Bayesian CT Perfusion Imaging in Ischemic Stroke

Thomas Pickersgill, Global Clinical Marketing Manager, Healthcare IT, Canon Medical Systems
Jeroen Tijhaar, Application Development Specialist, CT, Canon Medical Systems
Chloe Steveson, Senior Application Development Specialist, CT, Canon Medical Systems
Erin Angel, Senior Manager, Clinical Collaborations, Canon Medical Systems USA

Introduction

Stroke accounts for more than one in every 6 deaths in the United States[1]. In the treatment of cerebral ischemia, it is often said that "time is brain." The faster the clinician can detect areas of decreased blood flow and determine the optimal treatment pathway, the better the patient's chances for survival and recovery.

Advanced imaging now appears to have established its role in the standard workup of acute stroke. Recently published trials have demonstrated the benefit of advanced imaging for selecting patients who may benefit from endovascular treatment after the traditional time window of 6 hours after ictus[2,3,4]. Moreover, recent updates of the stroke definitions by the American Heart Association and American Stroke Association have large shifted from a clinical diagnosis to an advanced imaging-based diagnosis of stroke and stroke subtypes[5].

In one clinical trial the researchers demonstrated that 45% of patients treated with the clot removal procedure within the 16-hour time frame achieved functional independence 90 days after treatment, compared with 17% in the control group. Thrombectomy was also associated with improved survival: 14% of the treated group deceased within 90 days of the study, compared with 26% in the control group[4].

Similar to the aforementioned trial, another multi-center stroke treatment study investigated the response to therapy for stroke patients. This trial monitored the impact of mechanical thrombectomy patients who were last seen well 6-24 hour prior to treatment. Patients in the thrombectomy group were less impaired at 90 days post-treatment compared to the standard care group. Rates of functional independence at 90 days were 49% in the thrombectomy group, compared to 3% in the control group[3].

For perfusion analysis to be effective and accurate, the data needs to be taken with an imaging modality capable of acquiring temporally uniform dynamic images of the entire anatomy, have sufficient temporal sampling, and the perfusion algorithm which can represent flow characteristics and remain independent of the image acquisition and contrast injection processes.

CT perfusion was traditionally confined to imaging only a portion of the brain. With the introduction of the Aquilion ONE area detector CT in 2007, the scope of cerebral perfusion analysis was changed by enabling dynamic volume imaging of the entire brain with isophasic and physiological uniformity.

Dynamic volume, whole brain imaging on Aquilion ONE was recently paired with the Bayesian perfusion algorithm to produce advanced CT perfusion imaging. Bayesian is the latest advancement in CT perfusion algorithm science. This algorithm was originally developed for MRI DWI and PWI analysis[6]. The Bayesian algorithm is delay insensitive and adapts for contrast injection timing and flow characteristics. A key feature of the Bayesian algorithm is a lower noise CTP map[7], thus improving the visualization and quantification of CTP maps used for clinical diagnosis.

This paper reviews the principles of brain perfusion, discusses methods of measuring perfusion, and describes the unique benefits of whole brain CT perfusion imaging used in conjunction with the Bayesian perfusion algorithm.

The primary application of brain perfusion imaging in CT is to determine whether the patient has had a stroke and to assess the viability of the brain tissue. Stroke diagnosis and management is a significant focus in today's hospitals because stroke is the fifth leading cause of death in the United States and a major cause of serious long-term disability[8,9].

When a patient presents with stroke symptoms, a non-contrast CT is typically used to visualize bleeding and to rule out haemorrhagic stroke. However, in 85% of strokes there is no intra-cranial bleed[10]. Once a haemorrhagic stroke has been ruled out, a CT perfusion examination is performed. Perfusion measurements are used to visualize effects of ischemic stroke. Perfusion measurements help distinguish which areas of the brain show signs of irreversible damage and which areas of the brain may be saved through intervention. In this way, perfusion analysis can help clinicians estimate treatment response and develop therapeutic pathways designed specifically for individual patients. Routinely after a haemorrhagic stroke has been ruled out an angiogram of the carotid arteries will also be performed to assess possible causes of the patient symptoms[10].

Cerebral CT perfusion is discussed primarily in the context of characterizing stroke, but perfusion measurements are also valuable for a range of clinical applications such as the evaluation of vasospasm[11], vasculitis[12], assessment of perfusion after head trauma[13] and determining microvascular permeability in brain tumours[14].

Pathophysiology

Healthy brain tissue relies on continuous flow of oxygenated blood and requires a precise pressure balance to remain viable. Blood is supplied to the brain via four major arteries: the left and right carotid and vertebral arteries. When the brain is working properly, all blood flows into the brain from arterial inputs, remains in the cerebral vasculature (arteries, capillaries or vessels) and exits the organ through the veins (Figure 1).

