PET/CT cameras and brain imaging

Since the introduction of the first systems in 2001, the field of clinical PET/CT has experienced impressive growth in terms of system design and functionality, supportive software solutions and the availability and range of clinically approved PET tracers. Developments were initially directed towards the creation of solutions for implementation primarily in systemic oncology, rather than in brain studies. Over the intervening years, however, clinical brain PET imaging has benefitted tremendously through the use of available equipment and organisation. The number of clinical brain PET scans at a clinical site might not initially be sufficient to justify the acquisition of a PET/CT scanner, but as a supplementary element in a production line dominated by oncology, brain PET studies can play a very significant role.

There are no technical or practical limitations, as such, to the potential uses of PET/CT scanners for clinical brain PET scanning. Unenhanced CT of the head is performed initially and may be either of a clinical quality for diagnostic reading or a low-dose CT scan for the purpose of attenuation correction. The CT scanning has a duration of <1 min, so the number of CT slices, 4–128, is of no practical consequence in clinical routine. The number of CT slices does not significantly impact the clinical CT quality. All PET/CT systems have an axial field of view of 15–21 cm and will, thus, be able to acquire a full 3D brain volume in one bed position (see "Fact Box" next page).

PET/CT clinical indications in neurological and vascular diseases

Dementias

Dementia is a syndrome characterised by deterioration in multiple cognitive functions, associated with functional impairment and with a chronic course, due to a brain dysfunction. Neurodegenerative dementias are increasingly prevalent, given their strong association with aging of the population, and are one of the most relevant causes of disability and dependency among elderly people [1]. Alzheimer’s disease (AD) is the most common form, accounting for up to 70% of cases; among other types, the most frequent are vascular dementia, dementia with Lewy bodies (DLB) and frontotemporal lobar degeneration (FTLD). The neurodegenerative process of dementia presumably lasts over decades, with a long preclinical phase without symptoms and a “prodromal” phase, identified by the term “mild cognitive impairment” (MCI), during which symptoms are mild, with a cognitive performance below average but without functional impairment [2]. The differential diagnosis among the various forms is a critical and complex process, particularly in these early phases. An early diagnosis is important for disease management and proper treatment and also represents a relief for patients and caregivers [3]. The different forms of dementia affect specific brain areas and neurotransmission systems and have different neuropathological features, identified by PET imaging, such as regional neuronal dysfunction or abnormal protein depositions; PET imaging is thus considered a "biomarker” of disease in the current recommendations on diagnostic guidelines [4].
FACT BOX

Tips and tricks for the technologist:

Optimising scanner use
A 10-min $^{18}$F-FDG PET brain scan can be performed 40 min p.i. Whole-body $^{18}$F-FDG PET/CT is performed 60 min p.i. Thus, brain PET/CT scanning need not occupy a time slot for whole-body PET/CT if it is performed as the first scan in the morning. The two patients for brain and whole-body PET scanning are injected at the same time point with $^{18}$F-FDG when it becomes available, and the brain scanning will be finished before the whole-body PET scanning needs to commence.

Head movements

The most important duty of the technologist in order to accomplish a successful and diagnostic PET brain scan is to ensure secure head fixation during the scanning period, and to identify any head movements that nevertheless occur. Patients with neurological diseases may have difficulties in understanding and retaining instructions, have seizures during scanning, be agitated or suffer age-related degeneration in the spine. All of these factors may contribute to head movements during scanning. It is important (a) to identify these “at risk” patients prior to scanning through direct contact with patients, caregivers and referring clinicians and inspection of patient history and (b) to take appropriate measures. Such measures might be:

- Secure head fixation in a sturdy head holder, and placement of a leg rest under the knees to prevent downward patient movement.
- Placement of marks on the skin using a marking pen.
- Performance of a list mode acquisition or a range of short dynamic scans, e.g. $5 \times 2$ min. If head movements occur during the scan, a reconstruction of the first 5 min may be of sufficient clinical quality.
- Control for significant movement (>5–10 mm) at the end of scanning. If such movement has occurred, repeat CT for attenuation correction alone or in combination with a new brain $^{18}$F-FDG scanning sequence depending on circumstances.

