

## Review Article

# Computed Tomography Perfusion for the Diagnosis of Brain Death: A Technical Review

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**ABSTRACT:** Timely diagnosis of brain death (BD) is critical as it prevents unethical and futile continuation of support of vital organ functions when the patient has passed. Furthermore, it helps with avoiding the unnecessary use of resources and provides early opportunity for precious organ donation. The diagnosis of BD is mainly based on careful neurological assessment of patients with an established underlying diagnosis of neurological catastrophe capable of causing BD.

Ancillary testing, however, is tremendously helpful in situations when the presence of confounders prevents or delays comprehensive neurological assessment. Traditionally, four-vessel digital subtraction angiography and computed tomography angiography have been used for blood flow (BF) examinations of the brain. The lack of BF in the intracranial arteries constitutes conclusive evidence that the brain is dead. However, there is an apparent discrepancy between the BF and sufficient cerebral perfusion; several studies have shown that in 15% of patients with confirmed clinical diagnosis of BD, BF is still preserved. In these patients, cerebral perfusion is significantly impaired. Hence, measurement of cerebral perfusion rather than BF will provide a more precise assessment of the brain function.

In this review article, we discuss a brief history of BD, our understanding of its complex pathophysiology, current Canadian guidelines for the clinical diagnosis of BD, and the ancillary tests—specifically CT perfusion of the brain that help us with the prompt and timely diagnosis of BD.

**RÉSUMÉ :** Évaluer la perfusion cérébrale au moyen de la tomographie assistée par ordinateur pour diagnostiquer la mort cérébrale : une étude technique. Il est essentiel de diagnostiquer à temps la mort cérébrale (MC) dans la mesure où cela permet d'éviter la prise en charge des fonctions vitales des organes lorsqu'un patient est décédé, ce qui est inutile et contraire à l'éthique. En outre, cela permet d'éviter l'utilisation injustifiée de ressources et offre la possibilité de procéder de façon précoce à des dons d'organes précieux. Le diagnostic de la MC repose principalement sur une évaluation neurologique minutieuse des patients à laquelle s'ajoute un diagnostic sous-jacent d'un incident grave sur le plan neurologique, incident susceptible de provoquer la MC. Les tests auxiliaires sont toutefois extrêmement utiles lorsque la présence de facteurs de confusion (*confounders*) empêche ou retarde une évaluation neurologique complète. Habituellement, l'angiographie par soustraction numérique (ASN) portant sur quatre vaisseaux sanguins de même que l'angiographie par tomographie assistée par ordinateur (TAO) ont été utilisées pour les examens du débit sanguin (DS) du cerveau. L'absence de DS dans les artères intracrâniennes constitue une preuve concluante que le cerveau est mort. Cependant, il existe une divergence apparente entre le DS et une perfusion cérébrale (PS) suffisante. En effet, plusieurs études ont montré que le DS était encore préservé chez 15 % des patients dont un diagnostic clinique de MC avait été confirmé. Chez ces patients, la PS était significativement altérée. Par conséquent, la mesure de la PS plutôt que du DS fournit une évaluation plus précise de la fonction cérébrale. Dans cet article de synthèse, nous proposerons un bref historique de la MC. Nous nous pencherons ensuite sur sa physiopathologie complexe, sur les lignes directrices canadiennes actuelles pour le diagnostic clinique de la MC et sur les examens auxiliaires, en particulier l'évaluation de la PS par TAO, qui nous aident à diagnostiquer rapidement et à temps la MC.

