Recent advances in multidetector computed tomography (MDCT) have resulted in sub-second volumetric patient scanning, revitalising the role of MDCT in clinical practice. Such technological quantum leaps, combined with the availability and turnaround efficiency of CT, have had a notable impact on the imaging paradigms of neurological patients with stroke and cerebral tumour and those in intensive care after neurological disorders. Dynamic contrast-enhanced CT (DCECT) or (functional CT) is a brilliant example of a protocol that has undergone significant improvements, with considerable impact on patient care in the acute and chronic setting.

In the field of cerebral perfusion, CT compares well with other functional imaging modalities (e.g. magnetic resonance imaging [MRI], xenon CT, positron emission tomography [PET] and single photon emission CT [SPECT]) through the rapid, low-cost generation of meaningful functional images and the available user-friendly post-processing commercially available software packages, which interpret the data in a clinically relevant manner. The theory behind DCECT is the tracer kinetic analysis of rapid, intravenously injected contrast material (or contrast agent).

The purpose of this article is to review the clinical applications of functional brain CT imaging, suggest new clinical application fields, provide a critical review of the currently used tracer kinetics models and suggest possible solutions for more accurate functional maps.

**Methodology**

**Computed Tomography Imaging Technique, Indicator and Tracer Kinetics Models**

Functional CT relies on the triad of using CT as an imaging modality, an intravenously injected tracer or contrast agent and a model of tracer kinetic analysis. In the case of brain imaging, sequential acquisition of brain sections (one or more sections per second) in vivo is performed after rapid injection (typically 4–8ml/sec; 6ml/sec in our clinical protocol) of an iodinated non-ionic contrast agent (typically 40–50ml; 40ml of a 400mg/dl contrast agent in our protocol).

The iodinated contrast agent has the characteristic of remaining in the healthy cerebral vascular bed due to the existence of the blood–brain barrier. This is not the case in pathological cerebral tissue where the contrast agent may remain in the vessels at first pass but leaks rapidly into the interstitial tissue later. Tracer kinetic analysis methods for estimating microcirculatory parameters can generally be grouped into two classes: 1) model-independent approaches, which include numerical deconvolution-based methods, and model-dependent or parametric-fitting approaches. In the model-dependent approach, the tracer kinetics models used for parametric fitting of the dynamic imaging data are usually linear compartmental models, which can be further classified as conventional compartmental (CC) or distributed parameter (DP) models. A common objective of all the aforementioned approaches is the generation of parametric (functional) maps of the cerebral tissue, which can be summarised as blood flow (F), endovascular blood volume (v1), mean endovascular t1, lag time (tlag) (which corresponds to the difference in the contrast agent’s arrival times between arterial input function and tissue voxel), extravascular extracellular blood volume (v2), vascular permeability surface area product (PS) and extraction ratio of the contrast agent into the extravascular extracellular space (E). Three main models have been used for model-independent approaches, including the maximum slope model, equilibrating indicator model and central volume principle model. The maximum slope model requires very short injection times (i.e. 8–10ml/sec injection rate), which are not always tolerable by the patients, and is inclined to underestimate the cerebral F values. In addition, there is no general consensus regarding the reference arterial input function that is necessary for the calculation of the functional parameters. The equilibrating indicator model and central volume principle models require a mathematical operation called deconvolution.

Deconvolution can be realised in two ways. The first method is a parametric method whereby supplemental hypotheses regarding the anatomical structure or behaviour of the indicator are taken into account. The second method, the non-parametric method, can be performed with single singular-value decomposition and involves fewer source hypotheses. Deconvolution-based DCECT analysis offers fast and robust analysis (though noise sensitive) of the neurovascular disorders and has been an important strategy to assess stroke and characterise intracranial tumours. Among the linear compartmental models employed in the model-independent approach, the most popular is the maximum slope model.
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Figure 1: Distributed-parameter Model Analysis of Functional Computed Tomography Data Obtained in a Patient with Acute Left-sided Stroke Symptoms

A: The intravascular transit time ($t_1$) parametric map shows the prolonged transit time in the vascular territory of the middle cerebral artery on the right side.

B: The lag time ($t_{lag}$) parametric map demonstrates a slightly larger (compared with the $t_1$ map) region of abnormality on the right side.

C: The blood flow (F) map shows also the hypoperfused ischaemic region in concordance with the $t_{lag}$ map.

