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Use of Time Attenuation Curves to Determine Steady-State Characteristics before C-Arm CT Measurement of Cerebral Blood Volume

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Introduction: Cerebral blood volume (CBV) measurement by flat panel detector CT (FPCT) in the angiography suite seems to be a promising tool for patient management during endovascular therapies. A steady state of contrast agent distribution is mandatory during acquisition for accurate FPCT CBV assessment. To the best of our knowledge, this was the first time that steady state parameters were studied in clinical practice.

Methods: Before the CBV study, test injections were performed and analyzed to determine a customized acquisition delay from injection for each patient. Injection protocol consisted in the administration of 72 mL of contrast agent material at the injection rate of 4.0 mL/s followed by a 72 or 20 mL saline flush bolus at the same injection rate. Peripheral or central venous accesses were used depending on their availability. 24 patients were treated for different types of neurovascular diseases. Maximal attenuation, steady state length and steady state delay from injection were derived from the test injections' time attenuation curves (TAC).

Results: With a 15 % threshold from maximum attenuation values, average steady state duration was less than 10 seconds. Maximum average steady state duration with minimal delay variation was obtained with central injection protocols.

Conclusion: With clinically acceptable contrast agent volumes, the steady state is a brief condition thus fast rotation speed acquisitions are needed. The use of central venous injections decreases the variability of steady state's delay from injection. Further studies are needed to optimize and standardize injections protocols.

INTRODUCTION

Recently the feasibility of FPCT CBV measurement within the angiographic suite has been described in acute ischemic stroke patients [1, 2] (Fig 1). This study may also be of great interest during the endovascular management of other neurovascular diseases. Regarding brain arteriovenous malformations (AVM), the use of perfusion CT showed different perfusion patterns that could correspond to different pathological mechanisms that could lead to different treatment strategy [3]. After the use of flow-diverter stents some adverse event are still not fully understood and may be due to perfusion abnormalities [4].

The principle of this technique requires a steady state of brain parenchyma enhancement during whole aquisition [5, 6]. This steady state is a major prerequisite to ensure the reliability of FPCT CBV assessment. CBV measurement using C-Arm CT is not an everyday tool, and the acquisition protocol has not yet been codified. Various protocols have been described, using either venous or arterial injections [1, 7, 8]. The reality of the steady state during CBV acquisition is usually assumed but not verified, and this could be the cause of errors in measurements. The purpose of this study is to determine if a standard injection protocol ensures enough steady-state time for a reliable CBV measurement.

MATERIALS AND METHODS

Patient characteristics

Between May 2012 and January 2013, 24 patients (14 female, 10 male; age range, 19-84 years; median, 39 years) referred for endovascular treatment were prospectively enrolled for this study performed according to the guidelines of our institution, informed consent was obtained for each procedure.

CBV studies were acquired in the angiographic suite during 10 brain AVM endovascular treatments and 14 intracranial aneurysm flow-diverter stent-assisted treatments.

Test acquisitions

Before the CBV runs were acquired, a test perfusion acquisition was performed at a static postero-anterior viewing incidence, in order to obtain the TAC of tissue enhancement in brain parenchyma. It corresponded to a 3 images per second subtracted fluoroscopic acquisition during 30 seconds. It was initiated after an 8 seconds delay for central injections and a 12 seconds delay for peripheral injections, in order to minimize the X-ray dose.

FPCT CBV measurement

Both endovascular treatment and perfusion study were performed on a biplane angiographic system (Allura Xper FD20/10, Philips Healthcare, Best, the Netherlands) under general anesthesia. FPCT CBV was assessed before embolization for brain AVM and after stent delivery for aneurysms.

The CBV acquisitions on a C-arm system consist of two FPCT runs; a mask run without contrast, and a contrast-enhanced run during the steady state. The difference in attenuation per volume element between these runs corresponds to the contrast enhancement of the parenchyma. FPCT CBV measurement was performed as previously reported [5], but with a 5 seconds rotation time and a tailored acquisition delay from injection, i.e. calculated from test acquisition.