**Keywords:** brain death; neurological determination of death; computer tomography; computer tomography perfusion

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## Introduction

Brain death (BD) is a relatively new concept, which was first introduced in the 1950s following the advances in life-sustaining technologies including mechanical ventilation.<sup>1,2</sup> A subgroup of ventilated patients with recognized catastrophic cerebral

conditions was identified as brain dead due to irreversible cessation of all brain functions, including the brainstem reflexes.<sup>3,4</sup> A decade later in 1967, the first human heart transplantation surgery was successfully performed, and the donor was a patient diagnosed with BD. Following this historic event, the necessity of

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defining unified neurologic criteria for the diagnosis of BD was perceived.<sup>4</sup>

In 1968, the first set of neurologic criteria for the diagnosis of BD was developed by a Harvard ad hoc committee in the United States. Based on their criteria, the definition of BD is “irreversible cessation of all functions of the entire brain, including the brainstem.”<sup>5,6</sup> More than fifty years later, the principles of BD are still the same. However, the criteria for BD have been constantly evolving in parallel with the advances in neuroimaging.<sup>7,2</sup>

From a pathophysiological perspective, a catastrophic injury to the brain can lead to elevated intracranial pressure (ICP). When the ICP rises significantly, surpassing both the mean arterial pressure and diastolic perfusion pressure, it can cause a critical compromise of cerebral circulation, ultimately leading to its arrest. Raised ICP initially impedes cortical capillary blood flow (BF), and then gradually extends to the larger arterial branches, the circle of Willis, and eventually to the venous system. This adverse event usually leads to the gradual loss of brain function from the more rostral compartments of the brain including the cerebral hemispheres to the more caudal compartments in the brainstem. The loss of brainstem function also follows a rostral to caudal pattern and the medulla is usually the last part of the brainstem that stops functioning manifesting with the loss of respiratory drive in the patient.<sup>2,8</sup> However, in recent years isolated brainstem death has been identified as a new etiology of BD. In a subgroup of patients, isolated lesions to the brainstem or isolated disruption of the posterior cerebral circulation causes irreversible loss of functions of the brainstem, which consequently results in BD. In these patients, the BF to the anterior circulation might be preserved. Clinically, there is no difference between the whole brain and brainstem death. However, pathophysiologically isolated brainstem death does not follow the rostral to caudal brain function loss, as mentioned earlier.<sup>9,10</sup>

Although in theory the concept of BD could be thought of as straightforward, the diagnosis of BD can be very challenging. This is particularly true in critically ill patients who have been on mechanical life support. The diagnosis of BD primarily relies on a meticulous clinical assessment. Nevertheless, in various situations, where multiple confounding factors are present, a comprehensive clinical evaluation may not be feasible, and additional testing may be imperative to confirm the final diagnosis of BD.<sup>11</sup> Canadian guidelines recommend a minimum of two clinical criteria (established etiology capable of causing neurological determination of death (NDD) and a deep unresponsive coma) to be met before ancillary testing can be performed. A demonstration of global absence of intracerebral BF is considered by the Canadian guidelines to be standard for diagnosis of BD.<sup>12,13</sup>

## Defining BD

In Canada, the criteria for BD have been defined in accordance with the World BD project.<sup>7,12,13</sup> Before considering the diagnosis of BD, an established underlying cause of the neurologic catastrophe, capable of causing BD, is necessary. To establish the irreversibility of the condition, depending on the etiology, there is a waiting period. Patients should remain in a deep unresponsive coma during this time. In an ideal scenario, where confounding factors are absent, clinicians should conduct a comprehensive BD examination. The neurological evaluation must demonstrate no motor responses, except for spinal reflexes in response to maximal external stimulation. Brainstem reflexes such as corneal, pupillary,

vestibulo-ocular, gag, and cough reflexes should all be absent. Additionally, apnea testing should show no respiratory effort.

The presence of numerous confounders, including severe craniofacial and high cervical spine trauma (which may interfere with the assessment of the brainstem reflexes, and apnea test, respectively), the lingering effects of medications that affect level of consciousness, and/or the motor response can make the clinical diagnosis of BD impossible. The limitation of clinical evaluation in these situations led to introduction of ancillary tests including four-vessel digital subtraction angiography (DSA), computed tomography angiography (CTA), transcranial Doppler ultrasonography, nuclear scintigraphy, and recently CT perfusion scan (CTP) to support the diagnosis of BD. An ideal ancillary test should be readily available, non-invasive, fast, and most importantly with high sensitivity and specificity.