A distinct feature of the DP tracer kinetic model is the accurate calculation of the intravascular mean $t_1$ (accounting for the mean $t_1$ of the contrast agent to pass through the intravascular compartment) and the $v_1$. Second, the currently used DP model introduces the use of $t_{lag}$, which estimates the delay of the tissue concentration curve relative to the arterial input function, aiming at rapid identification of areas with varying degrees of hypoperfusion. Compared with the mean $t_1$ in the deconvolution-based model (which represents the $t_1$ of the contrast agent through the tissue voxel) or the time to peak in the maximum slope model (which is equal to the difference between the timepoint of the earliest density increase due to the arterial bolus arrival and the timepoint of the maximal density in the tissue), $t_{lag}$ theoretically corresponds more closely to the ischaemic region (see Figure 1). Identifying the volume of the non-functional brain tissue has important prognostic value, but identifying the volume of the potentially salvageable brain tissue could improve the clinical course of an acute stroke even more. The analysis of DCECT data 'peers' into the cellular biology of the infarcted brain and, in case of a substantial tracer leakage from the vessels, quantifies the extravascular $v_2$ and the vascular permeability surface product (PS) (see Figure 2). Loss of integrity of the blood–brain barrier resulting from ischaemia/reperfusion may lead to haemorrhagic transformation and poor clinical outcome. Because two major therapy strategies for acute stroke, namely anticoagulation and thrombolysis, are strongly related to the hazardous effect of haemorrhagic transformation, PS values can serve as a tool for selecting treatment options. Recent retrospective observations using MRI showed an early disruption of the blood–brain barrier in acute stroke, which could be quantified by means of DCECT, whereas its association with brain haemorrhage has not been demonstrated clearly.

In commercially available tracer kinetic models for ischaemic stroke where numerical deconvolution is used, the model calculates an ‘overall’ mean $t_1$ of the contrast agent through the vascular bed and the tissue of interest, as well as the area under the tissue residue curve (blood volume (BV), and subsequently the F can be calculated as BV x mean $t_1$.

Undoubtedly, at the presentation of blood–brain barrier disruption, BV parametric maps based on numerical deconvolution might not indicate low perfusion. However, the potential PS disorders are not accounted for in this case, partly due to the limited acquisition time (approximately 45s), which may not be sufficient for PS imaging.

Cerebrovascular Reserve Capacity

Patients with chronic steno-occlusive disease of the extracranial carotid artery represent a complex subgroup of patients who may present with neurological symptoms produced by thromboembolic stroke and altered cerebral haemodynamics. Extracranial to intracranial collaterals and leptomeningeal anastomoses may maintain normal perfusion in patients with carotid stenosis. Nevertheless, a percentage of patients have an insufficient collateral supply, which leads to haemodynamic compromise. The impaired cerebral haemodynamics can be identified by demonstrating an impaired vasodilatory response after challenging DCECT studies. The acetazolamide test is a reliable predictor of critically reduced cerebral perfusion and may unmask cerebrovascular reserve deficits, even in patients with asymptomatic carotid stenosis who have haemodynamic compromise.
The status of the cerebrovascular autoregulatory control has been examined with xenon imaging, PET, SPECT, DCEMRI, DCECT and transcranial Doppler ultrasonography. Recent studies with DCECT have demonstrated significant correlation of the measured perfusion values and the estimated cerebrovascular reserve with PET measurements. Compared with the conventional models, the DP model overcomes some shortcomings in the evaluation of the cerebrovascular response under the following circumstances:

- less than expected augmentation relative to the contralateral side;
- absent augmentation; and
- paradoxical reduction in-flow (steal phenomenon) are present.

Thus, the visualisation of cerebral perfusion symmetry and the obtained quantitative perfusion results can substantially assist in selecting the patients undergoing bypass surgery or can also be used to evaluate the efficacy of revascularisation procedures postoperatively.

Vasospasm
Vasospasm is a delayed entity seen largely in patients who have sustained subarachnoidal haemorrhage (SAH) from an aneurysm rupture. Its manifestation results in the greatest morbidity and mortality in these patients. A progression to infarction occurs in approximately half of the symptomatic cases. Early detection and neurointervention in the forms of intra-arterial drug infusion and/or angioplasty have promising results. Measurements of cerebral F can be useful in identifying patients at increased risk of cerebral infarction and thus guide therapeutic decisions and monitor response to therapy. PET, SPECT, xenon CT and transcranial Doppler sonography have already been applied for this purpose. Quantitative analysis in patients with SAH demonstrated prolonged times of $t_1$ and F values below 12ml/min/100g tissue. Nevertheless, the presence of massive subarachnoidal blood in the brain cisterns may not allow perfusion measurements of large brain territories, as the volume averaging of pathological tissue and subarachnoidal blood may lead to falsely increased F values. In this case, $t_1$ values are more reliable and useful for therapy monitoring.

