SVD+ Dynamic Volume CT: Delay Insensitive Brain Perfusion Analysis

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REFERENCES:


The primary application of brain perfusion imaging in CT is to determine if 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 third leading cause of death in the United States and the leading cause of serious long-term disability. When a patient presents with stroke symptoms, a non-contrast CT is typically used to visualize bleeding and to rule out hemorrhagic stroke. However, in 87% of strokes there is no intra-cranial bleed. Once hemorrhagic stroke has been ruled out, perfusion measurements are used to visualize effects of ischemic stroke. Perfusion measurements help distinguish which areas of the brain are beyond repair 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.

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, vasculitis, assessment of perfusion after head trauma and determining microvascular permeability in brain tumors.

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. Vasodilatation 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 infarct 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).

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 interventionaly using a clot retrieval device or by using pharmacetical agents such as thrombolytic repurfusion agents. Thrombolytic agents can dissolve blood clots and return flow to ischemic regions. However, in areas of infarct, these agents can cause increased risk of hemorrhage. Currently, thrombolytics are only proven effective if administered within the first 3 to 6 hours of stroke onset. Perfusion imaging may extend this window by identifying salvageable brain tissue and indicating patients with the potential to benefit from treatment.

Toshiba’s Neuro ONE protocol allows full stroke workup in a single examination that includes physiological and anatomical information about the entire brain. This uniquely comprehensive exam combines whole brain dynamic perfusion maps to analyze blood flow and characterize infarcted tissue as well as a 4D CT Digital Subtraction Angiogram (4D CT DSA) to help visualize obstructed vessels for treatment planning. 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
Several techniques can be used to image brain hemodynamics. For perfusion imaging of stroke, CT and MR are the most common modalities because they have good spatial and contrast resolution, and they can both be used to map the ischemic penumbra and assess viability of reperfusion therapies.

In MR, perfusion weighted imaging (PWI) can be combined with diffusion-weighted imaging (DWI) to characterize obstructed vessels for treatment planning. The entire exam is performed in less than five minutes with low contrast dose (50 mL of intravenous contrast) and low radiation dose.
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 the intact and penumbra. Until recently MR was viewed as the most comprehensive modality for stroke workup primarily because CT perfusion was limited by partial brain coverage (typically 4 cm or less), partial voluming of vessels, and artifact in the posterior fossa. Today’s CT scanners are now capable of high resolution, three dimensional imaging, essentially eliminating the previous concerns of partial voluming and artifact. The spatial and temporal limitations of CT perfusion were overcome with the introduction of Aquilion ONE and dynamic volume imaging. Dynamic volume perfusion imaging can be performed for the entire brain with 16 cm of anatomical coverage and with temporal uniformity.

Now that Aquilion ONE technology has overcome the previous limitations of CT perfusion, CT is quickly emerging as a new standard of care for brain perfusion analysis. Particularly for acute stroke patients, the fast exam time, widespread availability, high spatial resolution, low dose, and quantitative nature (linear contrast enhancement) of dynamic volume CT make 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.

**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-labeled 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 plotting CT number versus time. These graphs, called time density curves, represent the uptake and washout of contrast-labeled blood in an artery, in brain tissue and in a vein (Figure 5).

**Time Density Curves (TDC)** are plots of CT number versus time used to visualize temporal changes in contrast-agent concentration.

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.

**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 is the only CT scanner capable of dynamic volume imaging of the entire brain with temporal uniformity so that all contrast-labeled 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 that help clinicians characterize cerebral pathophysiology. The quantitative maps used in CT perfusion are as follows (Figure 6):

- **Cerebral Blood Volume (CBV)** is a measure of the volume of blood per unit brain tissue. CBV is reduced in the infarct core where tissues are no longer viable. CBV is useful for assessing the effects of autoregulation and is measured in mL/100 g of brain tissue.

- **Cerebral Blood Flow (CBF)** is the volume of blood running through the capillary blood vessels per unit time per unit brain tissue. CBF is measured in units of mL/min/100 g of brain tissue.

- **Mean Transit Time (MTT)** is the average amount of time that blood takes to

![Figure 5](image-url)
travel through the capillary vessels. MTI is sensitive to transient changes in pressure because it demonstrates the effects of vasodilatation associated with autoregulation. MTT is measured in seconds.

Time To Peak (TTP) is a measure of the relative time of peak enhancement for brain tissue. It provides an indication of delayed flow due to stenosis or occlusion and is useful for identifying collateralization. TTP is measured in seconds.

Delay is the relative arrival time of contrast medium in the tissue. It measures similar physiological information to TTP, but is not dependent on the size or shape of the arterial TDC. Because of its insensitivity to the arterial curve, Delay can be useful for quantitative comparisons and/or follow-up studies. Delay is measured in seconds.

Longer TTP or Delay may indicate delayed flow from collateralization. MTT, TTP, and Delay visualize vasospasm or vessel stenosis that can’t otherwise be seen.