Injection protocols

Injection protocols were identical for test acquisition and for CBV measurement. Contrast media injections were performed either through a 4F intra-atrial venous pigtail catheter or through a peripheral cubital vein access when central access was not available. We have used a literature inspired protocol [7], consisting in the injection of 72 mL of iodixanol (Visipaque 270, GE Healthcare, Mississauga, Canada) at the injection rate of 4 mL/s, followed by a saline flush at the same rate.

Post processing

Data from test injections were analyzed by using commercially available software, *2D Perfusion* (Philips Healthcare, Best, the Netherlands) and exported to *Excel* software (Microsoft, Redmond, Washington, USA). From a large region of interest drawn in the non-pathological hemisphere and avoiding major vessels the *2D Perfusion* software provides TAC with a 0.33 second time resolution (Fig 2). As steady state required strictness for the FPCT CBV measurement has not been previously evaluated in the literature we have arbitrarily chosen a 15% tolerance threshold from peak attenuation value. From this the steady state length and the delay from injection to the steady state's beginning were measured.

Raw data from test injections (i.e. digital subtraction angiography) were secondarily analyzed by two neuroradiologists (20 and 5 years of experience). They determined delay from injection to full opacification of venous sinuses, this is called the "bolus watching" technique and it would be related the steady state's beginning according to some authors [1, 7, 9](Fig 3). When using the "bolus watching" technique, the rotational acquisition is manually initiated after contrast agent injection when the superior sagittal sinus is opacified.

Finally, data from CBV acquisition were analyzed using the *CBV prototype software* (Philips Healthcare, Best, the Netherlands) in order to obtain CBV color maps.

Statistical analysis

Statistical analysis was performed using commercial statistical software *SPSS* (version 12.0, Statistical Package for the Social Science, Chicago, IL). Average steady state's length from different injection protocols were compared using Mann-Whitney *U* test.

Correlations between the two readers using "bolus watching" technique and the measured steady state delay from TAC were performed using Spearman correlation coefficient.

RESULTS

TAC analyze was possible in every case. 20 patients were explored using central venous injections and 4 using peripheral injections (Table 1).

There were no statistical differences between mean peak values of the three different protocols (central = 212, peripheral 72/72 = 201).

With central injections, mean lengths of the steady state were respectively 9.5 +/- 1.4 seconds (range 5.9 – 11.9) versus 8.2 +/- 0.9 seconds (range 6.9 – 8.9) with peripheral injections.

Central venous injections are associated with a longest mean steady state (central injections = 9.5 s, peripheral injections = 8.2 s; $p<0.047$) with a mean difference of 1.3 second (14 %).

The central protocols are also associated with less timing variation from injection to steady state when compared with peripheral injections. Mean delays are respectively 20.8 seconds versus 27.2 seconds and standard deviations are 2.0 seconds versus 5.0 seconds (Table 2).
When using peripheral access, the delay between injection and the beginning of the steady state was nearly 7 seconds later than with central injections. This is logical and corresponds to the time the contrast agent goes from the forearm to the right atrium.

When considering central venous injections, there was a significant agreement between the two readers regarding the timing determination of full opacification of venous sinuses according to concept of the "bolus watching" technique (correlation coefficient $r = 0.78$; $p < 0.005$). Delays from visual triggering and the steady state's delay measured on the TAC were correlated ($r = 0.75$; $p < 0.005$) but in few cases we have noticed significative differences with a maximum of 6 seconds.

DISCUSSION

The steady state of brain parenchyma contrast enhancement during whole acquisition is the key parameter to ensure the reliability of the CBV measurement in the angiographic suite. Most of recent publications on the subject only assume the reality of this condition during FPCT CBV acquisition.

To determine temporal characteristics of tissues enhancement and then apply a tailored timing for the CBV acquisition, we have used test injections at a price of a larger use of contrast media. The same volume was used for test injection and for final acquisition because it has been shown that if a smaller volume was used during test injection the measured delay would not be correlated to the final injection delay [10].

