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Perfusion Computed Tomography in Traumatic Brain Injury

Cino Bendinelli, Shannon Cooper, Christian Abel,
Andrew Bivard and Zsolt J. Balogh

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Abstract

Introduction: Almost 50 years ago, computed tomography (CT) revolutionized the management of traumatic brain injury (TBI) by imagining intracranial hematomas. This allowed prompt and accurate selection of patients who would benefit from surgical evacuation. Since then, unenhanced CT has been the gold standard imaging modality for patients with acute TBI. Today, multidetector CT can track intravenous contrasts flowing through brain creating maps that depict the speed and the amount of blood at capillary level. This imaging modality takes the name of perfusion CT. Perfusion CT is routinely used during the hyperacute phase of patients suffering from stroke to diagnose areas of penumbra (poorly perfused but still viable brain tissue) that may benefit from revascularization. Here, we summarize the current status of the research on the role of perfusion CT in patients suffering from TBI.

Methods: Inclusive literature research conducted on PubMed using the keywords "perfusion," "computed tomography" and "traumatic brain injury." Only articles published in English were considered for this review.

Conclusion: With a minimal logistic effort, perfusion CT provides clinicians with a multitude of additional information. Most patients with TBI show altered perfusion patterns. The maps generated with perfusion CT can predict the final size of cerebral contusions better than unenhanced CT. These maps can be used to clarify the status of brain autoregulation and possibly guide targeted therapies for intracranial hypertension. The integrity of the blood–brain barrier can also be evaluated with this technology and this might be crucial to predict and treat brain edema. Furthermore, perfusion maps can help physician to promptly and accurately predict the long-term functional outcomes of patients suffering from both mild and severe TBI.

Keywords: perfusion CT, severe traumatic brain injury, neuroimaging
Subject area: neuroimaging in traumatic brain injury

1. Introduction

Traumatic brain injury (TBI) remains a major cause of death and disability [1]. The heterogeneity of TBI is considered to be a one of the most significant obstacles to the development of effective therapeutic interventions [2, 3]. Physicians in order to understand, treat and prognosticate patients suffering from TBI do rely mainly on three parameters: [1] the Glasgow Coma Scale (GCS) is a rapid and reproducible test, which assesses overall neurologic function; [2] the unenhanced CT findings, which can detect skull fractures, hematomas, cerebral contusions and some indirect sign of brain swelling (i.e., ventricles size, midline shift, uncal herniation); [3] the intracerebral pressure (ICP) monitoring, which requires a quite invasive intracerebral or intraventricular probe, to calculate and help maintaining adequate cerebral perfusion pressure (CPP) [2–10]. This information routinely utilized in clinical management algorithms tend to compromise accuracy for simplicity and suffer from several weaknesses. For example, all patients with GCS below nine will be diagnosed as having a severe degree of TBI and, as such, will be admitted to intensive care intubated and pharmacologically sedated. Instead, patients with GCS higher than nine are most often discharged home or admitted to low intensity wards (especially if screening unenhanced CT appears normal). But GCS can also be affected by drug/alcohol assumption, and by systemic hypoperfusion making decision based on GCS alone often inaccurate [5]. Similarly unenhanced CT, despite its status of "gold standard imaging" for acute TBI, deprives clinicians from crucial information on brain tissue vascularity, perfusion and viability. Unenhanced CT underestimates the ultimate size of parenchymal lesions and does not afford insight into secondary ischemic injuries related to systemic hypotension, traumatic cerebral edema and intracranial hypertension [8]. Lastly, the clinical use of ICP monitors in patients at risk of brain swelling, which is often burdened by complications from its invasiveness, can often only provide an inaccurate reading. Calculating CPP using ICP and mean systemic arterial pressure (MAP) does not take into account cerebral vasculature autoregulation or cerebral regional differences often observed with more advanced technology [9, 10]. The efficacy of ICP monitoring-based treatment has been recently challenged in a large-scale randomized trial on more than 300 severe TBI patients. It appeared that ICP-based treatment (focused on maintaining ICP < 20 mmHg) was not superior to that based on imaging and clinical examinations alone in terms of survival and functional outcome [9].