## Ancillary Imaging BD Testing

The lack of BF in the intracranial arteries constitutes conclusive evidence that the brain is dead, although there are currently no agreed-upon universal criteria for determining BD by radiographic means. Having said that, there is an apparent discrepancy between the BF and sufficient cerebral perfusion. Several studies have shown that in approximately 15% of the patients with confirmed clinical diagnosis of BD, the intracranial BF is still preserved.<sup>5,6</sup> In fact, cerebral perfusion is more susceptible to the increases in the intracranial pressure, and lack of adequate perfusion results in loss of neuronal function and eventually irreversible neurological damage and BD. Therefore, measurement of cerebral perfusion rather than BF will provide a more precise assessment of the brain function.

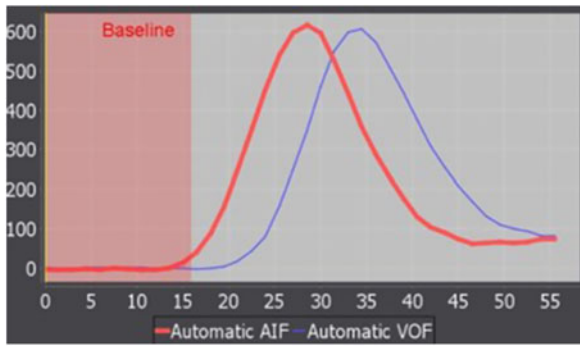
## CT Perfusion as an Alternative

CTP of the head is a specialized form of CT scan that involves acquiring multiple volumes of images while administering intravenous contrast. This technique analyzes alterations in the density of contrast in the blood on sequential imaging of the brain. As a result, it enables the evaluation of which regions of the brain are appropriately supplied with blood (perfused) and offers precise information regarding blood flow to the brain. CT perfusion is fast, noninvasive, and a readily available ancillary test that can be performed in all modern CT scanners. CTP is a useful technique for measuring blood flow to the brain and is commonly used for assessment of patients with stroke, brain blood vessel disease, and brain tumors.

## Technical details

Previously, CTP was limited to a single axial slice of the brain. However, with advancements in CT scanner technology and faster image acquisition, modern scanners can now conduct CTP with whole-brain coverage. A minimum of 10–12 cm coverage in the z-axis is essential for complete brain imaging via CTP. In instances where only partial brain coverage is achievable, tilting the head during scanning can optimize head coverage on CTP. For the purpose of BD declaration, whole-brain coverage of CTP is ideal. On scanners where only partial coverage of head is possible, CTP coverage should start from the level of foramen magnum and up.

Most scanners use 40–60 ml of intravenous contrast injected at the rate of 4–5 ml per second through a minimum of 18G cannula. Total time of acquisition varies from 60 to 90 seconds. The image acquisition for CTP starts before injection of contrast to acquire



**Figure 1:** The time density curve that shows the acquisition of images (till first 12 seconds) before contrast arrival, bell-shaped curve in the arteries (red) and vein (blue), and the total time of acquisition. In this case, the total time of acquisition was 55 seconds.

baseline images with no contrast and images are acquired at 15–20 time points with 2–6 seconds time interval in the arterial phase and 10–20 seconds in the venous phase (Fig. 1). The total number of images acquired during a CTP ranges from few hundred to few thousand images depending on the scanner type. The radiation dose for a CTP is equivalent to that of one or two plain-head CTs.

The acquired images are then post-processed for qualitative and quantitative assessment. Most scanners come with their own vendor-specific post-processing software. However, multiple vendor-neutral post-processing software packages are available for clinical use in most centers. Post-processing of CTP has been automated in most of these post-processing software packages. There is automated selection of intracranial arterial input function (AIF) and venous output function (VOF). However, in patients with suspicion of BD, no intracranial flow is expected. In these patients, the AIF and VOF are selected extracranially, preferably at the base of skull. In patients with suspected brain death and absent of intracranial BF, AIF and VOF are selected most of the time in the external carotid artery branches.