From this we first see that the steady state is a brief condition with an average duration shorter than 10 seconds in our study. It implies that acquisition time for the CBV measurement should be as short as possible, this being for the moment a technological limitation from the C-arm rotation speed. Depending on manufacturers, some actual angiographic suites allow 5 seconds rotation acquisition.

The optimal bolus geometry is an immediate increase in the enhancement of the tissues just before the acquisition of data, followed by a steady state in which the enhancement is stable during the whole acquisition. In reality, the actual bolus geometry is a gradual increase in the enhancement until a peak and then a gradual decrease.
Parameters influencing bolus geometry are described in the literature review by Cademartiri et al. [10]. Several studies report that time between injection and maximal attenuation is not affected by age, weight, height, body surface, blood pressure, heart rate or gender. A porcine study showed that a decrease in cardiac output produces a proportionally longer time to reach the maximal attenuation peak. Consequences of bolus characteristics have also been described in this article. When the injection rate is increased, the time to peak is shortened and the maximal attenuation is increased. This corresponds to a sharper TAC and a shorter steady state length. Thus with

the same amount of contrast media, injection rates faster than 4 mL/s would induce steady states shorter than in our study.

Bae et al. [11] showed that with fixed injection rates, time to peak enhancement in the aortic arch is determined by the volume and the traveling time of contrast media. With central venous injections this traveling time is significantly reduced (7 seconds in our study). The variability between patients due to different circulatory speeds is reduced when the traveling time is shorter, which means that the delay from injection to steady state is more reproducible.

The "bolus watching" technique is actually mostly used for CBV measurements by flat panel detector [1, 7, 9]. After the FPCT mask run has been acquired, the C-arm returns to the start position, and a standard 2D digital subtraction angiography (DSA) is initiated. The second rotation is manually initiated when large dural sinuses opacification is observed, assuming it to reflect the beginning of the steady state in brain parenchyma. To our knowledge this relationship does not seem to have been validated in humans. In our study there is a correlation between sinuses opacification and the steady state. But it may not be the guarantee for a FPCT acquisition during steady state as in some cases the timing difference with the actual beginning of the steady state can be as much as 6 seconds.

From our data we could determine a probabilistic timing with a 5 second acquisition initiated 24 seconds after contrast media injection and it would correspond to an acquisition during steady state for the majority of the patients of our study.

There are several limitations in our study. First there is a small number of patients in this study and the validation of the FP CBV measurement was not the purpose of this preliminary work. Secondly, the strictness of the steady state required for precise CBV measurement has not been determined in the literature, so we have arbitrarily chosen 15 %. Logically the steady state length would increase with a raise of the tolerance threshold. For example, in our study the average gain would be 1.7 second (+ 15%) if the threshold were increased from 15% to 20%. Thirdly those results may not be applicable to stroke patients because of vessel occlusion and blood supply from collaterals that could be responsible of a different steady state of contrast enhancement in comparison with normal tissues.
Finally, there are variety of ways to extend the steady state by manipulation of the injection protocol, and for example it would be of great interest to study slower injection rates, because with an equivalent volume of contrast agent it should induce a longest steady state, but also a lower peak enhancement and therefore a lower signal to noise ratio for FPCT CBV measurement.

CONCLUSION

Steady state of contrast enhancement in brain parenchyma is required throughout acquisition time for correct FPCT CBV measurements. With clinically acceptable contrast agent volumes, steady state is a brief condition thus fast rotation speed acquisitions are compulsory. The use of central venous injections decreases the

variability of steady state's delay from injection. The "bolus watching" technique is an interesting way to overcome inter-individual variability but may not always be the guarantee for steady state during the whole acquisition.

Further studies are needed to optimize and standardize injections protocols to allow a larger diffusion of the FPCT CBV measurement during endovascular stroke therapy.

Conflict of Interest

DR is employed by Philips Healthcare, the Netherlands..

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Table 1.

Injection protocols.

	Number of patients	Average age	Aneurysm / AVM
Central Injection	20	40,5	13 / 7
Peripheral Injection	4	43	1 / 3

Table 2.

Characteristics of the steady states.