It is of no wonder that these three pillars of TBI management have come under scrutiny recently, making sensible and grounded clinical decisions based on these limited and biased information alone resemble a dangerous gamble. As a possible result, most interventional studies investigating otherwise sensible therapeutic options have failed to identify successful treatments [4].

In terms of imaging, several relatively new technologies are available to better understand the complexity of TBI. Many are still research tools; some require long acquisition times and some others are poorly available and/or logistically difficult to organize in critically ill ventilated patients. Perfusion CT instead is a not logistically demanding imaging technique that provides detailed maps of intracerebral vascular flow and brain tissue perfusion and affords

direct insight into cerebral infarct and penumbra. Today, perfusion CT is routinely used in the early care of patients with acute stroke and other cerebrovascular disorders [11].

The aim of this chapter is to evaluate potential benefits and limitation of perfusion CT as advanced diagnostic modality for patients suffering from TBI. Specifically, we overview the technical aspects, present published research and try to predict the future role of this diagnostic approach in patients suffering from TBI.

2. Description of perfusion CT technology

Several advanced imaging techniques exist, which can provide information about cerebral perfusion, such as stable xenon-enhanced CT (Xe-CT), single photon emission CT (SPECT) and perfusion-weighted magnetic resonance imaging (MRI) [12]. These techniques have logistic barriers to routine universal clinical use as they require specialized equipment and staffing and are burdened by long acquisition times [12]. Some, such as the 33% xenon mix used in Xe-CT that causes transitory ICP raise, can also be deleterious for patients [13]. These constrains are particularly relevant during the acute phase of severe TBI; when patients, often seriously injured polytrauma patients are intubated and ventilated, with ongoing needs for blood transfusions, vasoconstrictors. These patients need prompt and straightforward imaging to guide subsequent therapeutic options. Perfusion CT provides information about brain circulation and cerebral perfusion which can be obtained rapidly using wildly diffuse multidetector CT scanners [11, 14]. A perfusion CT can be obtained in few minutes utilizing a standard of care (more so in trauma centers) multidetector CT scanners (and dedicated post processing software) and does not require specialized technologists. The effective dose of ionizing radiation required for a head perfusion CT is about 5 mSv. The radiation-associated risks are believed to be low and approximately equivalent to about 2 years of background radiation [equates to an excess lifetime cancer risk = 0.025% (about 1:4000)] [15].