Since the brain is surrounded by the skull, there is little room to expand to accommodate pressure changes. To maintain the delicate pressure balance, the cerebral vasculature has a unique autoregulation mechanism to automatically adjust flow. Blood flow is regulated primarily through vasodilation, vasoconstriction and collateralization. Vasodilation and vasoconstriction are the automatic dilation and constriction of vessels to regulate blood flow and maintain blood pressure. If a region of the brain is receiving inadequate blood supply, the vessels will automatically dilate to restore blood flow to the region. Likewise, if there is too much blood pressure in an area, the vessels will constrict to reduce flow. Collateralization is the redirection of blood to a region using small "detour" vessels called collateral arteries. Collateral arteries are typically small (often closed) arteries that can open, expand, or extend to redirect blood around a blockage. Autoregulation can compensate for small or transient changes in blood pressure, but once the vessels have reached their expansion limit, and if collateral flow is insufficient, the brain tissue will become ischemic (deprived of blood flow). When an area of the brain becomes ischemic, there are two possible consequences for the cells in that region. If the cells have been deprived of blood for an extended time, they will eventually become irreversibly damaged and die. These cells are unsalvageable and form a region called the ischemic core. Surrounding the infarct core are cells that are starved for blood but have not yet died and if blood flow can be restored, the cells will recover. This salvageable region is called the ischemic penumbra (Figure 2).

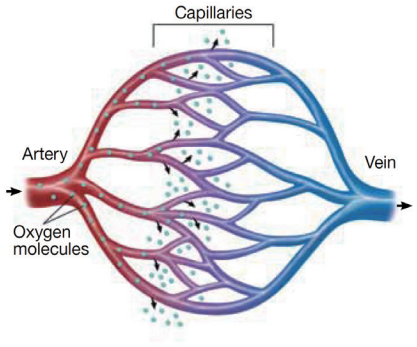


Figure 1 Blood enters the brain via the arteries and then flows to the capillaries where oxygen is released to the brain tissue. The deoxygenated blood then exits via the veins.

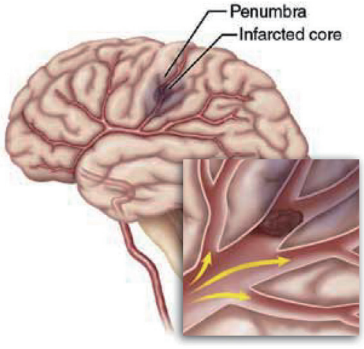


Figure 2 When a vessel is obstructed, brain tissue may become deprived of blood supply. Eventually, blood starved brain tissue will become irreversibly damaged causing an infarct core. Surrounding the infarct core is a region where the blood supply is reduced, but less critically, and the brain tissue can survive for a time. This area, called the ischemic penumbra, can be saved and is the target for stroke intervention.

For stroke patients, perfusion imaging is used to visualize ischemic tissue, and to quantify the infarct core and penumbra. The infarct core is used to diagnose acute stroke or confirm suspected diagnosis of stroke. The ischemic penumbra is measured to determine whether the patient is a good candidate for revascularization therapy. Revascularization can be performed interventionally using a clot retrieval device or by using pharmaceutical agents such as thrombolytic reperfusion agents. Thrombolytic agents can dissolve blood clots and return flow to ischemic regions. However, in areas of ischemic core, these agents can cause increased risk of hemorrhage. In recent trials, thrombolytics have proven effective if administered up to 24h after stroke onset[3,4].

Canon Medical Systems' Neuro ONE protocol allows full stroke workup in a single examination that includes physiological and anatomical information about the entire brain[15].

This uniquely comprehensive exam combines whole brain dynamic perfusion maps to analyse blood flow and characterize brain tissue viability, as well as a 4D CT Digital Subtraction Angiogram (4D CT DSA) to help visualize obstructed vessels for treatment planning[12,15-18]. The entire exam is performed in less than five minutes with low contrast dose (50 mL of intravenous contrast) and low radiation dose (typically less than 5 mSv for the entire exam).

CT or MR

In MR, perfusion weighted imaging (PWI) can be combined with diffusion- weighted imaging (DWI) to characterize the penumbra. Perfusion CT can be used to quickly visualize stroke effects by monitoring the flow of blood through the cerebral vasculature. Studies have demonstrated that in terms of patient selection for reperfusion therapies, CT and MR are equally proficient in characterizing regions of infarct and penumbra[19,20].

Traditionally CT perfusion was limited by partial brain coverage (typically 4 cm or less), partial volume effect of vessels, and artefact in the posterior fossa (Figure 3). Today's CT scanners are now capable of high resolution, three-dimensional imaging, essentially eliminating the previous concerns. The partial brain coverage limitations of CT perfusion were overcome with the introduction of Aquilion ONE. Dynamic volume perfusion imaging can be performed for the entire brain with 16 cm of anatomical coverage and with temporal uniformity (Figure 4). The Aquilion ONE technology has overcome the previous limitations of CT perfusion, making it an attractive alternative to MR for stroke evaluation. Another clear advantage of CT for acute stroke workup is that there is no contraindication for patients with metallic or electrical implants such as aneurysm clips or pacemakers (which can be common in stroke patients). Also, patient monitors or ventilators containing metal can be used during the CT exam. In the case of the Neuro ONE protocol on Aquilion ONE, the entire stroke workup can be combined into a single exam, thus minimizing contrast and radiation dose, and minimizing exam time.

