used for clinical SPECT imaging of brain hemodynamics in man (Wintermark *et al.*, 2005). Both technetium labeled lipophilic tracers cross the blood brain barrier after intravenous injection and are rapidly trapped intracellularly in the brain by enzymatic conversion, in proportion to the rCBF at the time of injection, thus creating a so-called frozen image (Figure 3) (Ichise *et al.*, 1997; Catafau, 2001). This is an important characteristic, as the tracer can be injected while the subject is performing a specific task, at the onset of an epileptic fit or at the moment of maximum central effect of a drug, while the acquisition can be done later. The SPECT images will reflect brain activity at the time of injection. The initial uptake of the tracer remains unchanged up to at least 2 hours post-injection, independent of rCBF changes occurring after the fixation time (Catafau, 2001).

In humans, a linear relationship and good correlation have been reported between rCBF measured with 99mTc-ECD and ^{133}Xe rCBF results in a limited range of flows, with a decrease at the upper end of normal resting values (Devous *et al.*, 1993).

An important limitation of SPECT is that, due to attenuation, scatter and partial volume effects, the photons registered are not with certainty derived from the actual region of interest, which precludes absolute quantification methods and, compared to PET, results in under- and overestimation of higher and lower rCBF regions, respectively (Peremans *et al.*, 2003). Hence, absolute rCBF measurement using SPECT has not been fully implemented and the region of interest (ROI) analysis of rCBF has become the preferred method of quantification (Catafau, 2001). This so-called semiquantification, which can be performed by normalizing the average regional counts to total counts of the individual brain, allows an estimation of the rela-
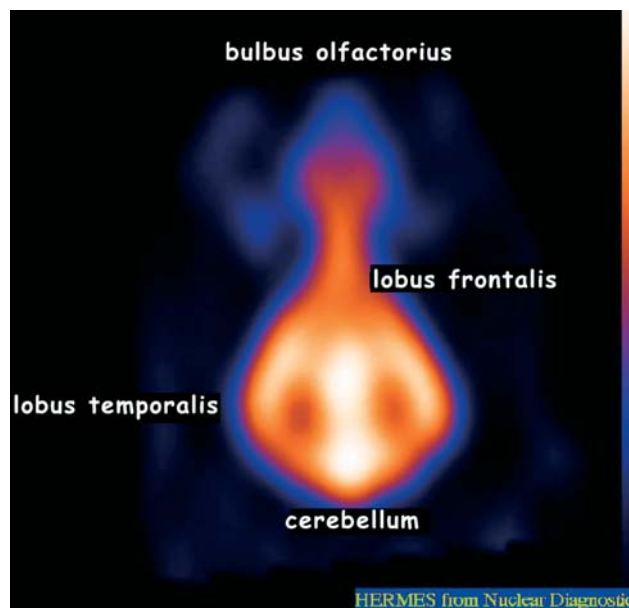

Figure 3. Single Photon Emission Computed Tomography. Horizontal image of a brain perfusion study in the dog obtained with ECD-SPECT. Tracer (ECD) injection was performed before isoflurane anesthesia.

tive rCBF distribution within the brain (Peremans *et al.*, 2001). Comparisons between counts in a ROI and those in an analogous region in the opposite hemisphere or those in a cerebellar hemisphere can also be used (Latchaw, 2004).

The two most important advantages of the SPECT technique for veterinary medicine are that images reflecting brain perfusion in the awake animal can be obtained by injecting the tracer in the awake animal before the acquisition under general anesthesia and that, compared to PET, it is more economical.

FUNCTIONAL IMAGING MODALITIES BASED ON THE MAGNETIC CHARACTERISTICS OF MATTER

Although it is possible to quantify CBF by using Magnetic Resonance Imaging (MRI) in humans and small animals, this technique is mostly used for measuring changes in CBF or differences between an "abnormal" brain region and the contralateral area as the normal reference region.

MRI methods can be used not only for measuring CBF, but also for the measurement of cerebral blood volume (CBV) and the interaction between cerebral blood flow and oxygen utilization, which is called the blood oxygenation level dependent (BOLD) contrast (Leontiev *et al.*, 2007).