Acquisition of perfusion CT involves the administration of intravenous iodine contrast with concurrent acquisition of images using a helical CT multidetector scanner in cine mode. This allows for measurement of the movement of contrast material through the vessels and tissues over time. Perfusion data are obtained by monitoring the first pass of a contrast material bolus through the cerebral vessels. The relationship between the contrast agent concentration and attenuation can be used to calculate the amount of contrast agent in a region. Time versus contrast concentration curves are generated for a reference arterial region and venous region as well as each pixel of the scan [11, 15]. Post processing of the data allows the generation of color coded maps and quantification of the perfusion parameters of cerebral blood flow (CBF), cerebral blood volume (CBV) and mean transit time (MTT) [16]. The CBF for each area is calculated as CBV/MTT. CBF is measured in milliliters per 100 g of tissue per minute (ml/100 g/min), and normal tissue has values around 40 ml/100 g/min while values of 20 ml/100 g/min or less are diagnostic for ischemia. The CBV is calculated as the area under the curve in a parenchymal pixel divided by the area under the curve in the reference venous pixel. CBV is measured in
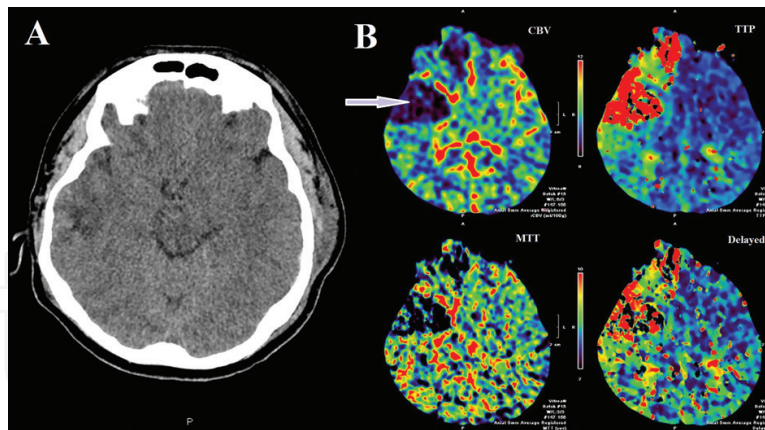
Figure 1. Axial computed tomography (CT) obtained 18 h from admission following a motor vehicle accident in a young male. (A) Noncontrast CT shows a left subgaleal hematoma, but no intracranial pathology. (B) Perfusion CT identifies an area of reduced perfusion on the right temporo-frontal lobe (white arrow): Cerebral blood volume (CBV) is reduced as per darker color, time-to-peak (TTP) is increased as per lighter color, and mean transient time (MTT) is decreased as per darker color. The axial image on the bottom right represents the delayed phase (which can be utilized by specific software to extrapolate permeability of brain–blood barrier).
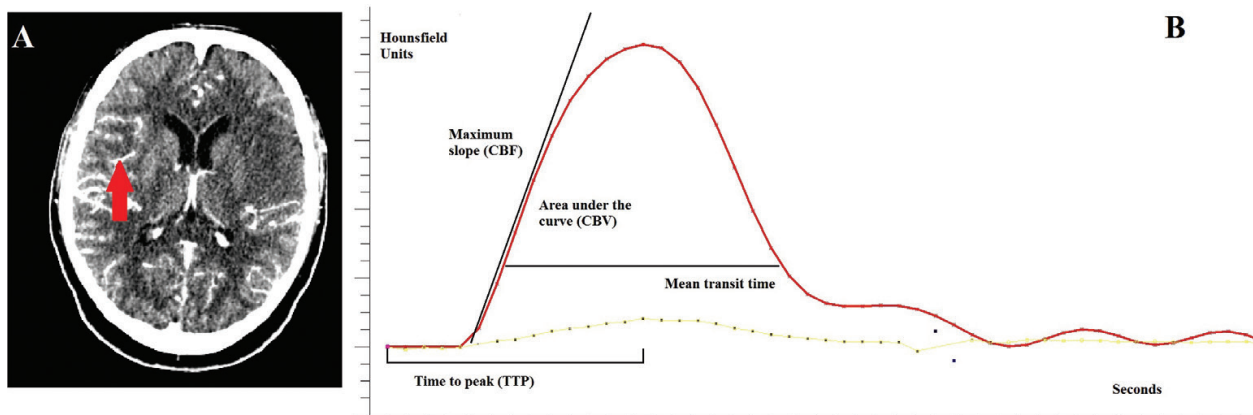
Figure 2. (A) An arterial input function (AIF, arrow on the axial CT scan) is used to calibrate the whole brain contrast change when post processing a CT perfusion. (B) the drawing depicts the rise and fall of the contrast over time (in seconds). The time from the start of the scan to the peak signal intensity is the time-to-peak (TTP); the maximum slope of the contrast enhancement being measured is the cerebral blood flow (CBF); and the area under the curve of the whole AIF is the cerebral blood volume (CBV). The time it takes for contrast to enter and leave the voxel is the mean transit time (MTT).

milliliters per 100 g of tissue (ml/100 g) and normal tissue has values around 4 ml/100 g, while values of 2 ml/100 g are indicative for a degree of ischemia. MTT is the average time taken by blood to cross the capillary network and is calculated from a deconvolution operation from the time concentration curve of each particular voxel and the arterial reference region. MTT is measured in seconds, and normal tissue has values around 5 s while values above 8 s are the rule in ischemic areas [11]. Perfusion CT thus provides a readily available means of examining brain perfusion and, by calculating MTT, CBV and CBF for different areas, can identify areas of abnormal perfusion and ischemia (**Figures 1** and **2**).