Traumatic Cerebral Contusions
Patients with traumatic brain injury frequently exhibit cerebral contusions, which may swell and cause increased intracranial pressure with secondary ischaemia. It is still assumed that traumatic contusions may represent irreversibly infarcted focal lesions and how their presence can predict outcome in patients with severe head trauma. Early conventional CT carried out on admission usually underestimates the extent and severity of the cerebral parenchymal lesions, which are better demarcated in the follow-up imaging. Traumatic cerebral contusions are characterised by low F and BV values and prolongation of the contrast agent $t_1$. Initial experience with perfusion measurements, in terms of F, showed the irreversibly damaged zone and the potential viability of tissue in the pericontusional zone. The prognostic value of the DCECT measurements in the brain injury has been already validated, whereas, in comparison with early non-contrast CT, BV and F maps may be more congruent with the findings of follow-up non-contrast CT scans.

Tumour Imaging
Brain tumours are readily recognised with contrast-enhanced CT imaging, in which they present with perifocal oedema and contrast enhancement patterns that are also used to differentiate different types of brain tumours. The use of DCECT in this field offers a numerically solid basis for differential diagnosis and assessment of the tumour characteristics beyond that of visual assessment. The illustrative maps of...
functional CT imaging of an intracranial tumour are shown in Figure 3. In terms of F and v1 values, cerebral perfusion assesses the increased tumour-inherent angiogenic activity and neovascularisation. However, the inclusion of large, healthy cerebral vessels in the tumour bed may lead to false estimation of v1 or v2 parameters or even in F calculations. The utilisation of independent component analysis of the dynamic source images has been proven to overcome this problem.17 The hyperpermeability related to the newly formed immature vessels can be quantitatively assessed by the PS and E parametric maps. The generated PS and E maps offer the additional advantage of tumour segmentation and delineation from the surrounding healthy tissue.18 There is no significant correlation of the v2 and E parameters with the tumour growth as it is demonstrated with the v1 and PS values.19 The latter provides a means of tissue mitosis monitoring, visualisation of the most malign tumour portions and therapy response.

New Applications of Brain Functional Imaging

Adverse neurological outcomes, such as stroke, in intensive care unit (ICU) patients may have devastating consequences, among them increased mortality risk and, among survivors, loss of independence and a diminished quality of life. Unenhanced CT remains the primary modality for assessing such situations. However, it has low sensitivity in the detection of ischaemia.10 Clinical and electrophysiological criteria for brain death may be misinterpreted due to drug intoxication, hypothermia or technical artefacts. Cerebral angiography, MRI, CT imaging after inhalation of stable xenon, electroencephalography, brain perfusion SPECT measurements and scintigraphy are possible methods for providing brain death diagnosis in comatose patients.11,22 DCECT may also be a reliable, safe and cost-effective method for defining brain death. However, there is only preliminary experience in this field.23

Limitations of Functional Brain Computed Tomography Imaging

Apart from the patient radiation exposure during the DCECT imaging, a possible limitation of the method is the limited anatomical coverage. The latter may result in an inadequate estimation of the infracted tissue or of the whole tumour volume and thus a lack of choices for the arterial input function because a large vessel perpendicular to the examined transversal section is missing. The possibility of performing subsequent dynamic measurements, each time applying a new contrast agent bolus, offers the advantage of greater anatomical coverage, although it should be considered that the contrast material may cause renal failure in patients with poor kidney function and, at the same time, is contraindicated in patients with hyperthyroidism or known allergic reactions. A toegglable technique has also been proposed to improve anatomical coverage. Nevertheless, the introduction of 64–256-row MDCT units may substantially contribute to greater anatomical coverage and provide reliable tissue perfusion measurements.24

Conclusion

Functional CT is a readily available, rapidly performed, viable alternative to other modalities used to measure cerebral perfusion. This technique can quantify tissue haemodynamics in the brain when the appropriate software is provided. In this article, we have highlighted the applications of functional (or DCE) CT not only in patients with acute stroke or cerebral tumour but also in a wide range of patients with other cerebrovascular diseases.