	Length	Delay	Peak Value
Central 72/20	9.5 +/- 1.4 s	20.8 +/- 2.0 s	212
Peripheral 72/72	8.2 +/- 0.9 s	27.2 +/- 5.0 s	201

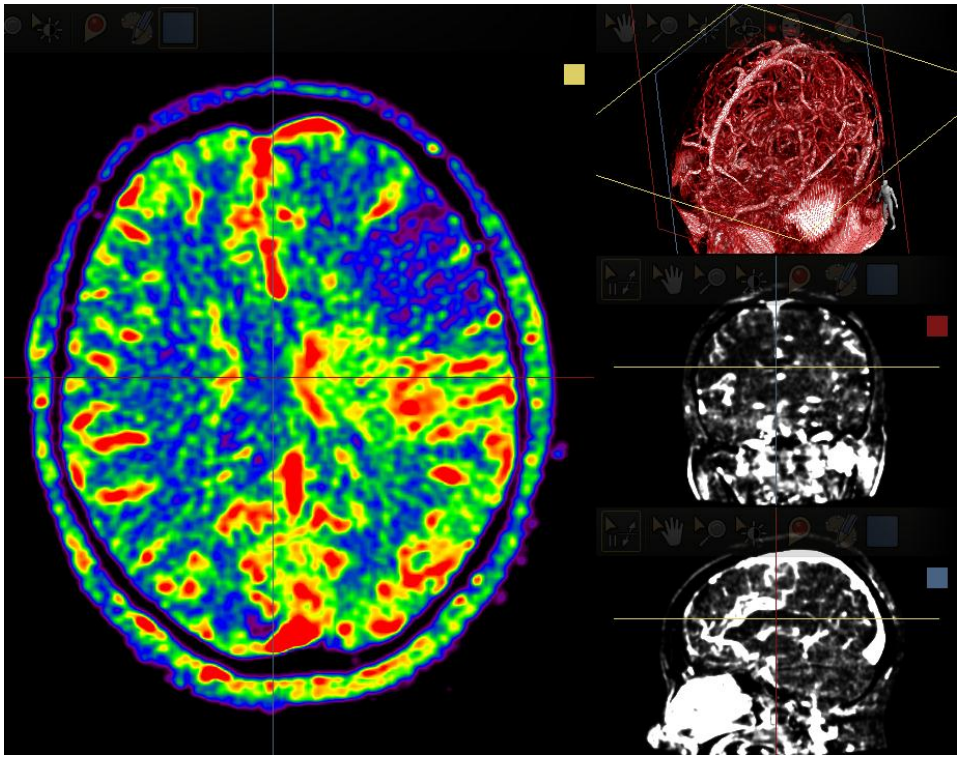

Fig 1.

A 55-year-old patient presenting with acute aphasia. Intracranial bleeding was ruled out by a CT scan and then the patient was admitted in the angiographic suite for endovascular early stroke therapy. Pre-interventional FPCT CBV measurement shows a decreased CBV area in the left middle cerebral artery anterior territory.