3. Perfusion CT and traumatic brain injury

Perfusion CT has revolutionized the diagnostic and therapeutic approach to acute ischemic stroke [17]. The prompt availability of perfusion maps and CT angiogram has transformed an irreversible condition requiring only supportive care and rehabilitation to a treatable neurological emergency. Neurologists use perfusion CT maps to define areas of ischemic penumbra and guide decisions on thrombolytic therapy [17]. As such, perfusion CT has now a well-established role in the acute management of stroke.

The potential role for perfusion CT in the management of TBI is still under investigation. A literature research including the terms "traumatic brain injury" and "perfusion CT" or "perfusion computed tomography" returned 185 results. Critical screening of the abstracts selected 18 papers that were considered as pertinent and relevant to this review and therefore they were analyzed and discussed in detail [16, 18–33]. **Table 1** illustrates the studies' characteristics and main findings. It appears that the published experience with perfusion CT in patients suffering from TBI is quite limited with a total of 540 patients investigated. Only three papers, including a total of 50 patients, were prospectively designed [24, 31, 33]. Almost all papers

First author, journal, year	Patients	Severity of TBI	Timing of CTP	Covered cerebral tissue	Studies' main findings
Wintermark [18] Radiology, 2004	130	Severe TBI	Admission	2 × 10 mm thick sections	Outcome prognostication Predicts raised ICP
Wintermark [19] Crit Care Med, 2004	42 subgroup [18]	Severe TBI and ICP monitor	Admission follow-up	2 × 10 mm thick sections	Correlation between CPP and CTP diagnose preserved or impaired autoregulation
Soustiel [20] Neuroradiology, 2008	30	Severe TBI and cerebral contusion	Within 48 h	4 × 6 mm thick sections	CBV maps depict pericontusion penumbra that later results in necrosis
Metting [21] Ann Neurol 2009	76	Mild TBI with normal CT	Admission	2 × 14 mm thick sections	Decreased CBF and CBV in frontal regions is associated with worse functional outcome
Escudero [16] Neurocrit Care, 2009	26	TBI or cardiac arrest	Unknown	4 × 8 mm thick sections	CTP can confirm brain death
Huang [22] J Trauma, 2011	22	Contusion on unenhanced CT	Admission	Not specified	Contrast extravasation predicts hemorrhage progression
Bendinelli [23] Injury, 2013	30 subgroup [31]	Severe TBI	Within 48 h	Whole brain 5-mm thick sections	CTP provided additional diagnostic information in 60% of patients

First author, journal, year	Patients	Severity of TBI	Timing of CTP	Covered cerebral tissue	Studies' main findings
Metting [24] PLoS One, 2013	18	Mild TBI with normal CT	Admission	2 × 14 mm thick section	CTP maps can predict brain dysfunction
Sarubbo [25] Neurorad, 2014	6	Cranioplasty after craniectomy	Before and after	Not specified	Cortical perfusion progressively declines after craniectomy
Wen [26] Brain In, (2015)	9	Cranioplasty after craniectomy	Before and after	Not specified	Cranioplasty increases CBF
Honda [27] Neurol Med, 2015	90	Severe TBI	Not specified	50-mm thick section	Higher CBF and lower MTT predictive for improved functional outcome
Jungner [28] Minerva Anest, 2016	17	Severe TBI or cerebral contusion	24 h	Whole brain 5-mm thick sections	Tracer extravasation shows altered blood–brain barrier around contusion
Trofimov [29] Adv Exp Med, 2016	25	Dishomogenous TBI patients	Not specified	Single 32 mm section	Positive correlation between cerebral oxygen saturation and CBV in frontal lobe
Songara [30] W Neurosurg, 2016	8	Cranioplasty after craniectomy	Before and after	Unclear	Brain perfusion improvement after cranioplasty
Bendinelli [31] W J Surg, 2017	50	Severe TBI	Within 48 h	Whole brain 5-mm thick sections	Perfusion abnormalities predict poor functional outcome at 6 months
Honda [32] Neurocrit Care, 2017	25	Severe TBI with ICP monitor	Within 7 days	Single slice	Cerebral perfusion disturbance when ICP >20 mmHg
Cooper [33] Injury, (submitted)	28 subgroup [31]	Severe TBI with ICP monitor	Within 48 h	Whole brain 5-mm thick sections	Perfusion disturbance predicts therapeutic requirement for intracerebral hypertension