If head movements occur, the CT attenuation and PET emission scans will no longer be aligned and significant artefacts may be present. If these artefacts were to pass unnoticed, an erroneous diagnosis would be made (e.g. Fig 1). For more details, see the EANM guidelines [7].
Figure 1 A–C: Examples of typical $^{18}$F-FDG PET images in healthy young subjects who moved their heads after low-dose CT (CT-AC), causing misalignment and quantitative reduction in regional activity. To the right are statistical surface projections (Scenium, Siemens) comparing the subjects with a database of age-matched controls. The observed changes could have led to misdiagnosis in a clinical setting if their cause had gone unnoticed, underlining the importance of head fixation. (A) Coronal images showing the consequence of movement (1.0 cm) in the scanner in the axial direction, with false reductions in uptake in the frontal areas bilaterally (red arrows). (B) Sagittal images showing the consequence of rotation of the head anteriorly (1.2 cm), with false reductions in uptake in the mesial frontal areas bilaterally (red arrows). (C) Transverse images showing the consequence of rotation of the head to the left (1.0 cm), with false reductions in uptake in the left cortical hemisphere and false increases in uptake in the right cortical hemisphere (red arrows).
PET imaging of brain glucose metabolism, using $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) as the tracer, is a validated and routinely used method to show regional abnormalities, some of which are typical for the different dementia syndromes [5–7]. AD is characterised by hypometabolism involving the temporoparietal association cortices, in particular the precuneus and posterior cingulate cortex (an example is provided in Fig. 2). Patients with DLB have a pattern similar to AD patients, the hypometabolism often extending to the occipital cortex and possibly sparing the posterior cingulate region. FTLD includes various syndromes, such as the behavioural variant of frontotemporal dementia (bvFTD), characterised by hypometabolism in frontal regions, and corticobasal degeneration (CBD), which typically shows asymmetrical cortical (frontoparietal) and subcortical hypometabolism contralateral to the affected hemibody (Fig. 3). The visual identification of these specific patterns can be supported by various automated methods, usually based on the normalisation of individual images to a reference space and then on the semi-quantification of abnormalities relative to the distribution observed in a group of healthy subjects [8, 9]. An example is provided in Fig. 2.
During the last decade, specific tracers able to visualise amyloid plaques in vivo have been tested and validated in humans. The first was the $^{11}$C-Pittsburgh compound B ($^{11}$C-PiB), which was able to bind fibrillar amyloid with a good correlation with post-mortem measures [10–12]. More recently, $^{18}$F-labelled compounds, patented by industrial companies, have been approved by regulatory agencies both in Europe and in the United States for use in patients with prodromal or atypical dementia. These tracers have been validated in phase II and phase III trials for their ability to discriminate healthy controls and patients with AD and to identify amyloid deposits in vivo, as compared with results at autopsy [13, 14]. Different strategies for visual reading of the images have been proposed for the different tracers, based on the use of quantitative indices such as the ratio of the mean standardised uptake value (SUV) across cortical regions to the SUV measured in a reference region, typically the cerebellum. In general, a positive image shows significant cortical uptake of the tracer, while a negative image shows variable uptake in white matter and no relevant cortical signal (examples are provided in Fig. 4).
Figure 4: Examples of typical positive (upper row) and negative (lower row) amyloid PET images, obtained using an \(^{18}\text{F}\)-labelled tracer [in this case florbetapir (AV-45)].