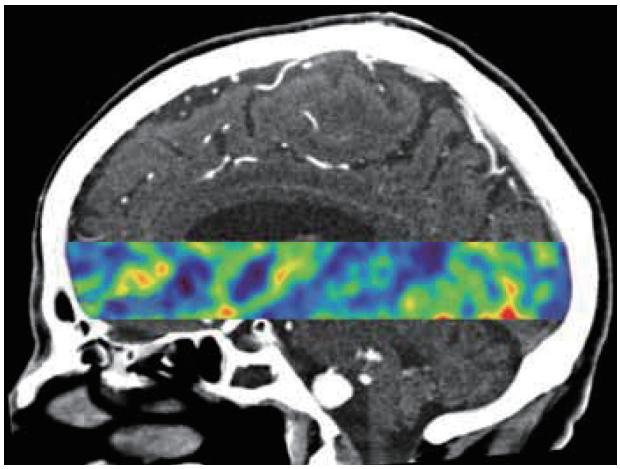


Figure 3 MDCT perfusion scanning: With a scanner that acquires less than the entire head in a rotation, the user has to make some sacrifices in either coverage or accuracy. This image shows accurate perfusion values over the narrow range that can be imaged dynamically without table motion using a conventional multidetector system.

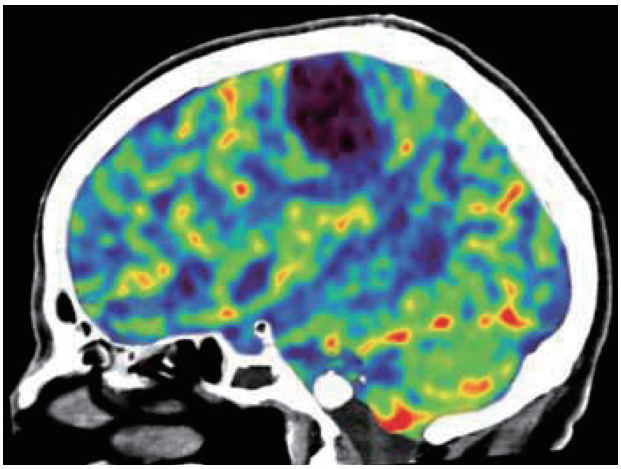


Figure 4 Dynamic volume perfusion scanning: With whole head volumetric coverage, the Aquilion ONE acquires accurate perfusion maps of the entire brain showing the large, superior lesion that would have been completely missed using conventional MDCT technology.

Although advanced imaging now seems to have established its role in the standard workup of acute stroke, there is still debate whether CT perfusion imaging or MR imaging should be used to visualize the infarct core and penumbra[21,22]. On the one hand, CT perfusion provides a more practical approach that does not delay treatment decisions since patients already undergo non-contrast CT and CT angiography imaging. On the other hand, MR diffusion weighted imaging (DWI) is still the reference standard in most centers for defining the ischemic core and there may be a mismatch between infarct measurements using CT perfusion and DWI[23]. It has been postulated that these differences may be a result of high image noise and low signal to noise ratios (SNR) in CT perfusion imaging compared to DWI[24].

CT Perfusion – Basic Principles

To measure cerebral perfusion using CT, intravenous contrast agent is administered to the blood stream and a series of CT images are acquired over time to observe arterial input, tissue uptake, and venous outflow of the contrast agent. Since blood remains in the vasculature, the tissue uptake is actually a measure of the blood in small vasculature and capillaries. As the contrast-labelled blood enters the anatomy, the contrast density increases to a peak enhancement and then decreases as that blood washes out of the region. Contrast density is determined by measuring the temporal change in CT number of an input artery, the brain tissue and an output vein. For each measurement, a graph is generated which plots the CT number (Hounsfield unit) versus time. These graphs, called time density curves, represent the uptake and washout of contrast-labelled blood in an artery, in brain tissue and in a vein (Figure 5).

In order to generate cerebral perfusion maps, it is necessary to generate a separate tissue TDC for every voxel in the brain. For simplicity, a single artery input and venous output are tracked throughout the dynamic scan. This results in one arterial TDC, one venous TDC and several tissue TDCs — one for each voxel in the brain. To generate the arterial and venous TDCs, regions of interest (ROIs) are automatically placed in optimally chosen large vessels that are perpendicular to the scan acquisition plane. Typically, the arterial ROI is chosen in an anterior cerebral artery or a middle cerebral artery. The venous ROI is often placed over the superior sagittal sinus, transverse sinus or torcular herophili.

Temporal Sampling

To perfectly sample the time density curves, imaging would have to be performed continuously throughout the exam (like filming with a video camera). But to minimize dose, images are only acquired frequently enough to reliably reconstruct the curves. To accomplish this, images are acquired intermittently as the contrast agent moves through the brain. CT numbers are recorded at each time point and time density curves are generated (Figure 5). The Aquilion ONE has the advantage that the entire brain can be imaged without table movement and, therefore, the sampling rate is not limited by the time it