**Quantitative and qualitative analysis of the CTP**

In common clinical practice, most of the CTP images are analyzed qualitatively on visual inspection of the colored maps from CTP. For

qualitative analysis for BD confirmation, we look for the presence of a matched marked decrease of both cerebral blood flow (CBF) and cerebral blood volume (CBV) (Fig. 2). Research has demonstrated that subjective, qualitative evaluation exhibits excellent inter-rater reliability among experienced readers and trainees. This is likely due to the decline in CBF and CBV in individuals with BD is global and prominently observed (as illustrated in Fig. 2), making it arduous to overlook or misinterpret.

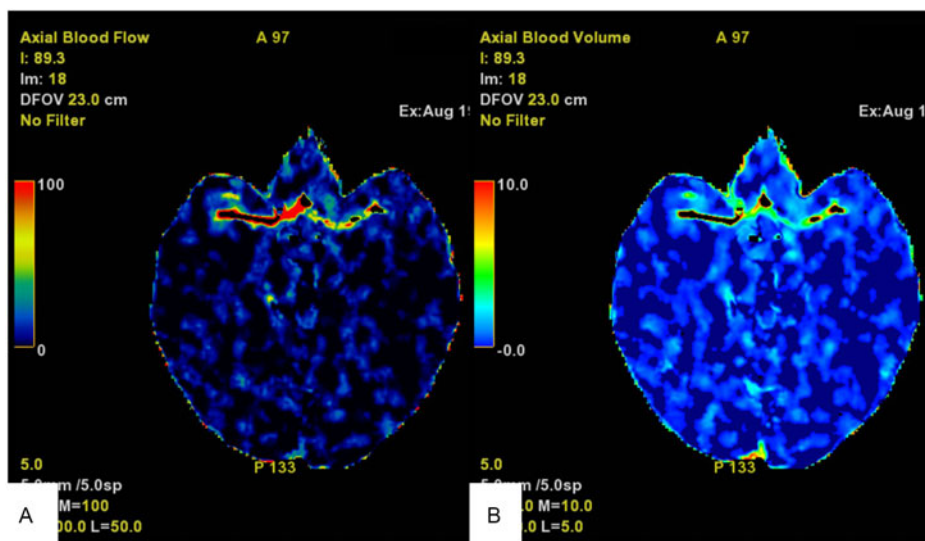
For quantitative assessment of CTP images, two consecutive axial cross-sections should show very low CBF and CBV. These axial regions of interest (ROIs) can be placed across any brainstem region. To confirm diagnosis of BD, the CBF and CBV should be less than 10 mL/1000 g/min and 1.0 mL/100 g, respectively, across the two consecutive cross-sections of brainstem.