Amyloid imaging is considered an early marker of the AD pathological process, reaching the threshold of positivity about 17 years before the clinical onset of overt dementia [15]. Appropriate criteria for the clinical use of amyloid PET imaging have been published recently [16]. In particular, this examination is advised for patients with persistent or progressive cognitive impairment that has an atypical or unclear clinical presentation or early onset (before 65 years of age). In subjects with MCI, amyloid imaging has a high positive predictive value for progression to AD [12]. A consistent finding across different amyloid PET imaging studies is that around 30% of cognitively normal elderly subjects have a positive scan, in agreement with the proportion of cognitively normal elderly subjects with an autopsy diagnosis of AD [17, 18]. These individuals might be at higher risk for subsequent development of dementia, but this is still a debated topic, currently under investigation. First, the expression of clinical disease is due to not only the amount of "pathology" in the brain but also the capacity of the brain to cope with damage, called the "reserve capacity." The concept of cognitive reserve is based on the observation that individuals with a high educational level and intelligence preserve a normal functional level for longer than less educated people, despite neurodegeneration [19]. Various PET studies have shown that cognitive reserve modulates the interaction between some measures of pathology and clinical severity [20–22]. Second, amyloid deposits are possibly the first event in the pathological cascade of AD, but by themselves do not account for cognitive decline: other factors, such as the
aggregation of hyperphosphorylated tau protein, play a central role in the onset and progression of neurodegeneration [2]. New PET tracers aimed at imaging tau aggregates are currently under development and preliminary results suggest that they may provide crucial information about the interplay of amyloid deposits and the earliest clinical signs [23].

Finally, a large panel of other PET tracers relevant to the investigation of dementias exists, e.g. tracers able to visualise different neurotransmission systems, such as the cholinergic or dopaminergic system, or to measure the occurrence of neuroinflammation, which is presumably a factor contributing to the progression of the neurodegenerative process [24]. These tracers, which are of utmost interest for a better understanding of the pathological processes of dementia, are still limited to dedicated research centres and are being evaluated in clinical trials.

**Epilepsy**

Epilepsy is one of the most common chronic neurological conditions, affecting 0.7% (0.5–1%) of the population. It has very significant social and professional consequences and is associated with increased mortality. Around 30–40% of patients with epilepsy suffer from focal seizures that are refractory to anti-epileptic drug treatment [25]. In these patients, surgical resection of the epileptic focus is the only treatment that can possibly cure the condition, and its success depends strongly on accurate presurgical localisation of the focal abnormality. $^{18}$F-FDG PET is one of the imaging modalities of choice for this purpose. The intravenous administration of the tracer has to be performed during EEG monitoring of the epileptic activity, which is a major determinant of the imaging findings. Indeed, while an “ictal” injection, during a seizure, will show the increased perfusion and metabolism in the epileptic focus, an “interictal” injection will depict the dysfunctional cortex (often including the epileptic focus and some regions of seizure propagation) as a hypometabolic area compared with the surrounding cortex [26]. Interictal imaging is preferable, given that truly ictal images require coordination of radiotracer availability and seizure onset and duration, which is difficult to assure. Interictal $^{18}$F-FDG PET has a sensitivity above 80% for identification of the epileptic focus in temporal lobe epilepsy [27–30]. The contribution of $^{18}$F-FDG PET imaging is particularly relevant when no lesion is identified on magnetic resonance imaging (MRI) or in the case of multiple abnormalities as it limits the need for invasive recording [26, 31]. Indeed, it has been reported that MRI-negative temporal lobe epilepsy patients with clear unilateral anterior temporal hypometabolism show the same positive outcome as patients with a morphologically visible lesion [32]. An example of a “non-lesional” patient with a positive PET is shown in Figure 5. PET can also be decisive in situations of multifocal lesions or multifocal epileptic activity. In tuberous sclerosis, an autosomal dominant disorder characterised by multiple cortical malformations (tubers), the most hypometabolic tuber is concordant with invasive localisation of the epileptic focus in a majority of patients [33].
Other PET tracers have shown promising results in specific applications: for example, $^{11}$C-flumazenil, a GABA antagonist, could be useful to localise pathological brain tissue in temporal lobe epilepsy, with increased uptake on the pathological side [34]. $^{11}$C-AMT (α-$^{[11]}$C)-methyl-L-tryptophan) displays positive uptake in the most epileptogenic tuber in tuberous sclerosis in about 70% of cases [33]. These tracers are used in specific research settings and are not currently applied in clinical practice.