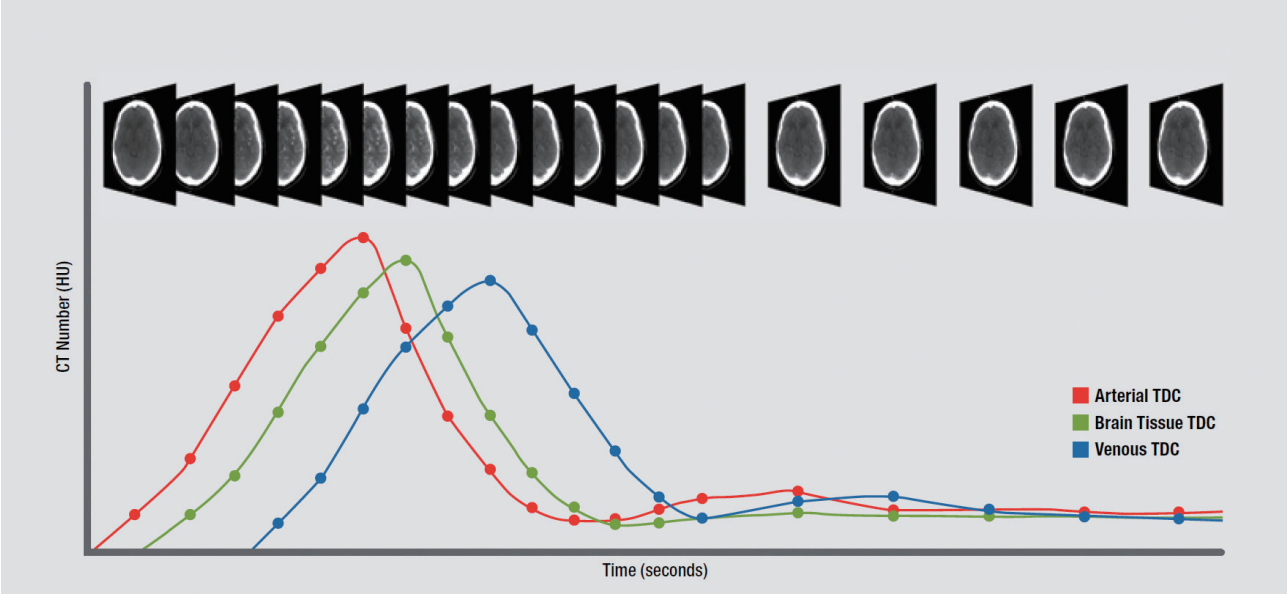


Figure 5 In order to create brain perfusion maps, the Time Density Curve (TDC) is measured in an artery, in a vein, and at each voxel in the brain tissue to visualize the uptake of contrast-labeled blood.

would take for the table to move the length of the brain. This dynamic volume imaging allows the sampling rate to be adjusted, depending on the application, to ensure an accurate measurement of the TDC while maintaining low dose.

Temporal Uniformity

To obtain accurate and complete perfusion maps, the scanner must image the entire brain at a single instance in time so that the flowing intravenous contrast does not have time to change during the acquisition. With 16 cm of coverage, the Aquilion ONE CT scanner is capable of dynamic volume imaging of the entire brain with temporal uniformity so that all contrast-labelled blood is visualized at the same point in time.

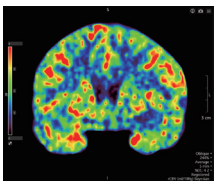
Quantitative Maps

In perfusion studies, the TDCs are used to calculate several parameters at each location in the brain thus generating quantitative perfusion-related maps, which help clinicians characterize cerebral pathophysiology. (Figure 6). Each of the perfusion maps can indicate pathologies or different flow irregularities. Longer TTP or Delay may indicate delayed flow from collateral autoregulation. MTT, TTP, and Delay visualize vasospasm or vessel stenosis that cannot otherwise be seen.

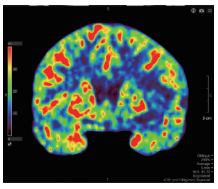
Consider, for example, a patient with an ischemic stroke caused by an occlusion in the middle cerebral artery. The occlusion will reduce the perfusion to the affected region of the brain as demonstrated by decreased CBF. This reduced flow will trigger an autoregulatory response and feeding arteries will dilate to restore flow to the region. This vasodilation is depicted as increased MTT (analogous to the length of time it takes for a log to float down the wider parts of a river as opposed to the rapids). If blood is restored via collateral circulation, the more tortuous path of collateral vessels means it will take more time for blood to reach the region. This delayed time of arrival is visible in the TTP and Delay maps. Autoregulation maintains blood supply to the region as demonstrated by an increase or maintained CBV until the vessels can no longer dilate and collateralization cannot maintain cerebral reserve, at which point CBV will decrease demonstrating infarct. In this example, the mismatch between CBF and CBV represents the ischemic penumbra.

Perfusion algorithms

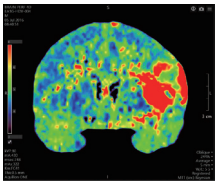
There are several ways to calculate perfusion parameters from the TDC's, including the maximum slope method, gamma-variate, moments-method, deconvolution and Bayesian methods.



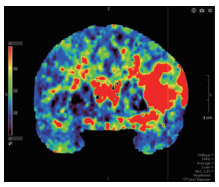
Cerebral Blood Volume (CBV)
- Volume of blood per unit brain tissue
- In units of mL per 100 grams of brain tissue
- CBV permits evaluation of autoregulation



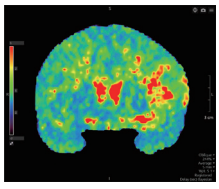
Cerebral Blood Flow (CBF)
- Amount of blood flowing through capillaries per unit time per unit tissue
- In units of mL per minute per 100 grams of brain tissue
- CBF identifies areas of low blood flow



Mean Transit Time (MTT)
- Average time for blood to move through capillary vessels
- In units of seconds
- An increase in MTT can indicate a vasodilatory response to reduced flow



Time To Peak (TTP)
- Length of time for brain tissue to reach peak density enhancement
- In units of seconds
- TTP is an indicator of delayed flow due to stenosis or occlusion
- TTP is also helpful in identifying collateralization



Delay
- Relative arrival time for contrast in tissue voxels
- In units of seconds
- Delay maps differ from TTP in that Delay time is independent of contrast injection delivery

Figure 6

SVD+

There are several types of deconvolution that can be used for perfusion analyses. Singular Value Decomposition (SVD+) is a delay insensitive SVD algorithm that uses an innovative technique to account for delayed blood flow and perform calculations with fast computation times. SVD algorithms are often viewed as the most accurate method because they rely on less assumptions than other methods, however these algorithms are sensitive to noise and in some occasions, can result in underestimation of high MTT and CBF values and overestimation of low CBF values in certain conditions.

Bayesian

Canon Medical Systems has now introduced the Bayesian post-processing algorithm to the CT perfusion application.

The Bayesian algorithm has been designed as an algorithm to be independent of clinical protocols and acquisition techniques. With the aim of improving patient diagnosis by increasing the accuracy of hemodynamic parameter measurement in CT perfusion.

The Bayesian method is a probabilistic algorithm, which is based on Bayes theorem[25]. The Bayes theory of probability was first published in the 18th century. The theory allows the combination of experimental data and a priori information regarding the parameters of a model (such as CBF and MTT values), to generate a robust probability distribution for these parameters[26,27]. Thanks to this probabilistic approach, the hemodynamic parameter measurements are more robust in comparison to other algorithms[25].

The Bayesian method uses a delay insensitive probabilistic approach to CT perfusion. The delay insensitive approach enables the algorithm to calculate a delay in CT perfusion independent of MTT values, that considers autoregulation, which help provide accurate measurements of delay values. This approach has been validated in a number of clinical studies and digital phantom tests[7-9,28-31].

When performing CT perfusion, high levels of noise often prevent the accurate measurement of penumbra volumes when using deconvolution-based methods. In comparison, the Bayesian method has been proven in multiple studies to be more robust against noise to reliably measure CT perfusion parameters when SNR is low[6,30,31].

A study by Boutelier et al.[6] assessed CT simulated data. The authors observed that, when SNR o r CBV decreased, the quality of measurements degraded much faster with alternate algorithms as compared to the Bayesian algorithm. The Bayesian algorithm outperformed other methods on MTT and CBF measurements, especially at low SNR. Testing showed that the Bayesian method did not overestimate low CBF or underestimate high CBF. Furthermore, the MTT values of other methods did not correlate with the true perfusion values which, when tested in comparison to the Bayesian algorithm provided reliable positively correlated results[6,31]. (Figure 7).

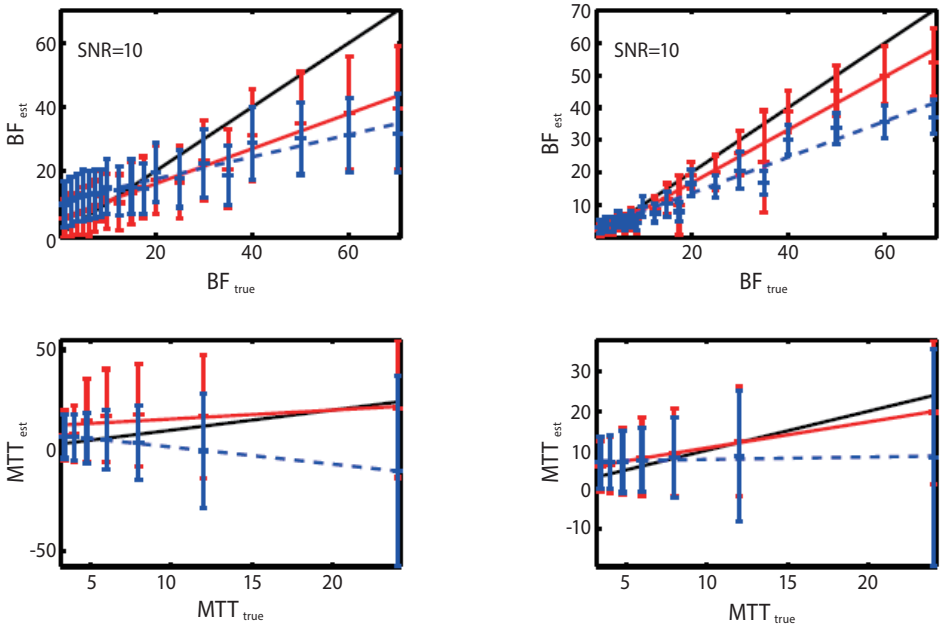


Figure 7 True vs Estimated MTT and CBF Parameters validated on CT phantom data[6].
Blue: SVD. Red: The Bayesian Algorithm. Black: True Values.
BF true – True phantom Blood Flow Value. BF est -Calculated Blood Flow Value from SVD and Bayesian algorithms.
MTT true – True phantom Mean Transit Time Value. MTT est - Calculated Mean Transit Time Value from SVD and Bayesian algorithms.

Finally, this study showed that the Delay map provided by the Bayesian algorithm is strongly correlated with the true delay as the SNR increases. The Bayesian algorithm delay map is independent of MTT values[31] (Figure 8).

Sasaki et al.[7] aimed to investigate whether quantitative values generated by the Bayesian Algorithm applied to CT perfusion data, were more accurate than those generated using delay-insensitive algorithms. The authors compared the accuracy of these algorithms by using a previously tested and validated digital phantom. This work confirmed that the Bayesian algorithm provided CBF, CBV, and MTT maps that were strongly correlated with and close to the true values. More specifically, the Bayesian MTT map was estimated with better agreement than those produced using the delay-insensitive SVD algorithms (Figure 9).

Other studies directly evaluated Bayesian and other deconvolution methods[32-39]. De Havenon et al. and Dunleavy et al.[33,35] reviewed 114 stroke patients. The authors concluded that, although both infarcted and hypo-perfused volumes were viable prognostic tools regardless of the deconvolution method used, the Bayesian-based mismatch was the only ratio able to give an indication of the patients status. Titelbaum et al.[39] also compared the quality of parametric maps computed using the Bayesian algorithm with other methods and concluded that the Bayesian method produced values closer to the physiologic consensus.

In CT perfusion studies, Bayesian has been reported to outperform SVD based algorithms, in particular for CBF and MTT computation[9]. Within Vitrea, the Bayesian algorithm produces similar CT perfusion maps to the SVD+ algorithm (CBV, CBF, MTT, TTP, Delay). The Bayesian and SVD+ algorithms are both available within Vitrea for a variety of acquisition protocols from all CT systems.

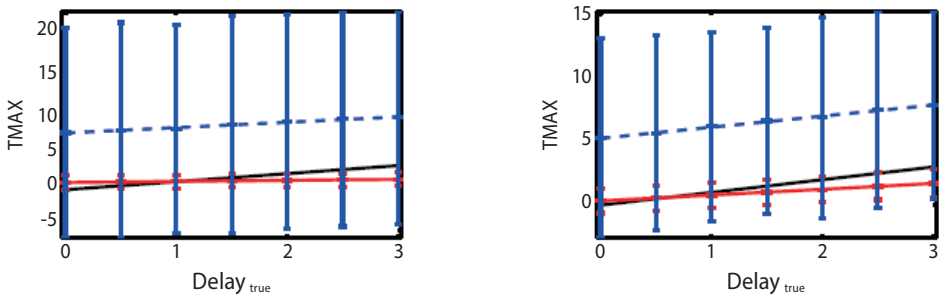


Figure 8 True Delay vs estimated Tmax Parameter validated on CT phantom data.[6]
Blue: SVD. Red: The Bayesian Algorithm.

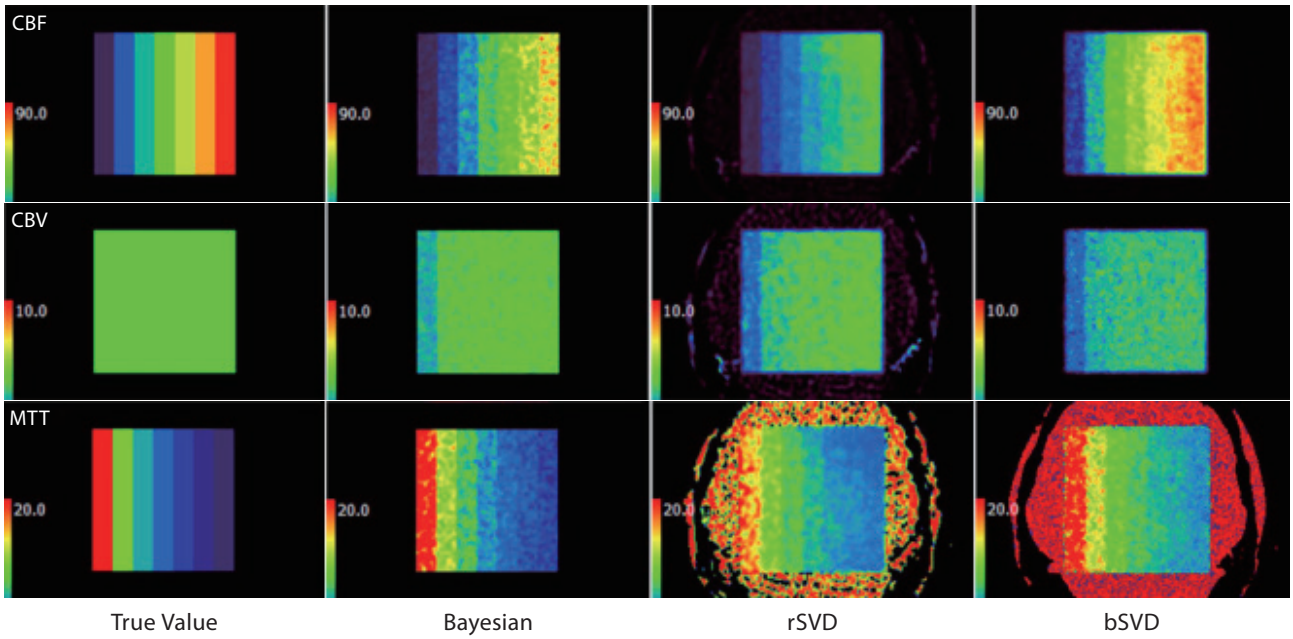


Figure 9 Perfusion maps generated with a digital phantom using different deconvolution algorithms. Color maps of CBF, CBV and MTT generated with the Bayesian based method, singular value decomposition algorithm, and block-circulant singular value decomposition algorithm appear to be roughly comparable to the true values, although an improvement with the Bayesian based method can be seen. No distinct gradation in the vertical direction is found in any of the algorithms, indicating insensitivity to the tracer delay[7].