**CTP for BD**

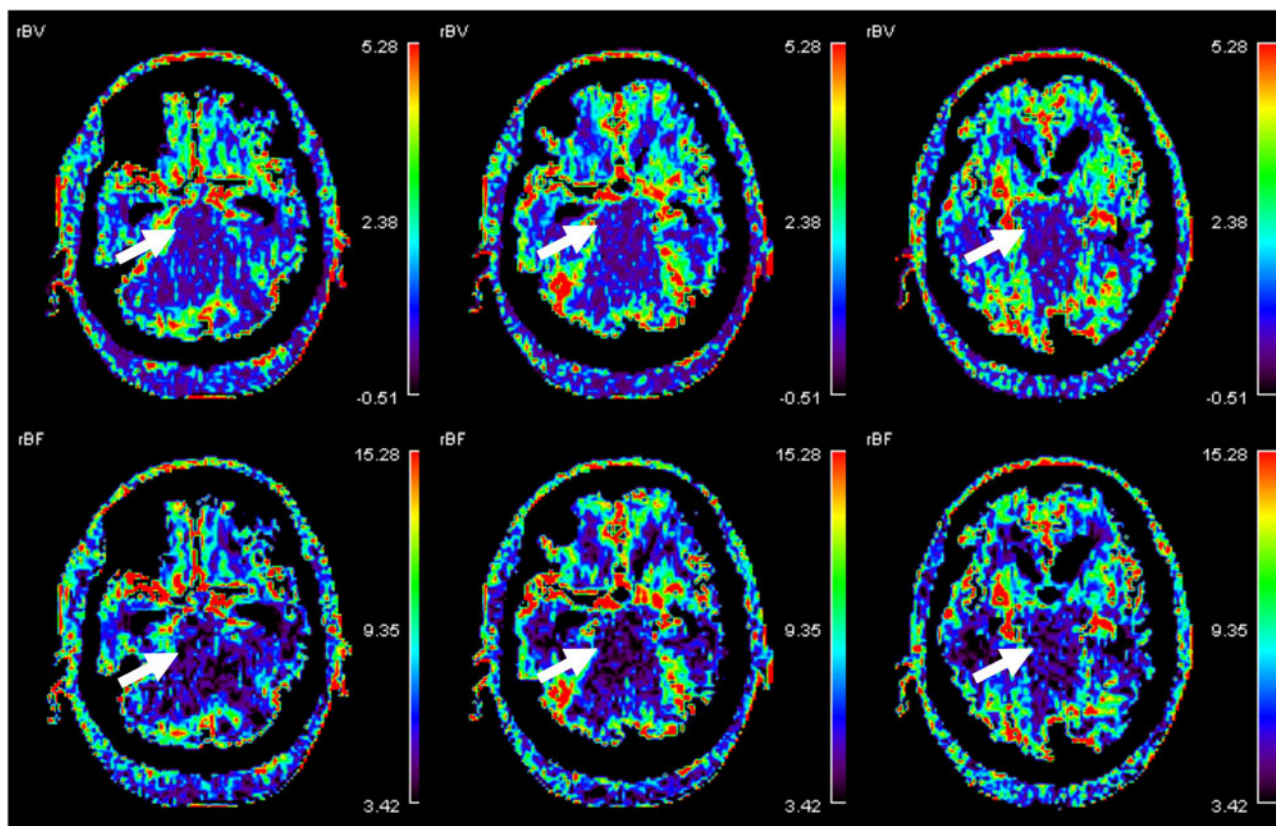
Perfusion imaging, such as the CTP, has shown a high sensitivity and specificity in the diagnosis of BD.<sup>16</sup> CTP studies are based on the first passage of contrast bolus through the blood vessels (from the arterial to capillary to venous phase) and therefore are less operator-dependent. In addition, CTP is noninvasive and readily accessible 24 hours a day in most centers handling stroke patients. CTP provides both qualitative as well as quantitative assessment of the brain perfusion. For BD determination, the two key CTP parameters are CBV and CBF.

Normal brain function is dependent on normal CBF, which is 50–60 ml/100 g/min. If the CBF drops to 35 ml/100g/min, protein synthesis and normal function of the neurons will be discontinued. When it further drops to less than 20 ml/100g/min, electrical activity ceases resulting in no functional activity on the electroencephalogram, and eventually at less than 10 ml/ 100g/min, irreversible neuronal injury occurs.<sup>17</sup> Therefore, the presence of BF in the large arteries is not necessarily disproving of the diagnosis of BD.<sup>1,13–15</sup>

Shankar et al.<sup>16</sup> were the first to demonstrate the role of CTP in confirmation of BD. They found that the addition of CTP to CTA increased the sensitivity of CTA in BD confirmation. The findings indicate that intracranial perfusion was absent in all patients, except for two cases in which the brainstem showed no perfusion but the rest of the brain had preserved perfusion. These patients had initially been diagnosed with intracranial hemorrhage,



**Figure 2:** CT perfusion colored maps in a patient of suspected brain death. This shows diffuse markedly decreased cerebral blood flow (a) and cerebral blood volume (b). These are classic CTP findings for patients with brain death.