**Amyotrophic lateral sclerosis**

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that has an incidence of 2–3/100,000 new cases per year [35] and is characterised by progressive muscle paralysis associated with degeneration of motor neurons in primary motor cortex, brainstem and spinal cord [36]. ALS-mimicking conditions include pure upper motor neuron disease (primary lateral sclerosis, PLS), pure lower motor neuron disease (progressive muscular atrophy) and FTLD, the latter sharing with ALS similar cognitive symptomatology.
PET represents a valuable tool in the diagnostic work-up and for the differentiation of ALS from mimicking diseases. Various radiotracers (\(^{11}\)C-flumazenil [37], \(^{11}\)C-(R)PK11195 [38], \(^{18}\)F-DPA-714 [39], \(^{11}\)C-(L)-deprenyl-D2 [40]) have been used to assess changes in regions affected by ALS, including those for the evaluation of activity in the white matter [38–40], which plays a significant role in the progression of the disease. However, most of the PET studies in ALS have been performed using \(^{18}\)F-FDG, focussing on patients and normal controls as a comparison group and looking for ALS-related metabolic patterns. Patients with ALS usually demonstrate diffusely decreased \(^{18}\)F-FDG uptake in primary and supplementary motor and premotor cortices as well as clusters of relative hypermetabolism in the mesiotemporal regions, occipital cortex, cerebellum, corticospinal tracts and upper brain stem (Fig. 6), reflecting a complex neuropathophysiology involving degeneration of grey matter and areas of reactive microglial activation. The presence of astrocystosis and activated microglia in corticospinal tract, midbrain and pons has also been supported by findings from \(^1\)H-magnetic resonance spectroscopy (increased myo-inositol [41]) and other PET investigations (increased uptake in peripheral benzodiazepine receptors [38, 39] and astrocytes [40]).

Figure 6: Comparison of \(^{18}\)F-FDG PET findings in ALS patients and controls using statistical
parametric mapping. Statistically significant differences (p<0.05 false discovery rate) are highlighted on an MRI T1 template. (A) sagittal view; (B) coronal view; (C) transverse view. Clusters of significant hypermetabolism are seen in the midbrain, cerebellum, medial temporal lobes and corticospinal tracts.

Recently the potential of 18F-FDG as an important biomarker for the diagnosis of ALS has been confirmed by two investigations in which extremely large patient cohorts were recruited [42, 43]. Both studies analysed the diagnostic ability of PET in ALS and found that it showed a sensitivity of about 95% in separating patients from controls [42, 43] and of 71% in separating ALS from PLS [43]. Pagani et al. [42] reported in 195 ALS patients a mixed 18F-FDG hypermetabolic–hypometabolic pattern, with marked hypometabolism in the frontal, premotor and occipital cortices and relative hypermetabolism in white matter, midbrain and the medial temporal cortex.

PET findings have also been compared in patients with sporadic ALS without mutations of ALS-related genes, patients with ALS and comorbid FTD and patients with ALS carrying the C9orf72 mutation [44]. More widespread cortical and subcortical involvement, especially in the frontotemporal cortex, was associated with a more severe clinical course in those with the C9orf72 mutation.

In addition, PET has a promising role in discriminating ALS from ALS-mimicking pathologies, thereby contributing to recruitment of suitable subjects for clinical trials and allowing early interventions when appropriate [45]. Longitudinal examinations, identifying significant changes over time, and novel PET/MRI technology, providing a simultaneous assessment of structural and functional lesions, will in the future play a pivotal role in better understanding theopathophysiology of this complex and fatal disease.