Measuring CBF in MRI can be accomplished by using dynamic susceptibility contrast or arterial spin labeling techniques (Belliveau *et al.*, 1991; Detre *et al.*, 1992). Whereas the PET technique is still considered to be the 'gold standard' in CBF measurements in humans, MRI is gaining in popularity (Feng *et al.*, 2004).

Dynamic susceptibility-weighted (DSC) bolus-tracking MRI or contrast agent dynamic perfusion, which is commonly referred to as perfusion-weighted MRI

(PWI), relies on the measurement of the T2 or T2* decrease during the first pass of an exogenous endovascular tracer through the capillary bed, as this contrast medium induces a change in intravascular magnetic susceptibility (Figure 4) (Grandin, 2003; Latchaw, 2004). The tracer used is a conventional chelate of gadolinium, injected into a peripheral vein (Rosen *et al.*, 1990). PWI is routinely combined with diffusion-weighted MRI (DWI), which images the microscopic movement of water to obtain a so-called perfusion/diffusion ratio. A PWI/DWI mismatch has been used to diagnose early cerebral ischemia in man (Davis *et al.*, 2005).

Semi-quantification of regional CBF can be performed by calculating the ratio or difference between the values in a region of interest (ROI) in the abnormal area and a "mirror ROI" placed in the contralateral area considered to be a normal reference (Wintermark *et al.*, 2005). If an adequately calibrated arterial input fraction (AIF) is available, absolute quantitative CBF maps can be obtained (Ostergaard *et al.*, 1998b). Several studies in man have demonstrated a good correlation between the absolute CBV and CBF values obtained with this technique compared to PET or Xenon enhanced CT (see next paragraph), when arterial input was determined (Ostergaard *et al.*, 1998a; Hagen *et al.*, 1999). Other authors, however, report methodological problems, which continue to limit the wide implementation of quantitative imaging with this technique (Latchaw, 2004).

Arterial spin labeling (ASL), also called arterial spin tagging, uses magnetically labeled arterial blood water as an endogenous flow tracer that is analogous to the ^{15}O-H$_2$O used in PET measurements of cerebral blood flow (Detre *et al.*, 1992; Wintermark *et al.*, 2005). Due to its simplicity and cost efficiency, ASL-based MRI technique has played a dominating role in the functional MRI (fMRI) domain, as compared to the contrast-agent dynamic perfusion-weighted MRI method (Feng *et al.*, 2004). CBF is determined in a semi-quantitative way by performing a simple subtraction between the averaged control and label images (Wintermark *et al.*, 2005). Although these techniques are now being successfully applied to clinical human settings, there are still unsettled methodological issues regarding the absolute quantification (Calamante *et al.*, 1999).

X-RAY BASED TOOLS

To measure CBF using Xenon enhanced Computed Tomography (XeCT), acquisition of a baseline structural scan without xenon inhalation is followed by serial scans at regular intervals during xenon inhalation. Several studies in man showed that this technique provides accurate, quantitative measurements of the CBF. After the data have been obtained, the absolute CBF can be calculated. However, these calculations are based on the assumption that the end-tidal xenon concentration is identical to the arterial concentration, which may not be the case, for example in patients with pulmonary disease (Wintermark *et al.*, 2005; Coles, 2006).
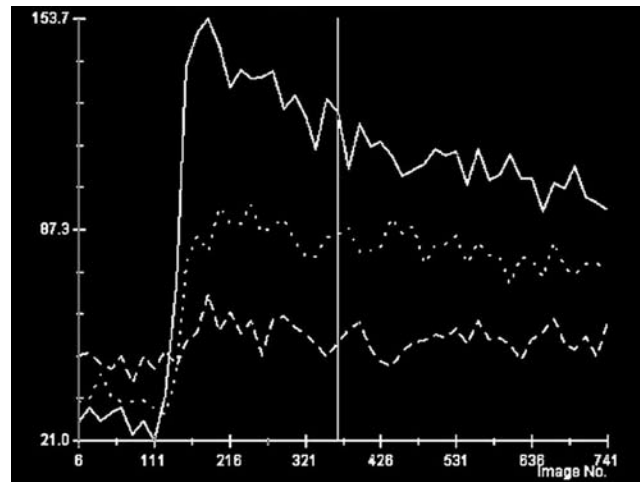

Figure 4. Functional MRI. MR perfusing study of a normal canine brain. There is a measure of signal intensity (y-axis) versus time (x-axis) as the contrast agent washes in and out on the first pass. The top line indicates an artery. The white matter is indicated by the dashed line. A vein is represented by the dotted line.

Dynamic perfusion CT (PCT) involves sequential acquisition of axial data and uses first-pass tracer methodology following bolus infusion of intravenous iodinated contrast material after the acquisition of unenhanced scans (Coles, 2006). It provides a quantitative determination of CBF. The main disadvantage is that only a certain region of interest can be scanned, as acquisition needs to be performed during the first pass of the tracer. Consequently, coverage of the whole brain becomes impossible (Latchaw, 2004).

ULTRASOUND-BASED TOOLS

Another tool for the assessment of changes in cerebral hemodynamics in man and small animals is the use of transcranial Doppler ultrasound flowmetry. By placing a Doppler probe over the temporal bone window, (changes in) cerebral blood flow velocity (CBFV) can be measured in the middle cerebral artery (MCA) (Nishiyama *et al.*, 1999; Conti *et al.*, 2006). In humans, ultrasound measurement of blood flow volume (BFV) in the internal carotid artery (ICA) can be used, as this correlates well with CBF in the corresponding hemisphere (Rothoerl *et al.*, 2003; Soustiel *et al.*, 2003). Mean flow velocity (MFV) can be used as a surrogate measure of changes in CBF, but only when the diameter of the insonated vessel does not change significantly, as a significant change in the diameter would alter the relation between the flow velocity and the actual blood flow (Conti *et al.*, 2006). The mean diameter change in the large cerebral arteries (carotid, middle cerebral artery, vertebral artery) during craniotomies in humans was reported to be less than 4%, with the smaller arteries showing larger changes in response to changes in PaCO$_2$ and blood pressure (Giller *et al.*, 1993). This constancy of diameter suggests that under such conditions transcranial Doppler velocities may closely reflect blood flow through the insonated artery.

One limitation of this technique is that CBF impairments that are confined to a rather small area or that are secondary to a single vessel pathology may be masked by a remaining and otherwise preserved hemispheric flow (Soustiel *et al.*, 2002). Also, as for any Doppler-based technique, attention should be given to minimizing user-related variations and errors (Wintermark *et al.*, 2005).

DYE-BASED TECHNIQUES

Another non-invasive technique for measuring regional blood flow is the combination of near-infrared spectroscopy (NIRS) with indocyanine green (ICG) dye dilution (Keller *et al.*, 2003). This technique uses a spectrophotometer with three laser diodes of different wavelengths, placed on the forehead. Optical density changes can be recorded by the NIRS system. After one minute of baseline data accumulation, ICG is injected intravenously and ICG concentrations are calculated based on the changes in optical density. The dye dilution curves are then recorded digitally so the rCBF can be calculated.

Preliminary data in healthy human volunteers indicate that the measurements are in agreement with the corresponding values obtained by perfusion-weighted MRI. Moreover, in patients with acute ischemic stroke, the measurement of indocyanine green kinetics by means of NIRS provided a useful tool for the detection of reduced perfusion (Terborg *et al.*, 2004; Bein *et al.*, 2006).

However, more validation data by additional comparisons with standard methods are needed (Keller *et al.*, 2003). Up till now, absolute CBF quantification has not been possible (Terborg *et al.*, 2004).

CONCLUSION

It can be concluded that, in the face of changes in blood pressure, brain perfusion is kept constant by autoregulation. However, changes in the cerebral blood flow can occur as a result of an increased or decreased arterial partial pressure of both oxygen and carbon dioxide.

All the above mentioned techniques for measuring the CBF can be used in small animals. However, with the exception of ultrasound Doppler and the NIRS and ICG dye dilution techniques, all of the techniques require sedation or general anesthesia in small animals. On the other hand, ECD- and HMPAO-SPECT are capable of providing images of awake veterinary patients without the influence of anesthetics, by injecting the tracer prior to anesthesia. However, in patients needing sedation or even general anesthesia before intravenous tracer injection, the influence of sedatives or anesthetics cannot be ruled out.