**Figure 3:** CTP images for a patient suspected to be brain dead show matched marked decrease (arrow) in the cerebral blood flow (bottom row) and cerebral blood volume (top row) in the brainstem but preserved perfusion in the rest of the brain. These are the perfusion findings for isolated brainstem death.

cardiac arrest, and hemorrhagic shock. These results underscore the importance of evaluating brainstem perfusion to confirm the diagnosis of BD.

Sawicki et al.<sup>20</sup> have shown that the CBF was less than 10 ml/100g/min and the CBV was less than 1.0 ml/100 g in ROIs in all brain regions including the brainstem in all the 50 patients with the confirmed diagnosis of BD. Interestingly, CTA of 7 out of 50 patients showed preserved intracranial BF. Therefore, based on this study, CTP has 100% sensitivity, and CTA has 86% sensitivity for the diagnosis of BD. It is also just worth noting that the 10ml/100g/min is a short duration and may not necessarily result in irreversible neuronal injury. The duration and depth of ischemia should indeed be taken into consideration. As in the case of patients with suspected BD, these patients usually have prolonged duration of ischemia.

In another study, that examined 27 patients who had a confirmed BD diagnosis based on their neurological examination, the combined sensitivity of CTA and CTP to confirm the absence of the CBF was 89%. They concluded that these two studies could be an alternative to the traditional 4-vessel angiography particularly when DSA is not accessible.<sup>7</sup> Similar to Shankar et al. study,<sup>16</sup> they had one patient (patient was admitted with severe traumatic brain injury) with preserved BF in the bilateral cortical hemispheres, but with an absence of BF in the posterior fossa. The patient was eventually diagnosed with BD.<sup>7</sup>

### Isolated Brainstem Death (IBD)

The internationally agreed-upon definition of death now includes permanent brainstem loss.<sup>6</sup> While in ancillary tests radiologists look

at CBF across all areas of the brain, it may be of great value to assess the brainstem separate from the rest of the brain. Isolated brainstem death (IBD) can be declared when there is a match perfusion defect in more than one axial slice.<sup>6</sup> The CTP imaging modality was the first ancillary test to objectively demonstrate IBD.<sup>6</sup>

In patients with IBD, the declaration of BD is delayed due to inconclusive CTA showing BF in the large vessels of the bilateral hemispheres, while CTP shows a lack of perfusion in the brainstem. Although the pathophysiology of IBD is not well-understood, it is described in brainstem stroke. In fact, IBD due to the vertebrobasilar artery occlusion and brainstem infarction is a well-recognized cause of irreversible coma and BD. In these patients, complete lack of perfusion to the brainstem results in cessation of brainstem function and brainstem reflexes while the BF to the rest of the brain is preserved (Fig. 3).<sup>21,22</sup>

According to a study, IBD in five patients concurred with the clinical exam demonstrating absence of brainstem function.<sup>6</sup> In addition, six more patients in the study showed defects in the brainstem that was not consistent with complete IBD.<sup>6</sup> All six patients were then declared dead within a week of CTP imaging.<sup>6</sup> The detection of absent or severely reduced blood flow to the brain, as indicated by CTP, may be a potential marker of poor prognosis in patients with brain injury, including brainstem dysfunction. Early recognition of such markers could help the healthcare team initiate appropriate end-of-life discussions and organ donation conversations in a timely manner, avoiding delay until it is too late. Furthermore, these findings could help in providing important information to the families of the patients, setting realistic expectations, and guiding them toward making informed decisions about end-of-life care

options. By detecting early signs of neurological damage, CTP could potentially assist in preventing futile interventions and minimize unnecessary suffering for patients and their families.