**Stroke**

*Background*

Stroke is the third leading cause of death globally and the second most frequent cause of death in the developed world after coronary artery disease [46]. It is also a major cause of chronic disability, particularly among the elderly population. The annual stroke rate is in the range of 1.4–4 per 1000. Approximately 30% of cases are attributed to cerebral haemorrhage and 70% to cerebral ischaemia. Stroke may arise as a result of a combination of different factors. Ischaemic strokes can be produced through thrombotic, embolic and haemodynamic mechanisms. Clinically infarcts are commonly considered as *atherothrombotic* (local thrombosis in relation to atheroma of the vascular wall), *cardioembolic* (embolism of cardiac origin, e.g. atrial fibrillation, recent myocardial infarction, aortic valve disease) or *lacunar* (occlusion of one of the small penetrating end-arteries at the base of the brain, often resulting from microatheroma formation). A lesion between 3 and 15 mm in diameter is commonly regarded as a lacune. Occasionally, an ischaemic infarction may turn into a haemorrhage. The clinical
symptoms are of sudden onset and depend on the location and size of the lesion. Infarcts, particularly the lacunar ones, may be clinically silent or transient. If the symptoms last <24 h, the term transient ischaemic attack (TIA) is used. While TIA's generally do not cause permanent brain damage, they are a serious warning sign and should not be ignored. There are many risk factors for stroke: age, gender, ethnicity, heredity, hypertension, cigarette smoking, hyperlipidaemia, diabetes mellitus, obesity, fibrinogen and clotting factors, oral contraceptives, erythrocytosis and haematocrit level, prior cerebrovascular and other diseases, physical inactivity, diet and alcohol consumption, illicit drug use and genetic predisposition [47].

Nuclear imaging has been used extensively in the study of neurovascular diseases over the past five decades and has yielded important knowledge on the pathophysiology of acute stroke. In clinical practice, however, the primary methods of choice in the diagnostic work-up of acute stroke and neurovascular diseases are CT and MRI scanning. At the moment non-enhanced CT of the brain remains the mainstay of imaging in the setting of an acute stroke (Fig. 7) since it is fast, inexpensive and readily available. Its main limitation is the low sensitivity in the acute setting, where MRI has an advantage. PET/CT is not indicated in acute stroke. However, diagnostic CT of the brain is easily available in all PET/CT systems and can provide important additional information relevant to the interpretation of any functional defects found, e.g. in dementia. Knowledge of the various presentations of neurovascular disease becomes important in the differential diagnosis of vascular dementia (VaD), AD and mixed dementia (AD with concomitant stroke or small vessel disease).
Figure 7: Patient with diabetes mellitus, hypertension and multiple previous TIA’s. CT angiography showed occlusions of the right internal carotid and right vertebral arteries. There are typical watershed infarctions in the centrum semiovale on T2-weighted MRI (red arrows). PET measurements of rCBF at baseline using $^{15}$O-water show discrete hypoperfusion in the right hemisphere, which is particularly pronounced above the infarcts (white arrow). During acetazolamide stimulation, the perfusion was increased by 60% in the left hemisphere, but decreased by 9% in the right middle cerebral artery territory, consistent with cerebrovascular steal (green arrow, same scale as baseline). The patient refused reconstructive vascular surgery and sustained an ischaemic stroke during an infection-induced hypotensive episode in the same risk areas as had been defined on PET 2 months earlier (hypointense lesions, orange arrows), demonstrating the clinical validity of the method.

Furthermore, quantitative measurements of the regional cerebral blood flow (rCBF) using positron emission tomography (PET) still occupy a specialised clinical niche within nuclear imaging for evaluation of the haemodynamic response in patients with cere-
brovascular occlusive disease prior to revascularising surgery.

**Dementia and stroke**
Many of the risk factors mentioned in the preceding section are shared between dementia and stroke. About 30% of dementia patients will show signs of cerebrovascular disease that may be synergistic with AD in producing the clinical syndrome of dementia. Mixed dementia is the second most common form of dementia after AD (10–20%), while VaD alone accounts for 10% of cases. VaD increases in prevalence with age [48]. It may arise from multiple cortical infarctions, strategic strokes and subcortical white matter lesions [49]. The neuropsychological characteristics of VaD may be different from those seen in AD. Disturbances in frontal-executive functions (Fig. 8), rather than memory, are often the more dominant feature and memory impairment may be absent in some patients with significant cognitive deficits.