Radiation and contrast dose

Being a dynamic scan, it is imperative that CT perfusion protocols are designed to maintain low radiation exposure and low doses of iodinated contrast, while ensuring diagnostic quality of the perfusion maps. The Neuro ONE protocol is designed with patient safety in mind. The protocol combines multiple exam types (CT perfusion and full brain 4D CT angiography) into a single acquisition while maintaining a low radiation dose of 5 mSv or less. These low doses are achievable because of a combination of scanner characteristics such as fast rotation time and low dose intermittent scan acquisition. By combining exam types into a single acquisition, the Neuro ONE protocol enables a single low dose injection of iodinated contrast (around 50 mL) administered with an injection rate of 5 mL/sec.

Conclusion

The Aquilion ONE provides a uniquely comprehensive exam to aid in the reduction of diagnosis time for patients experiencing serious cerebrovascular conditions, such as stroke. By pairing low dose whole brain imaging with the Bayesian perfusion algorithm, the Aquilion ONE produces advanced and accurate CT perfusion maps for evaluating cerebral blood flow and brain tissue viability.

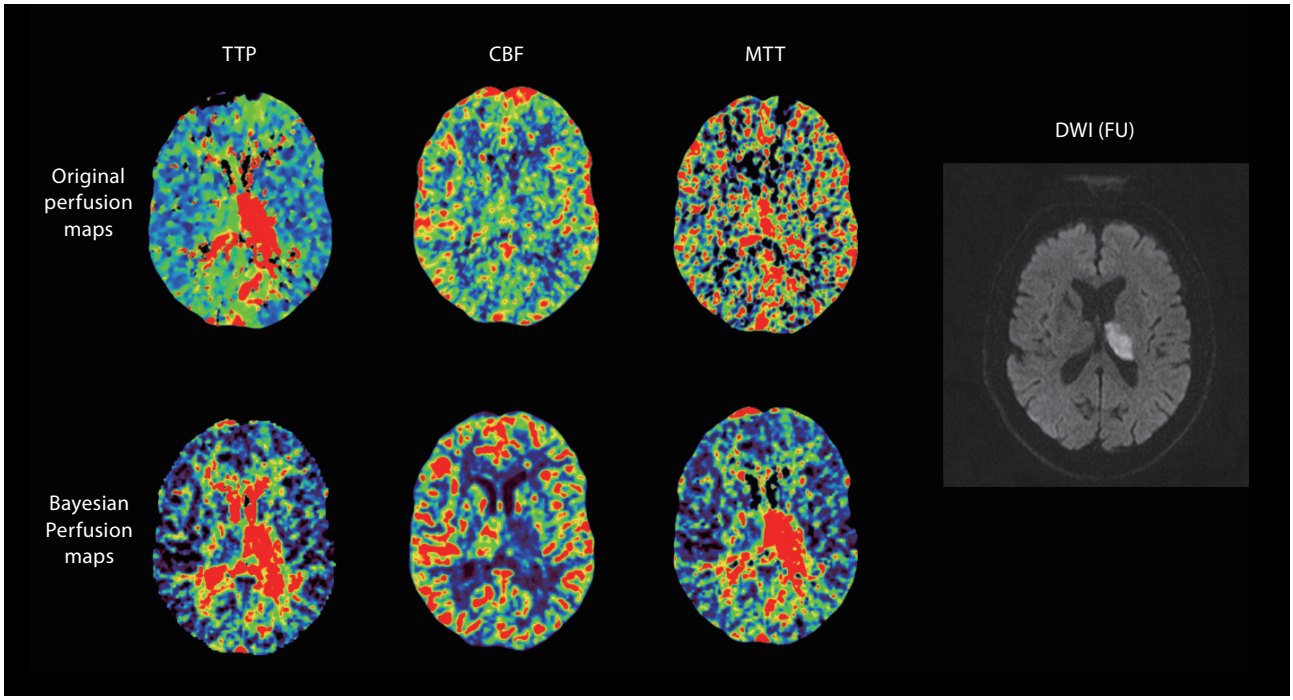
Recent clinical trials have demonstrated the value of CT perfusion imaging to define infarct and regions of penumbra in stroke patients, to enable clinical decisions and treatment planning. The same studies have shown that patients who received treatment up to 24h after the onset of a stroke benefited significantly from improved functional outcomes in comparison to control groups[3,4]. As a result, the Aquilion ONE and Vitrea solution produce maps providing more information physicians can use to accurately and quickly diagnose cerebrovascular disorders.

Multiple studies have shown that the Bayesian method is less sensitive to noise and results in better assessment at low signal-to-noise ratios, and therefore may improve diagnostic performance for infarct detection. The Bayesian method has been shown to accurately measure infarcted and hypo-perfused volumes, help clinicians understand the patients collateral flow and thus help give an indication of the patient status. The accuracy, robustness and adaptability of the Bayesian algorithm could help impact clinical practice and patient assessment[31].