Table 1. Studies published in English on the use of perfusion CT in patients with traumatic brain injury (in chronologic order of publication).

obtained a perfusion CT on admission following the standard of care unenhanced brain CT [18, 19, 21, 22, 24], while some timed the perfusion CT at the time of the first follow-up unenhanced CT [24, 31, 33], and two just before and after cranioplasty [25, 26]. Patients with severe TBI were most often investigated, with only one group investigating a total of 94 patients suffering from mild to moderate TBI [21, 24]. Most studies report perfusion CT maps produced using 64-slice multidetector CT scanner, which are limited to a small portion of the brain

(usually two or four adjacent slabs taken just above the orbit), while a few and more recent papers benefited from technology improvements (320-slice CT scanner) and investigated the whole brain [23, 28, 31, 33].

4. Outcome prediction

Several authors have investigated the role of perfusion CT to help functional outcome prediction in the heterogeneous population of patients suffering TBI. Wintermark et al. investigated with perfusion CT performed at admission a consecutive series of 130 patients with severe TBI (following standard unenhanced CT). The perfusion maps, specifically the number of arterial territories with oligemia (reduced regional CBV and CBF but not to the severity of ischemia), predicted poor functional outcome at 3 months, while hyperemia (increased regional CBV and CBF) was associated with a favorable functional outcome [18]. The subcohort of these patients who received an ICP monitor were presented in a subsequent study: perfusion parameters were correlated with CPP allowing to discriminate between patients with preserved or disrupted vascular autoregulation, and this was associated with functional outcome at 3-month follow-up [19].

A prospectively designed study aimed at investigating the relationship between whole brain perfusion CT and functional outcome [31]. Fifty patients with severe TBI and who required follow-up unenhanced CT within 48 h from admission (the design selected the sickest TBI patients, excluding those whose neurology improved quickly, and did not require follow-up imaging) were examined with whole brain perfusion CT. This was a selected severe TBI population burdened by high (14%) mortality, and the perfusion maps were found to be often (67%) abnormal with areas of ischemia in 35% of patients. Poor functional outcome (defined as a Glasgow outcome scale-extended of four or less at 6-month follow-up) occurred to more than half of the population and was best predicted by perfusion CT findings. Logistic regression analysis showed that, among the most commonly used parameters used for outcome prognostication, preintubation GCS was a moderate predictor (AUC = 0.74), thus confirming several prior studies, but the inclusion of perfusion CT variables (specifically the presence of abnormal findings) in the model improved the performance of the prediction model to AUC = 0.92 [31]. Similarly, a study on 90 patients with severe TBI investigated with Xe-CT and perfusion CT confirmed that perfusion abnormalities (specifically low CBF and high MTT) were predictive for poor functional outcome [32].

Furthermore, overall absence of CBF has helped a prompt diagnosis of brain death as demonstrated in a study on 27 patients investigated with perfusion CT and CT angiogram [16].

The role of perfusion CT in outcome prediction of patients with mild-to-moderate TBI has been investigated by the van der Naalt group [21, 24]. In 76 patients with mild TBI and normal unenhanced CT, a perfusion CT was obtained on admission. Perfusion maps with decreased CBF and CBV in the frontal and occipital gray matter were associated on logistic regression analysis with a poorer functional outcome at 6-month follow-up [21]. Furthermore, when compared to the healthy controls, patients with post-traumatic amnesia were found to have

reduced CBF in frontal gray matter and caudate nucleus [24]. Similarly, when neuropsychological tests were obtained in a subgroup of these patients, reduced perfusion of the frontal and parietotemporal regions was associated with impairment in executive functioning and emotion [24].

Taken together, these studies suggest a potential role for perfusion CT in early prediction of functional outcome in both the severe and less severe TBI population. These promising results are burdened by the limited experience but are consistent with similar previous studies, which utilized Xe-CT to prove the concept that an insight in cerebral circulation allows a more accurate functional outcome prediction [34, 35].

5. Perfusion CT and cerebral contusion

The role of perfusion CT in patients with cerebral contusions has been investigated by Soustiel et al. [20]. In this retrospective study on 30 patients, perfusion maps obtained 48 hours from injury predicted contusions progression better than unenhanced CT. Specifically, areas of hypoperfusion around the contusions resulted in areas of brain necrosis at follow-up unenhanced CT (CBV-derived maps showed congruence with the unenhanced CT at 7 days in 60% of lesions). This small study confirms the presence of a degree of ischemia around cerebral contusion (a regional secondary brain injury), which without perfusion CT would run completely undiagnosed till fully established and irreversible, and therefore, visible on unenhanced CT. Although not investigated in this study, it is foreseeable that overall intracerebral pressures (as measured by an ICP monitor) would be completely normal in these patients as the remaining brain adapts to the localized swelling. This kind of findings is exactly what physicians treating TBI patient need in order to craft appropriate and individualized therapeutic options. For example, in a recent study on 22 TBI patients with cerebral contusions, who were investigated acutely with contrast-enhanced CT and perfusion CT, the presence of contrast extravasation (identified in 40%) was predictive for hemorrhage progression [22]. Usually, hemorrhage progressions are otherwise diagnosed either by observing increased ICP (if monitored) or worsening GCS (if not three already) or by scheduling follow-up unenhanced CT (which may cause deleterious delays to diagnosis and treatment).

6. Cerebral perfusion pressure and perfusion CT

Wintermark et al. [19], in a subgroup of the previously mentioned severe TBI patients, studied the correlation between invasive ICP, CPP and perfusion CT findings. About 60% of patients were shown to have a weak dependence between CBF and corresponding CPP values (most likely due to preserved autoregulation), while the rest of the patients showed a strong dependence between CPP and CBF (disrupted autoregulation group). The relationship between perfusion CT findings and invasive ICP and calculated CPP has been more recently investigated by Honda et al. [27]. The perfusion maps of 25 patients with severe TBI and ICP monitor were obtained with

combination of Xe-CT and perfusion CT. The CPP values were positively correlated with CBF, negatively correlated with MTT and did not correlate with CBV. If this well reflects the expected physiology and Monro-Kellie hypothesis, it is interesting to notice that the correlation between CPP and CBF was disturbed by intracerebral hypertension (defined as ICP above 20 mmHg). In patients without intracerebral hypertension, CBF values did not correlate with CPP (preserved autoregulation), while in patients with cerebral hypertension, the CBF negatively correlated with the CPP value (disrupted autoregulation). In our experience, with 28 patients with severe TBI and ICP monitor investigated with perfusion CT within 48 h from trauma, the presence of abnormalities on perfusion maps (specifically, the presence of ischemia) was associated with the requirement for increased level of intervention for cerebral hypertension [33]. Two small studies investigated the functional outcomes before and after cranioplasty in patients suffering from severe TBI treated with decompressive craniectomy. An improvement of neurocognitive functions was observed after cranioplasty (especially if done within 3 months from trauma). Interestingly, serial perfusion CTs (performed in a subgroup of nine patients) also confirmed an improvement in cerebral perfusion in both the operated and the contralateral side [26, 30].