Vascular disease will often give rise to a regional decrease in activity encompassing the infarcted area and neighbouring areas to varying degrees (Fig. 8). Cases of vascular disease may also be metabolically silent. It is important to be familiar with the concept of diaschisis, the idea that damage to one part of the nervous system can have effects at a distance due to loss of input [50]. Thus, it was demonstrated as long ago as 1964, using the Lassen-Ingvar krypton-85 method [51], that stroke patients had a strikingly low rCBF measurement also in the structurally intact healthy hemisphere [52]. The most common forms are **crossed cerebro-cerebellar diaschisis** [53], where damage to one hemisphere leads to depression of the contralateral cerebellar hemisphere; **thalamo-cortical diaschisis**, where damage/stroke in the thalamus leads to depression of the ipsilateral hemisphere [54]; and **cross cerebello-cerebral diaschisis**, where damage to one cerebellar hemisphere leads to depression of the contralateral cerebral hemisphere [55]. Furthermore, decreased activity in cortical areas may be evident if the infarct is located subcortically, involving and undercutting white matter tracts (Fig. 8). Thus, for each individual area of decreased metabolic activity in patients evaluated for dementia using 18F-FDG PET/CT, it is necessary to determine whether the reduction in activity can be explained by local or distant neuronal damage/vascular lesion.
Figure 8 A–C: Examples of typical $^{18}$F-FDG PET images in patients referred for PET/CT or PET/MRI for evaluation of dementia. To the right are statistical surface projections (Scenium, Siemens) comparing the subjects with a database of age-matched controls. (A) PET fusion with simultaneously acquired T1-weighted MRI: transverse images. The red arrows indicate circumscribed lacunar infarcts with decreased activity uptake involving the left head of the caudate and the anterior thalamus; these lesions are undercutting projections to the structurally intact left frontal lobe, giving rise to a moderate reduction in activity (green arrows). FTD could have been considered, but this is vascular dementia. There is also an infarct in the pons (not shown). (B) CT and PET transverse images. CT shows extensive subcortical hypointense signals (leukoaraiosis) indicative of subcortical ischaemia (red arrows) that cannot alone explain the pattern of cortical metabolic reduction (green arrow), suggesting a mixed vascular and neurodegenerative origin. (C) CT and PET/CT transverse images show a subcortical infarct in the right temporal region (red arrow), leading to a larger metabolic defect in the temporoparietal cortex (green arrow) through disruption of subcortical–cortical circuits. The PET image alone could be misread as demonstrating signs of neurodegeneration in the absence of supportive correlation with CT.
Chronic cerebrovascular disease
Atherosclerotic internal carotid artery occlusion causes approximately 10% of TIAs and 15–25% of ischaemic strokes in the carotid territory. The 2-year risk of ipsilateral ischaemic stroke while a patient is receiving medical therapy is 10–15% [56]. This risk, however, depends on the capacity of the brain tissue to compensate, e.g. by increasing the regional oxygen extraction fraction (rOEF). Increased rOEF indicates that the last defence before stroke has been mobilised. In symptomatic patients with increased rOEF, the 2-year risk of ipsilateral ischaemic stroke is 30–40%, while it is only 5% in symptomatic patients with normal rOEF [57]. In the event of symptomatic occlusions of the carotid arteries to the brain, a revascularising surgical procedure may be considered: the so-called extracranial–intracranial bypass operation (EC-IC). In the most common version of the EC-IC bypass operation, a branch of the external carotid artery, usually the superficial temporal artery, is anastomosed to a branch of the internal carotid artery on the occluded side, usually the meningeal artery. The procedure is not without risk, and there is a 10–15% likelihood of perioperative stroke [58, 59]. Thus, the overall risk is the same as in medically treated symptomatic patients over 2 years. Consequently, only the subgroup of high-risk patients should be considered for the operation. Supportive symptoms and findings that may predict haemodynamic failure and high risk of stroke and death are usually manifested as repeated TIAs or stroke, with typical subcortical “watershed” infarcts on T2-weighted MRI (Fig. 7), ortho-
static limb shaking, impaired vasoreactivity to acetazolamide challenge and increased rOEF on PET scanning [60].