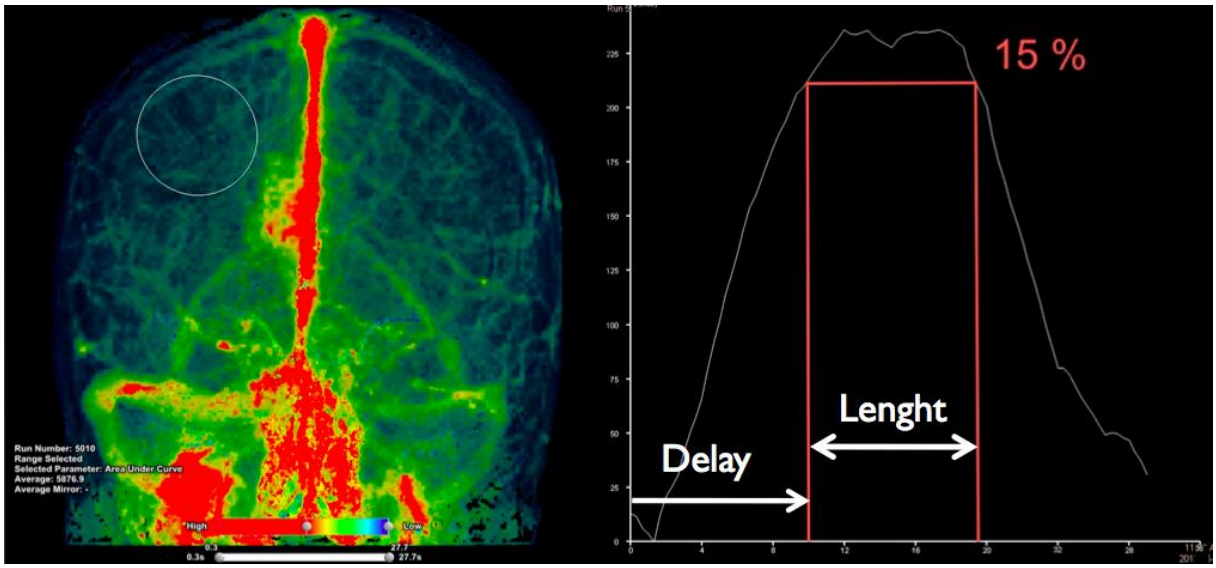

Fig 2.

A circular region of interest is drawn in a brain antero-posterior projection to obtain the TAC using the *2D perfusion* software. From this, the steady state's characteristics are determined with a threshold of 15% from the peak attenuation value.

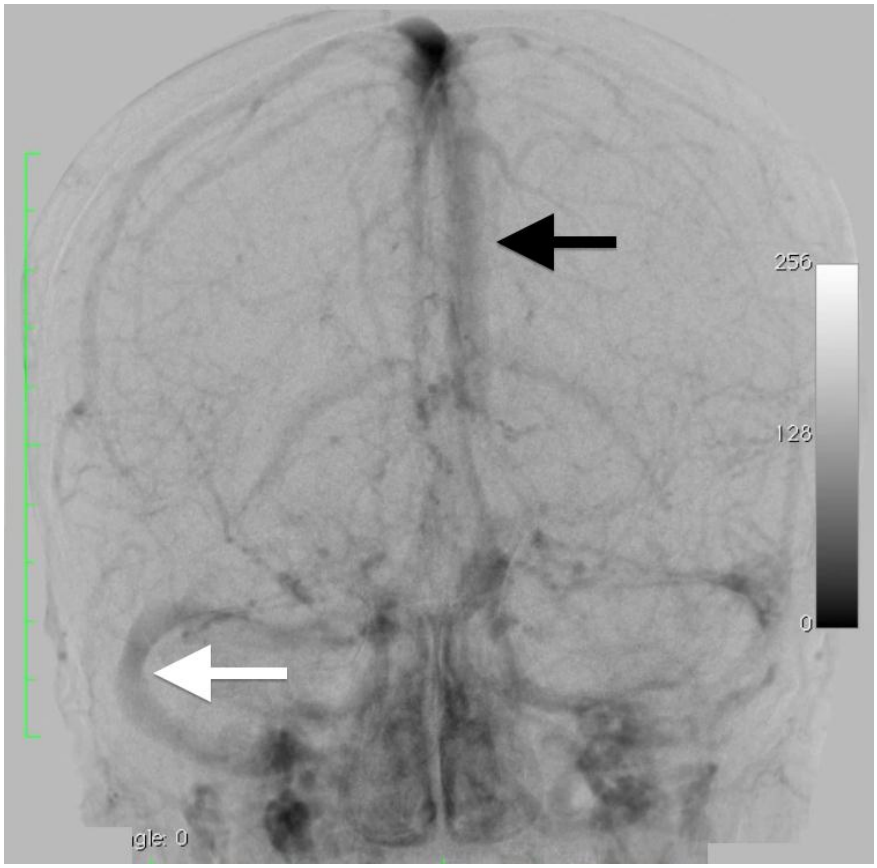

Fig 3.

Homogeneous opacification of the venous sinuses is considered by some authors to reflect the steady state's beginning. Superior sagittal sinus (black arrow) and lateral sinus (white arrow) opacified.