### Additional Ancillary Imaging Flow Studies

Traditionally, CTA has been employed as a tool to confirm cessation of the intracranial BF in patients with the clinical diagnosis of BD.<sup>3,8,11</sup> The sensitivity of CTA for supporting the diagnosis of BD is highly variable and depends on the methodology and the criteria that are used for this diagnosis.<sup>14</sup> Many false positive and false negative results in different studies make this modality less accurate for establishing the diagnosis of BD when clinical assessment is impossible due to the presence of confounders.<sup>15,14</sup> Despite these limitations, many centers still use CTA as an ancillary test for confirming the diagnosis of BD, primarily since CTA is the most readily and widely available noninvasive imaging modality.

Four-vessel DSA has been considered the gold standard to show cessation of BF in the anterior and posterior circulations of the brain, as DSA was one of the first imaging modalities to demonstrate intracranial BF.<sup>8</sup> However, this modality is invasive, time-consuming, expensive, and it is not accessible in all centers 24 hours a day. In addition, studies showed false negative results with this modality, where the BF (particularly in the posterior circulation) was present, but the patients were clinically confirmed to be brain dead.<sup>8</sup>

The main explanation for this phenomenon is the discrepancy between the BF, brain perfusion, and the brain function; flow is described as the constant and steady movement of the blood in the arterial blood vessels, which results in opacification of the vessels in CTA, and DSA studies.<sup>16</sup> In contrast to blood flow, blood perfusion refers to the circulation of blood within the brain's capillary bed, which cannot be evaluated via CTA or DSA studies. Efficient perfusion to the brain tissue is critical for proper brain function, defined as the continuous integration of inputs and the production of appropriate responses to internal and external stimuli in both the cerebrum and brainstem. Normal brain and brainstem function can be evaluated via meticulous neurological examination, provided that confounding factors are not present. In summary, while both CTA and DSA assess blood flow, they do not provide information regarding brain perfusion or its function.

It is important to note that the findings of CTP can be demonstrated on other imaging techniques used for assessment of brain perfusion such as magnetic resonance perfusion, single photon emission computed tomography, or positron emission tomography. However, CTP is more readily and widely available and has the least contraindications for use.

### Future Directions

CTP has been proposed as a triage tool for diagnosis and prognosis of critically ill patients with known high mortality rates. Small clinical studies have shown that CTP is a useful triage tool in patients with severe traumatic brain injury when performed at the time of their hospital admission.<sup>24</sup> Changes in the brain illustrating BD were present on admission CTP in 75% of patients who died in the first 48 hours of hospital admission. The highest sensitivity and specificity were seen for the brainstem changes on CTP.

Similar results were seen on CTP done at the time of hospital admission in comatose patients after out-of-hospital cardiac arrest.<sup>17</sup> In the pilot study, CTP had 100% sensitivity and specificity in diagnosing brainstem death early on admission.<sup>17</sup>

Both prospective studies were small but critical to show 100% positive predictive value, that is, when CTP showed BD, none of

these patients were proven not dead (or alive) on follow-up. The early prediction of mortality outcome in these patients with a proven high mortality rate may help decisions for withdrawal of life support. It may also facilitate procurement of organs for transplant in eligible patients.<sup>16–19</sup> It will be interesting to find out the results of larger prospective studies on these patients.<sup>27–28</sup>

While CTP provides promising opportunities as an ancillary tool for evaluating BD, there are noteworthy limitations that must be considered. These limitations include the timing and accessibility of the test, as well as the variability in software and hardware configurations across different centers, which may contribute to errors. Availability and extensive use of fully automated or semi-automated post-processing commercial softwares have significantly reduced these variabilities.

### Conclusion

Determining BD is a complex and delicate matter. While clinical assessment remains the gold standard for BD determination, ancillary tests are increasingly utilized to support this process. Recently, CTP studies have shown remarkable outcomes, indicating that this technique could potentially revolutionize our approach to confirming BD. Furthermore, CTP may be explored for other clinical indications in the future, highlighting its potential as a valuable diagnostic tool.

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**Competing interests.** None.

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