Clinical Examples

Images courtesy of Ewoud Smit MD, PhD, Radboud University Medical Center, Nijmegen, the Netherlands.

Case 1 - Left Thalamic infarct



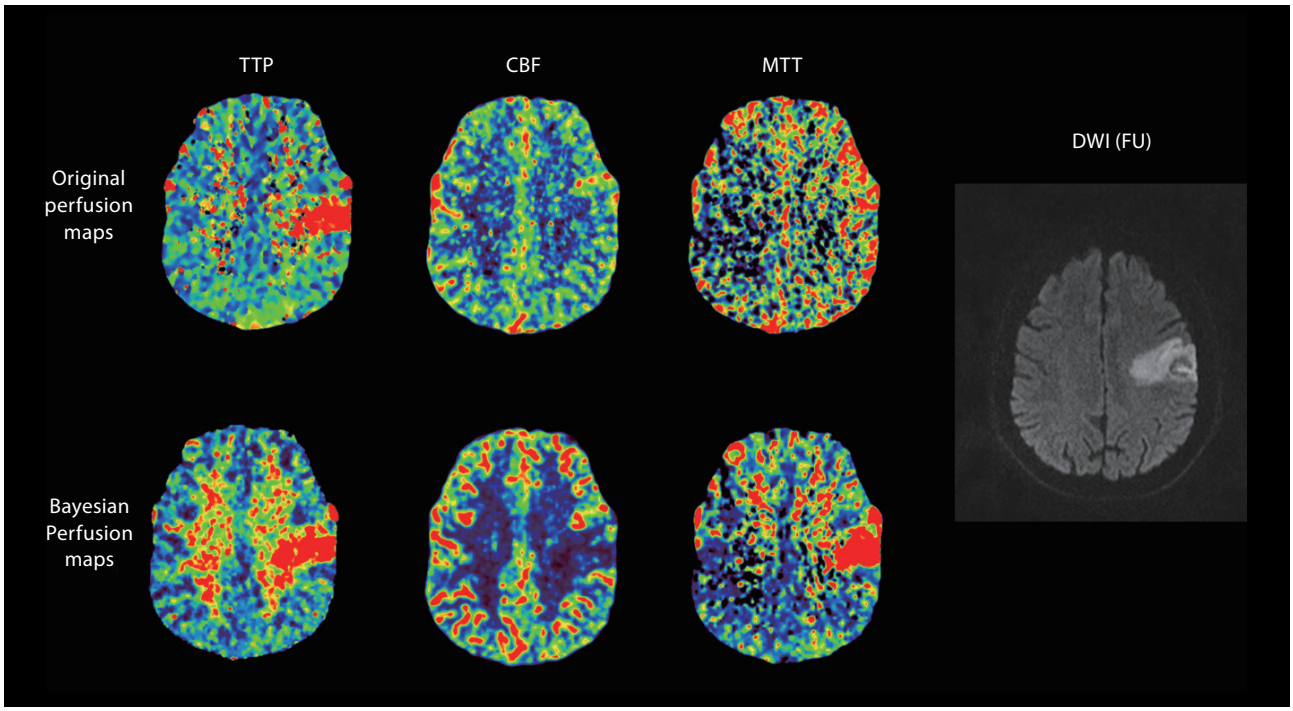
Patient history

A 76-year-old patient with a history of hypertension and hyperlipidemia presented to a primary stroke center with sudden onset of aphasia and right sided hemiparesis. CT perfusion imaging was performed within one hour of symptom onset. The patient received intravenous thrombolysis after intracranial hemorrhage was excluded. CTA images showed a left posterior cerebral artery occlusion in the posterior cerebral artery.

Original CT perfusion maps show delayed blood supply with increased time to peak in the left thalamus, but no perfusion deficit on cerebral blood flow and mean transit time maps, consistent with penumbra. The perfusion maps computed with the Bayesian perfusion method also show an increased TTP in the left thalamus, but with clear decrease of CBF and prolonged MTT, consistent with an infarct core.

Follow-up MR-DWI imaging on day 3 shows an infarct in the left thalamus strongly corresponding to the infarct core on Bayesian perfusion.

Case 2 Left MCA infarct



Patient history

A 66-year-old patient with a history of hypertension, hyperlipidemia and diabetes woke up with symptoms of right sided hemiparesis and dysarthria. The patient was last seen well two hours before CT perfusion imaging was performed at a primary stroke centre.

Perfusion imaging computed with the original perfusion maps show delayed blood supply with increased time to peak in the left frontal lobe, however no perfusion deficit on cerebral blood flow and mean transit time maps, consistent with penumbra. The perfusion maps computed with the Bayesian perfusion method also show an increased TTP in the left frontal lobe, but with clear decrease of CBF and prolonged MTT, consistent with an infarct core. Follow-up MR-DWI imaging the next day shows an infarct in the left frontal lobe (primary motor cortex) corresponding to the infarct core displayed on the Bayesian perfusion maps.

The patient received intravenous thrombolysis and no intra-arterial thrombectomy as CT angiography did not show a proximal occlusion.

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