It certainly appears that we have a very limited understanding of the degree and location of perfusion abnormalities and that we do not know how to act once these are identified and quantified; it also appears that physicians tend to treat severe TBI patients and their CPP very homogenously despite quite obvious differences in autoregulation mechanisms and degree of hypoperfusion and ischemia. These interesting studies, albeit preliminary, certainly suggest a potential crucial role for perfusion CT. Perfusion maps will clarify almost real time the extent and the degree of perfusion deficits and the association with MAP and CPP. This will help physicians to diagnose disrupted autoregulation and predicting patients who will benefit from ICP monitors and aggressive treatment of cerebral hypertension.

7. Cerebral oxygen saturation and perfusion CT

The relationship between cerebral oxygen saturation and brain perfusion maps has been investigated in a heterogeneous cohort of patients with a degree of TBI ranging from severe to moderate [29]. The authors obtained perfusion maps using single slice technology and compared with frontal cerebral oximetry in 25 patients (16 with cerebral ischemia on perfusion CT maps). A proportional dependence was observed between cerebral tissue oxygenation and CBV, but not with CBF and MTT. Possibly, vasospasm and cerebral autoregulation were responsible for the lack of maintained relationship between cerebral oxygenation and CBF (which should otherwise be observed considering that CBF=CBV/MTT) [29].

8. Cerebral permeability perfusion CT

When the blood–brain barrier is altered, contrast material extravasation can be observed during the delayed phase of perfusion CT. This has been observed in stroke patients and recently in a

small study of TBI patients. Seventeen patients with severe TBI and three controls were investigated with perfusion CT within 48 h from admission. Increased permeability was observed in the pericontusional area in patients who later developed increased ICP [28]. This is extremely relevant as small molecular permeability will influence capillary hydrostatic and oncotic pressures and influence edema development. Possibly, osmotic treatment (such as hypertonic saline) might be efficient only when all or most of the brain has an intact blood–brain barrier. The implications of understanding and diagnosing blood–brain barrier dysfunction are huge. Potentially perfusion CT might help selecting patients for osmotic therapy rather than the use of sedation agents and/or craniectomy.

9. Future of perfusion CT

The routine imaging protocol for multiple injured trauma patients includes an unenhanced cerebral and cervical CT and an enhanced thoracic-abdominal-pelvic CT. Routinely, also patients with risk factors for cerebrovascular injuries (deceleration, seatbelt mark on the neck, massive facial bleeding) will have the neck and cerebral vasculature evaluated by enhanced CT. Early detection of cerebrovascular injuries is crucial as these arterial injuries can be repaired, stented or otherwise medically treated to minimize the risk or the extent of embolic strokes. We can foresee a near future in which brain perfusion CT becomes part of admission imaging for patients with TBI. The prompt availability of brain perfusion maps might have a huge impact on understanding and treating TBI. With or without the involvement of neurologist and interventional neurologist, these patients might be offered a better targeted treatment and their families are made aware of long-term outcomes by making decisions such as palliation or further treatment based on a more thorough understanding of cerebral perfusion and secondary brain injury.

10. Conclusion

In this chapter, we have identified, reviewed and discussed several aspects of implementation of perfusion CT in clinical diagnostics and research of TBI disease. These include assessment of TBI pathogenesis and prediction of functional outcomes, development of guidance for osmotic treatment, selection of patients for trial inclusion and development of regiments for surgical intervention. Perfusion CT imaging is a technology readily available and ripe for use in the vast majority of patients suffering from TBI. Perfusion CT should be considered in the context of audited research in patients with clinically proven severe TBI and possibly in patients with a less severe degree of TBI. Evidently, perfusion CT possesses eminent potentials and demonstrates a superior efficacy when compared to traditional noncontrast CT.

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