Consider, for example, a patient with an ischemic stroke caused by an occlusion in the middle cerebral artery. The occlusion will cause reduced perfusion to the affected region of the brain as demonstrated by decreased CBV. This reduced flow will trigger an autoregulatory response and feeding arteries will dilate to restore flow to the region. This vasodilatation 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.

DECONVOLUTION

There are several ways to calculate perfusion parameters from the TDCs, including the maximum slope method, gamma-variate, or moments method and deconvolution methods.

Deconvolution methods have become a gold standard for analyzing brain perfusion because the algorithms are well suited for mapping perfusion parameters in the brain, they avoid unrealistic assumptions about venous outflow, and they allow for slower and safer contrast injection rates (4–6 mL per second as compared to approximately 10 mL per second for other algorithms).

Deconvolution is a “cause and effect” approach to perfusion analysis. As the bolus travels through the arteries on its way to the tissue, it has a certain shape as a function of time. Its shape is shown by the arterial TDC and is considered the “input function.” When it interacts with the tissue (travels through the capillaries, etc.), it changes shape. This new shape is shown by the tissue TDC. The perfusion properties of the tissue are contained within the way the shape of the arterial TDC is changed into the tissue TDC. If it were possible to administer the contrast bolus as a perfect impulse of contrast (rising to its peak and falling back to baseline instantaneously), the shape of the tissue TDC would only contain information about the tissue’s perfusion properties since the input function was an impulse and had no shape. The resulting TDC is known as the impulse residue function. Residue simply means what happens to an impulse bolus of contrast going through tissue. Put another way, the impulse residue function represents what the tissue TDC would look like if the entire contrast bolus was administered at the same instant in time.

The impulse residue function is ideal for calculating perfusion metrics because it is based purely on tissue perfusion and is independent of the size or shape of the arterial input function. However, since the arterial TDC is not an impulse, its shape will effect the shape of the tissue TDC, so the impulse residue function cannot be directly measured. With imaging, it is possible to measure two of the three functions in the perfusion process: the arterial TDC and the tissue TDC. Using these two measured functions, it is possible to mathematically solve for the impulse residue function using a method called deconvolution (Figure 7).

Mathematically, the tissue TDC is the result of “convolving” (similar to “multiplying”) the arterial TDC with the tissue’s impulse residue function. In the same way that division undoes multiplication, deconvolution undoes convolution. Therefore, in order to calculate the impulse residue function, the tissue TDC is “deconvoluted” from (similar to “dividing by”) the arterial TDC.

In other words, deconvolution is the mathematical process used to solve for tissue properties independent of the size or shape of the arterial TDC. The impulse residue function that is produced from deconvolution represents the inherent perfusion properties of the brain tissue.

Once the impulse residue function is derived, MTT can be calculated from the residue function. The CBV is calculated as the area under the tissue TDC divided by the area under the venous TDC, and CBF is calculated using the central volume principle:

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\text{CBF} = \frac{\text{CBV}}{\text{MTT}}
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SINGULAR VALUE DECOMPOSITION (SVD)

There are several types of deconvolution that can be used for perfusion analysis. Singular Value Decomposition (SVD) algorithms are often viewed as the most accurate method because they do not rely on assumptions about the shape of the residue function.

Some of the problems associated with standard SVD algorithms for brain perfusion are: noise sensitivity, inaccurate MTT values due to autoregulation or collateral flow, and inability to account for natural blood flow dynamics.

In the case of autoregulation, standard SVD algorithms can produce incorrect
MTT values because delayed flow can appear on the MTT maps. For example, if a patient has an occlusion, arteries in neighboring regions may compensate by redirecting blood to that region. Even though the occluded region is getting adequate blood supply and the tissue may remain viable, the MTT will appear deceptively high in that region because greater anatomical coverage means greater distance between the input artery and some brain tissues. SVD+ is a delay insensitive SVD algorithm that uses an innovative technique to account for delayed blood flow, minimize noise, and perform calculations with fast computation times. The SVD+ algorithm is unique in that it shifts the artery curve so that it always begins prior to the contrast arriving in the tissue curve. The SVD+ algorithm also uses a unique pre-conditioning technique that stabilizes the algorithm to ensure fast calculation times while minimizing noise and ensuring delay insensitive calculations of MTT.