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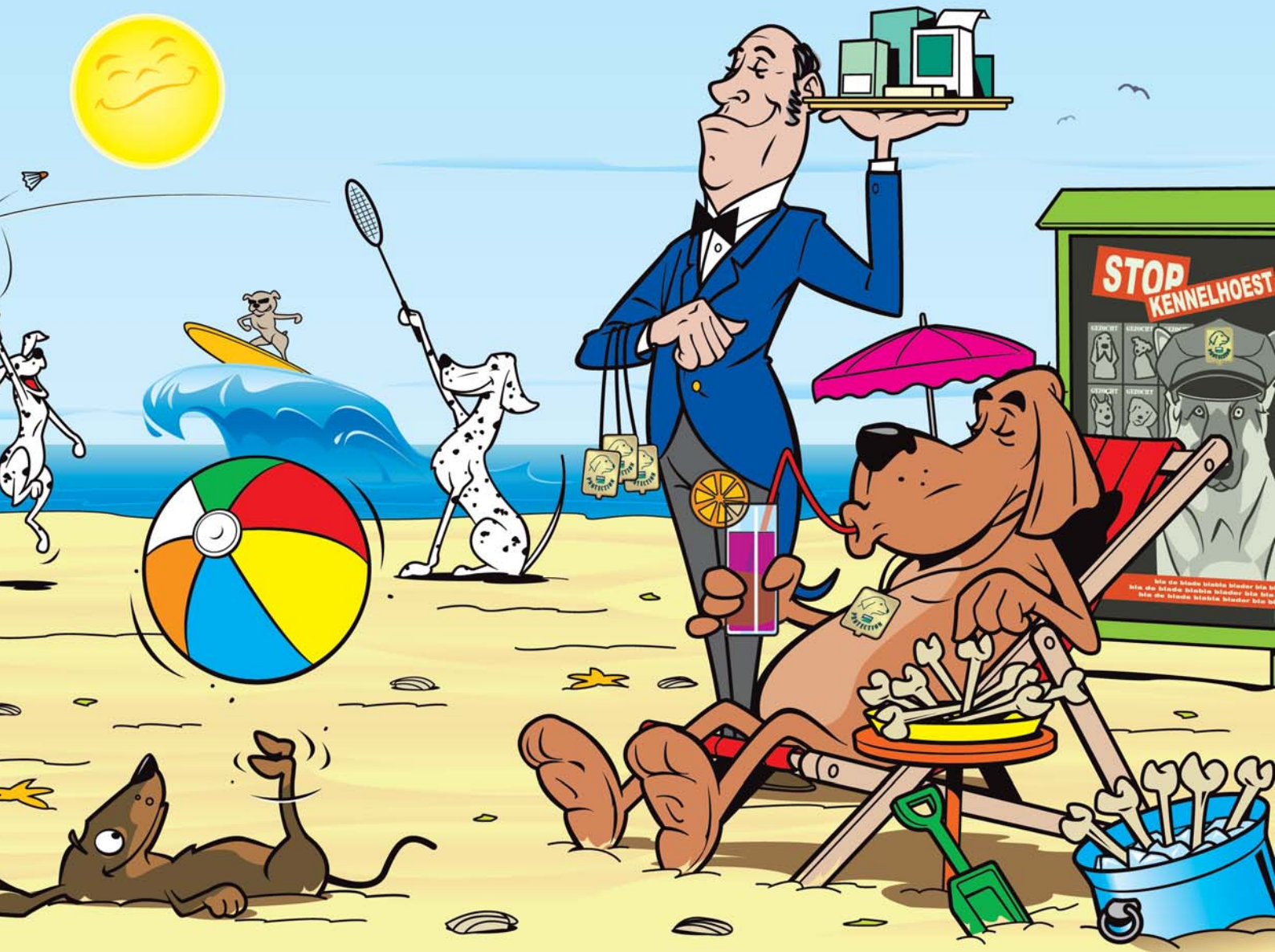
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