

# Chapter 2

## Measurement Techniques

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

### 2.1 Development of CBF Measurements

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

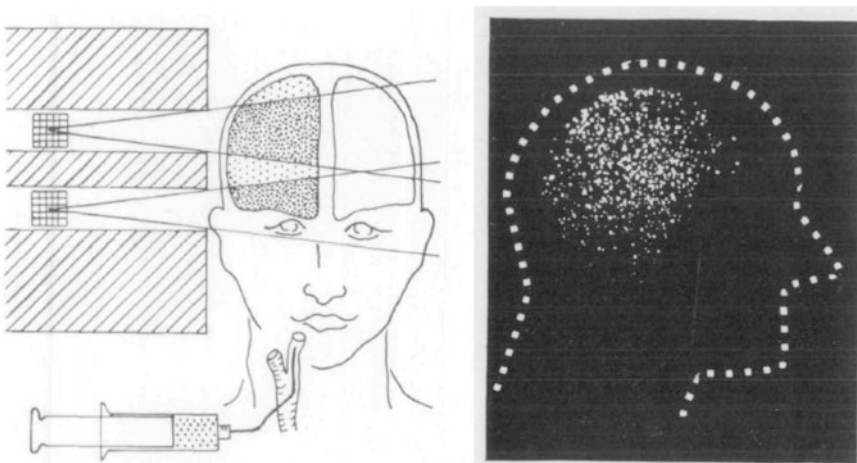
Nearly all imaging methods developed subsequently rely on the same principle to quantify CBF; that of tracking the passage of blood through the use of a tracer. Such tracers can be exogenous (where a tracer is injected into the bloodstream) or endogenous (where a property of the blood is tracked); the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

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

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

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

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



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

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

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

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

A similar methodology is positron emission tomography (PET), which can be used to measure a number of cerebral parameters, including regional CBF, regional CBV and regional oxygen extraction fraction. In order to measure CBF, a tracer such as  $^{15}\text{O}_2$ ,  $\text{C}^{15}\text{O}_2$  or  $\text{H}_2^{15}\text{O}$  is used; this is injected and, when coupled with an arterial blood sample measurement, the Kety-Schmidt model can be used to estimate CBF. The tracers are normally occurring biological substances that have been labelled with positron emitting radioisotopes, hence the name. Dynamic perfusion CT (PCT) is based on a bolus infusion of iodinated contrast into a vein; images are reconstructed in the same way as the methods above.

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

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

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

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

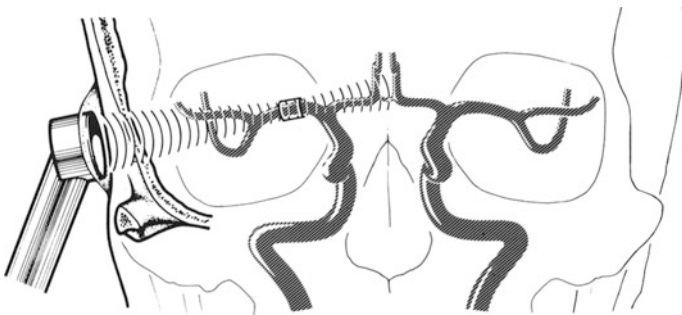
## 2.2 Transcranial Doppler

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

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

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

The first study to measure human cerebral arterial diameters directly was performed by Giller et al. (1993), who found that during craniotomy, there was only a small change in large arterial vessel diameter in response to changes in both ABP and end tidal CO<sub>2</sub> (the authors quoted an average of 4 % in response to changes of 30 and 14 mmHg respectively). It should be noted that the sample size used was



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

very small, except for the CA and ACA, which have sensitivities in diameter of 0.3 and 0.78 %/mmHg PaCO<sub>2</sub> respectively (compared to sensitivities to changes in ABP of 0.28 and 0.46 %/mmHg respectively). Note that the authors measured outer diameter, not the more relevant inner diameter, but the value for the CA is very similar to that of Willie et al. (2012).

Poulin et al. (1996) concluded that there was little change in the cross-sectional area with CO<sub>2</sub>, although they did not offer evidence directly to substantiate this statement, other than stating that the total power of the Doppler signal remained relatively constant (the signal power being taken to be a measure of cross-sectional area). It is worth noting that Numan et al. (2014) in their recent investigation of static autoregulation found no significant difference between the results obtained using TCD and other CBF estimation methods.

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

Willie et al. (2012) used ultrasound imaging to measure both CBFV and vessel diameter in the left ICA and the right VA simultaneously, as well as CBFV in the MCA and PCA; this was done for wide variations in both PaCO<sub>2</sub> (15–65 mmHg) and PaO<sub>2</sub> (36–434 mmHg). For changes in PaCO<sub>2</sub>, the ICA diameter was found to change in a strongly non-linear manner (from -6.6 % at 15 mmHg to 11.5 % at 65 mmHg, with a regression slope of 0.36 %/mmHg), but the VA diameter showed no change. No change in either diameter was found for changes in PaO<sub>2</sub>. The fractional change in CBF (ICA, VA) or CBFV (MCA, PCA) was found to be approximately 4 %/mmHg (PaCO<sub>2</sub>), although this was higher in hypercapnia than in hypocapnia, and -1.5 %/‰ (SaO<sub>2</sub>) in the ICA, MCA and PCA compared to -3 %/‰ in the VA. As the authors say, the cerebral vasculature is “exquisitely sensitive” to PaCO<sub>2</sub>, being slightly less sensitive to PaO<sub>2</sub>.

Serrador et al. (2000) also examined changes in MCA diameter and found no change in diameter either for changes in PaCO<sub>2</sub> (in the range 24–45 mmHg) or ABP (in the range baseline to baseline minus 40 mmHg). A later study measuring MCA diameter as a function of end-tidal CO<sub>2</sub> using MRI, Verbree et al. (2014), found that the relationship was non-linear and the authors used this to explain previous published results where the changes were found to be not significant. They quoted a study that gives a 3.8 %/mmHg increase in CBF, which would tally very closely with the ICA and give a diameter sensitivity of 0.4 %/mmHg, again very close to the ICA. There thus seems to be strong evidence that the sensitivity is non-zero at baseline conditions.

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

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

	ICA	MCA	PCA	ACA	VA
CBF/ABP	NS [L]				
D/ABP (%/mmHg)	0.28 ± 0.17 <sup>G</sup> -0.11 <sup>-L</sup>	NS <sup>S</sup>		0.46 ± 0.12 <sup>G</sup>	0.03 ± 0.01 <sup>G</sup>
CBFV/ABP (%/%)	0.22 ± 0.05 <sup>L</sup>	0.24 ± 0.07 <sup>L</sup>			
CBF/PaCO <sub>2</sub> (%/mmHg)	4.0 ± 0.38 <sup>W</sup>				4.4 ± 2.1 <sup>W</sup>
D/PaCO <sub>2</sub> (%/mmHg)	0.3 ± 0.09 <sup>G</sup> 0.36 <sup>W</sup>	NS <sup>S</sup>		0.78 ± 0.18 <sup>G</sup>	0.2 ± 0.1 <sup>G</sup> NS <sup>W</sup>
CBFV/PaCO <sub>2</sub> (%/mmHg)		2.9 ± 0.47 <sup>W</sup> 3.8 <sup>V</sup>	3.0 ± 0.62 <sup>W</sup>		
CBF/SaO <sub>2</sub> (%/%)	-1.71 ± 1.3 <sup>W</sup>				-3.3 ± 1.4 <sup>W</sup>
D/SaO <sub>2</sub>	NS <sup>W</sup>				NS <sup>W</sup>
CBFV/SaO <sub>2</sub> (%/%)		-1.39 ± 0.5 <sup>W</sup>	-1.19 ± 0.3 <sup>W</sup>		

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

Overall, the experimental results are found to be mostly consistent with each other. The sensitivity to  $\text{SaO}_2$  appears to be most consistent: both CBF and CBFV exhibit a consistent increase of approximately 1.5 %/% decrease in  $\text{SaO}_2$ , with the vessel diameter remaining invariant; the VA shows approximately twice this sensitivity, which implies that the supply vessels in the neck are more sensitive than those in the brain.

The behaviour in response to changes in  $\text{PaCO}_2$  is much more heterogeneous between vessels. The two studies for ICA diameter sensitivity are in very good agreement with each other, but other vessel diameters are both less and more sensitive; the results for CBFV sensitivity, however, are reasonably consistent at around 3 %/mmHg with the VA showing slightly greater sensitivity of 4.4 %/mmHg. Interestingly, CBFV appears to be more constant than CBF, although this is a somewhat tentative conclusion based on the current data.

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

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

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

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



## 2.3 Near Infra-red Spectroscopy

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

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

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

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

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

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

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

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

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

NIRS was first used to measure CBF by Edwards et al. (1988), essentially using O<sub>2</sub>Hb as a tracer together with the Kety-Schmidt model. To induce a change in O<sub>2</sub>Hb, arterial saturation is perturbed (for example through breathing 100 % oxygen): an increase in this saturation will result in an increase in O<sub>2</sub>Hb and, through making a number of assumptions, an expression for absolute perfusion can be derived. Thus CBF can be measured non-invasively with only one additional measurement (that of arterial saturation). This method is of course very similar to other indicator methods, but can be repeated more regularly since there is no ingestion of a radioactive substance; although the temporal resolution is obviously still much poorer than for TCD and a stimulus is still required. CBV can also be measured in a similar manner, Wyatt et al. (1990). The use of phenylephrine has also been proposed to measure autoregulation, Wagner et al. (2011).

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

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

$$TOI = \frac{O_2Hb}{O_2Hb + HHb} \quad (2.2)$$

and Tissue Haemoglobin Index (THI), defined as:

$$THI = k(O_2Hb + HHb) \quad (2.3)$$

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

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

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

## 2.4 MRI

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

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

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

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

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

## 2.5 Arterial Blood Pressure

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

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

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

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

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

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

## 2.6 Autoregulation Tests

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

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

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

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

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

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

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

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

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

The **transient hyperaemia** test has been shown to give results that are strongly correlated with clinical status in patients with neurosurgical disorders, Giller (1991). In healthy volunteers, it has been found to be highly reliable when used repetitively to detect changes in autoregulation at different CO<sub>2</sub> levels, Mahajan et al. (1998). It has been shown that factors such as the length of carotid artery compression and magnitude of the decrease in CBFV can significantly affect the transient hyperaemic response, although the effects on estimates of cerebral autoregulation have not been quantified, Cavill et al. (1998). Smielewski et al. (1996) compared results obtained

with the transient hyperaemia and thigh cuff tests at different levels of CO<sub>2</sub>. The responses were both significantly associated with CO<sub>2</sub> and there was a linear correlation between THRR results and ARI, although the THRR results were found to be more reproducible than ARI from single tests.

Passive cyclic leg raising has been proposed as a test by Elting et al. (2014), who examined whether fluctuations in the ABP could be increased and hence whether estimates of cerebral autoregulation would be more reproducible and less variable. Although they found that there was a correlation between phase and gain reproducibility and MABP variability in the rest condition, the manoeuvre only increased the reproducibility of the gain; it was found that during the leg raising end-tidal CO<sub>2</sub> increased in variability, reducing its utility. This is a common difficulty with this and similar manoeuvres that needs to be carefully considered.

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

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

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

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

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

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

## 2.7 Conclusions

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

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

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