In the event of carotid occlusion, the affected hemisphere receives its blood supply from communicating arteries of the circle of Willis and collaterals between the extracranial and intracranial arteries. If these are not sufficiently developed, there will be a pressure drop in the most distant arterioles of the arterial tree at the border zones between vascular territories (watershed areas). This will initially be compensated haemodynamically by vasodilation, which will stabilise rCBF and can be measured as an increase in regional cerebral blood volume (Fig. 9). Metabolic compensation will follow via an increase in oxygen extraction from the capillary blood, the rOEF rising from 30–40% to 70–80%. In patients with exhausted perfusion reserve, rCBF will behave in a pressure-passive manner. The arterioles are maximally dilated, and rCBF will change with the perfusion pressure. If the patient experiences a longer lasting pressure drop (e.g. due to systemic infection, cardiovascular disease, dehydration or blood pressure-lowering drugs) and the compensatory mechanisms are insufficient, an ischaemic infarction will develop (Fig. 7) [61, 62]. Acetazolamide (Diamox) is a carbonic anhydrase inhibitor and a potent vasodilator of the cerebral vessels that increases rCBF by 20–60%. Only arterioles that are not already dilated will respond to acetazolamide, while the haemodynamic response in affected regions will be either reduced, unaffected or negative. The last-mentioned phenomenon is called “cere-
brovascular steal" or the "reverse Robin Hood effect". The increased rCBF in the unaffected hemisphere decreases perfusion pressure and rCBF in the affected hemisphere (Fig. 9). EC-IC bypass surgery can reverse these changes [63] and may increase the cognitive performance [64], but the clinical benefit in terms of stroke risk and survival is still controversial. In a recent randomised clinical trial, 195 patients were randomised to either optimal medical treatment or surgery based on PET measurements of increased rOEF in the symptomatic hemisphere (the COSS study). The study endpoint was 2-year stroke recurrence, the rate of which was found to be 21% in the surgical group and 23% in the medically treated group. The latter was far below the expected rate of 40% from prospective observational investigations, and the study failed to demonstrate a significant difference in the two treatments [58].

Figure 9: A schematic representation of the vascular response to carotid occlusion and vasodilation using acetazolamide. The two internal carotid arteries are represented as two arrows connected by the circle of Willis, which subsequently supplies feeding arteries to the two hemispheres. The bars in the hemispheres represent the vasodilatory state of the arterioles in brain tissue. In the healthy brain (top row), acetazolamide dilates the arterioles and increases rCBF symmetrically in the two hemispheres by 20–60%. In carotid artery occlusion (lower row) — represented by the black box in the left carotid — the ipsilateral hemisphere is fed through a more or less patent collateral
blood supply in the circle of Willis; these arterioles are dilated because of the ensuing decrease in perfusion pressure, which stabilises rCBF. When the arterioles in the unaffected contralateral hemisphere are dilated, the perfusion pressure will decrease even further ipsilaterally. Depending on the residual vasodilatory capacity, the rCBF will be increased, unaffected or decreased. The last-mentioned phenomenon is known as the cerebrovascular steal phenomenon.

The measurement of vasoreactivity in response to acetazolamide requires quantitative assessment of the rCBF using either $^{15}$O-water PET or the stable xenon-CT SPECT method [65]. Both methods are available only in specialised units. $^{15}$O-water has a half-life of only 2 min and an on-site cyclotron is required for on-line continuous production of the tracer. Furthermore, quantification of rCBF measured in mL blood flow per 100 g tissue per minute necessitates arterial cannulation and continuous blood sampling with radioactivity measurements for kinetic modelling with calculation of parametric images.

In the acetazolamide challenge, rCBF is measured at rest and approximately 20 min after injection of 500–1500 mg acetazolamide i.v. The baseline rCBF image is subtracted from the acetazolamide-stimulated rCBF image, and all images are fused to T2-weighted/FLAIR MRI. The baseline rCBF image allows estimation of the extent of infarction and hypoperfusion around the areas of signal change on MRI. Regions of interest are drawn on the three major intracerebral artery territories in both hemispheres for quantification of rCBF and reactivity. However, as compromised haemodynamic reactivity is often in the watershed areas, the subtraction image is the most efficient way of directly revealing the location of increased and decreased rCBF.

Acetazolamide challenge is also used in combination with transcranial Doppler flow measurements. To date there have been virtually no reports of adverse effects of acetazolamide challenge [66]. One case report did, however, cite a stroke episode 24 h after injection, which could have been related to the mildly diuretic effect of acetazolamide [67].

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References