When using SVD+, all delayed flow from autoregulation is viewed in the TTP and Delay maps rather than in the MTT map as with the standard SVD approach. The Delay map holds important clinical information that can only be measured using delay insensitive SVD such as SVD+. The SVD+ algorithm also enables whole brain perfusion by accounting for natural differences in contrast arrival time between the measured input artery and peripheral brain tissues. As it is defined, MTT maps relate to vasodilation of cerebral vasculature, but in standard SVD algorithms, MTT is also affected by the time it takes for contrast to arrive in the tissue. (Figure 7). Therefore, clinicians accustomed to viewing MTT maps from standard SVD algorithms may be surprised to find the MTT maps from SVD+ appear less "sensitive" to reduced flow than standard MTT maps. In reality, the sensitive nature of the standard SVD MTT maps was due to delayed flow as opposed to actual reduced travel time through the tissue. Keep in mind that overestimation of MTT leads to underestimation of CBF. With SVD+, the sensitivity to delayed flow is visible in the TTP and Delay maps and separated from the MTT map to ensure the maps appropriately represent perfusion and to help the clinician separate delayed flow from perfusion deficit.

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, as well as the noise reduction capabilities of the SVD+ algorithm. 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 4-6 mL/sec.

CONCLUSION

The world's first dynamic volume CT system, the Aquilion ONE, produces a uniquely comprehensive exam to reduce diagnosis time for patients experiencing serious cerebrovascular conditions, such as stroke. By pairing low dose whole brain imaging with the delay insensitive SVD+ perfusion algorithm, the Aquilion ONE produces advanced CT perfusion maps for evaluating cerebral blood flow and brain tissue viability. SVD+ is a delay insensitive SVD algorithm that uses a novel technique to account for delays between the arterial input function and the tissue curve, minimize noise and perform calculations with fast computation times. The delay insensitive nature of the SVD+ algorithm enables more accurate perfusion calculations by separating out the effects of delayed flow, thus avoiding overestimation of MTT and underestimation of CBF.

As a result, the Aquilion ONE produces new maps providing more information physicians can use to accurately and quickly diagnose cerebrovascular disorders. The following clinical case studies will demonstrate clinical applications of whole brain imaging using the SVD+ perfusion algorithm.
CASE STUDY: TRANSIENT ISCHEMIC ATTACK (TIA)
A 55-year-old female presented with vision changes and facial numbness. She has had two previous TIA's and was admitted to the emergency room for an acute stroke workup. Whole brain CT DSA and delay insensitive perfusion maps were acquired simultaneously using the Neuro ONE protocol on an Aquilion ONE CT scanner.

A normal variant is seen in the 4D CT DSA images where a dominant left vertebral artery is present, with the right vertebral artery terminating at the posterior inferior cerebellar artery (PICA). The right posterior cerebral artery (PCA) fills slowly from a patent P1 segment arising from the basilar artery and the posterior communicating artery.

The CBF, CBV, and MTT perfusion maps show no asymmetry or abnormality. The TTP and Delay maps clearly show evidence of delayed enhancement in the PCA territory.

This patient was discharged with medical treatment of low dose aspirin and statins. In this case, the delay insensitive nature of the SVD+ algorithm helped clinicians differentiate between ischemic tissue damage and a normal variant of the arterial structure.

CASE STUDY: LEFT MCA OCCLUSION
46-year-old female patient presented with right-sided weakness, right-sided facial drooping and expressive aphasia. Brain perfusion and 4D CT DSA were performed on an Aquilion ONE scanner using the Neuro ONE acute stroke protocol.

The whole brain perfusion maps shown below in axial and coronal plane show a small infarct core surrounded by a large area of ischemia in the middle cerebral artery (MCA) territory characterized by decreased CBF, and increased MTT, TTP and Delay.

This area of decreased perfusion directly corresponds to the CT DSA images which show a thrombus in the left MCA territory.
CASE STUDY: EXTENSIVE RIGHT-SIDED PERFUSION DEFECT
A 56-year-old male presented with a left-sided weakness and suspected cerebrovascular accident (CVA). The Neuro ONE acute stroke protocol was performed on an Aquilion ONE CT scanner.

The perfusion maps show a severe perfusion defect affecting almost all of the right MCA and PCA territories. The CBF is decreased, as is the CBV, indicating a large area of cerebral infarction. The decrease in MTT indicates insufficient flow within the brain tissue, which is further evidence of infarction. Increased time to peak enhancement, as shown on the TTP maps, is evidence of an occlusion of the right internal carotid artery (ICA) and near-occlusion of the MCA. There is also an old infarct in the right parietal lobe.

CT DSA shows total occlusion of the ICA affecting the right side. There is also a clot causing a focal occlusion of the M3 segment of the MCA.

CASE STUDY: LEFT M2 BRANCH OCCLUSION
Male patient 87-years of age presented with acute onset of right-sided facial drooping and difficulty with speech. Stroke workup was performed using the Neuro ONE protocol on an Aquilion ONE CT scanner. CT DSA and whole brain SVD+ perfusion imaging demonstrate asymmetrical perfusion in the left hemisphere.

The TTP and Delay maps show delayed enhancement to the left MCA territory, while reduced CBF and CBV suggest a large cerebral infarction at the anterior cerebral artery/middle cerebral artery (ACA/MCA) watershed.

The CT DSA images show an embolus of the M2 segment of the MCA.
REFERENCES:


