CT perfusion for acute ischemic stroke: Vendor-specific summary maps, motion correction and application of time invariant CTA

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CT Perfusion for Acute Ischemic Stroke
Vendor-Specific Summary Maps, Motion Correction and Application of Time Invariant CTA

F. Fahmi

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CT Perfusion for Acute Ischemic Stroke
Vendor-Specific Summary Maps, Motion Correction and Application of Time
Invariant CTA
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CT Perfusion for Acute Ischemic Stroke

Vendor-Specific Summary Maps, Motion Correction and Application of Time Invariant CTA

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Chapter 1

General Introduction
General Introduction

The Role of CTP in diagnosis Acute Ischemic Stroke

Stroke is still a dominant cause of mortality and morbidity, ranking third as cause of death and second as cause of disability worldwide\(^1\), \(^2\). Acute ischemic stroke accounts for 73%-86% of all the stroke cases, while 8%-18% concerns intracranial hemorrhage\(^3\), \(^4\).

Brain tissue lacks a sufficient energy store and therefore requires continuous supply of oxygen and glucose. Consequently, ischemic stroke causes very rapid deterioration of the brain tissue. Time is therefore a critical factor in diagnosis and treatment of acute ischemic stroke\(^5\)-\(^8\). Moreover, recanalization methods are useful only in a restricted time window after onset of the stroke (4-6 hrs) because the intravenous and intra-arterial thrombolysis promote hemorrhagic risk increases with time\(^9\), \(^10\). The limited time available in an acute setting combined with available treatment methods for acute ischemic stroke sets the requirements for better diagnostic imaging methods.

There are at least 3 issues that need to be addressed in diagnosis of acute stroke: the presence and extent of hemorrhage needs to be determined, the presence and location of intravascular thrombi has to be detected, and deficits in local tissue perfusion need to be determined\(^11\), \(^12\). A set of CT examination protocols form a standard workflow for addressing these issues in acute ischemic stroke patients\(^13\): Non contrast CT (NCCT) is used to exclude acute hemorrhage and large areas of clearly infarcted tissue and to select patients for thrombolysis\(^9\), \(^14\), CT Angiography (CTA) is used for thrombus analysis and CT Perfusion (CTP) measures brain perfusion (Fig 1).

![Fig 1. Example of NCCT (a), CTA (b) and CTP analysis (c)](image)

In CTP analysis, areas with brain perfusion defects can be detected directly after the onset of clinical symptoms. CTP enables the depiction of infarct core (sometimes referred to as Non Viable Tissue – NVT, irreversibly damaged core, red area in Fig. 1c) and infarct
penumbra (sometimes referred to as Tissue at Risk – TAR, salvageable brain part, green area in Fig 1c) of patients with acute ischemic stroke. The location and size of infarct core and penumbra as well as the ratio of their sizes are important in choosing the most suitable therapy and also provide valuable information for predicting the benefit of treatment.

In addition, CTP is considered to be fast, increasingly available, safe, affordable and provides ease of patient monitoring. It typically takes less than 10 min to perform a CTP examination. This therefore does not hinder thrombolytic treatment, which can be started at the CT scanner table immediately following completion of the non-contrast CT, with appropriate monitoring. There is increasing evidence that these advantages allow a firm role for advanced CTP imaging in the management of stroke patients.

Principles of Computed Tomography Perfusion (CTP) Imaging

The method of brain perfusion imaging using Computed Tomography (CT) is still a relatively new concept compared to nuclear medicine and magnetic resonance (MR). The original principles and first framework of perfusion imaging on CT were published in 1980 by Leon Axel et al. while practical CT perfusion (CTP) performed on modern CT equipment was described in the 90's by Ken Miles et al. and subsequently developed in many research groups around the world. Nowadays, almost all CT vendors provide post processing software packages to accommodate CTP application for clinical use.

CTP is based on the imaging of brain perfusion by monitoring the dynamic passage of an iodinated contrast agent bolus through the cerebral vasculature and tissue. CTP source images are acquired every 1 to 3 seconds for approximately 1 minute to record the first pass of contrast during wash-in and was-out, represented by time-attenuation curves of individual voxels (Fig. 2). Various mathematical models, based on deconvolution or alternative techniques, are then used to derive quantitative estimates for local perfusion parameters.
Fig 2. Time Intensity Curve of different type of brain part (adapted from presentation of R.Gupta, “CTP: How to do it right”, AAPM 2011 Summit on CT Dose)

CTP result provide several maps indicating perfusion parameters: Cerebral Blood Volume (CBV) defined as the total volume of blood in a given unit volume of the brain (ml·gr⁻¹), Cerebral Blood Flow (CBF) defined as the volume of blood moving through a given unit volume of brain per unit time (ml·gr⁻¹·s⁻¹), Mean Transit Time (MTT) defined as the average of the transit time of blood through a given brain region (s), and Time To Peak (TTP) defined as time needed for maximal intensity of the curve (Fig 3).

Acquired CTP source images are fed into software package for detailed analysis, including construction and quantization of the above perfusion maps. Computation of quantitative perfusion maps typically requires some user-defined inputs, including the Arterial Input function (AIF), Venous Output Function (VOF), segmentation of the brain part and mirror line definition. The AIF is determined on the central portion of a large intracranial artery, preferably the anterior cerebral artery in order to minimize effects of volume averaging. An attempt should be made to select an artery with maximal peak contrast intensity. The venous output Function (VOF) is most commonly taken at the superior sagittal sinus. Segmentation of brain part is conducted by generating a cerebral mask using certain threshold values. Setting the mirror line bisecting the brain into hemispheres allows for comparison of the contrast passage between affected and contralateral hemisphere. These user-defined inputs must be chosen optimally since selection of appropriate inputs is critical for producing quantitatively accurate perfusion maps.
Based on the recorded time-intensity plots and using the user input defined above, so-called summary maps are created that image the estimated infarct core and penumbra. These summary maps then allow for calculation of core and penumbra volumes\textsuperscript{15, 16, 27, 41} (fig 3).

**Fig 3. Perfusion maps and a summary map**

**Pitfalls in CTP**

With the increasing availability of CTP applications, it becomes important to better understand the potential pitfalls in the acquisition procedure. Most known pitfalls include lack of standardization, patient motion, volume averaging, inappropriate and inconsequent user-defined input settings for AIF and VOF selection, segmentation of brain mask and mirror line position; chance of missing small infarcts due to the low resolution of CTP analysis, and changes in perfusion due to extracranial and intracranial stenosis\textsuperscript{42}.

Despite its wide availability, there is currently no standardized method for conducting the perfusion analysis\textsuperscript{43}. Such lack of standardization impedes interpretation of individual studies and hampers multicenter clinical trials\textsuperscript{44}. Several algorithms have been developed, applying different perfusion models\textsuperscript{26, 38, 45}. Inter-vendor differences may contribute to the variability in CTP analysis results\textsuperscript{46}. Such vendor-specific differences include both specific hardware for CTP image acquisition and software settings\textsuperscript{47-49}. An example is the inclusion or not of a bolus tracer delay factor in the respective algorithms\textsuperscript{50}. 
Different results for perfusion parameters produced from different commercial software packages have been observed\textsuperscript{51}.

The lack of standardization may affect not only the primary perfusion parameters but obviously also the summary maps that increasingly form the basis for clinical decision making. The summary map uses all perfusion maps to quantitatively describe and locate both the infarct core and the penumbra area in a single depiction. However, it is unknown to what extent infarct core and penumbra volume estimates depend on the specific software packages supplied by the vendors.

A second important pitfall encountered during CTP acquisition is related to patient motion. CTP analysis relies on the assumption that a certain position in the source images is associated with the same anatomical position in each time frame\textsuperscript{52, 53}. In clinical practice, this assumption is violated by the patient’s head movement during image acquisition. Head movement during perfusion image acquisition has been recognized as a source of inaccuracy in cerebral blood flow measurements in other modalities\textsuperscript{54, 55}. Head movement during CTP acquisition may deteriorate the results as well. However, information of the extent of head motion during CTP acquisition as well as the effects on the accuracy is still lacking.

**Head Movement Compensation Strategy**

Some methods have been proposed to minimize head movement during CTP acquisition. Movement can partly be limited by a foam headrest that provides the patient with a comfortable position\textsuperscript{54, 56}. Other acceptable methods for use in human studies are molded plastic masks, tapes, orthopedic collars and straps, and vacuum-lock bags\textsuperscript{54, 56}. However, such methods are not able to eliminate movement entirely. The more restrictive methods may be uncomfortable, reducing their acceptability by patients and potentially even giving rise to further movement to relieve discomfort\textsuperscript{57}. From studies using Positron Emission Tomography (PET) it is concluded that even with headrests, sudden or gradual head movements are frequently observed during image acquisition\textsuperscript{56-58}.

CTP software packages are usually capable of correcting only small head movements. Thus, most software packages provide image registration features that allow compensation within a limited range of rotation and translation, sometimes even limited to only in-plane movement.
In clinical routine, a radiologist usually first visually checks the CTP datasets for any head movement, and decides whether the set is suitable for accurate perfusion analysis. If the movement seems surmountable, registration available in software analysis packages is applied to correct the motion. Otherwise, those time frames of the CTP acquisition that disturb the perfusion analysis are removed from the series. In extreme cases with very excessive movement, the whole CTP dataset is discarded. This visual inspection is performed for all 25-30 time frames and is commonly conducted in 2D maximum intensity projections. This is considered to be a time consuming process, and the identification and correction of out-of-plane head movement is sometimes difficult. The procedure also relies on the subjective interpretation whether CTP data sets are considered suitable for analysis or not. Automated procedures for exclusion of unsuited CTP data are therefore desirable, substituting manual work by radiologists.

Time frames within a CTP dataset when movement occurred are sometimes removed before the perfusion analysis. This results in a reduction of information and increases the uncertainties in calculating the perfusion parameters. Nevertheless, rejecting valuable patient data should be avoided if possible, and correction of the motion would be the best solution to compensate head movement. Considering the extent and range of typical head movement occurring during CTP acquisition, a fully 3D registration method seems to be the best solution to correct the motion for better CTP analysis.

**CTP based CTA: Time-Invariant CTA (tiCTA)**

An acute ischemic stroke CT work-up protocol consists of 3 examinations: NCCT to rule out hemorrhage, CT Angiography for visualization and analysis of vessels and CT brain perfusion (CTP) for perfusion analysis. The similarities between all of these examinations have suggested the idea to simplify the workflow. Instead of having 3 CT examinations, there is a possibility to conduct only 2 types of examination: with and without contrast; or even one. This strategy not only reduces radiation dose and contrast medium load to patients, but most importantly saves precious time in this acute setting.

The difference between CTP and CTA is the dynamic aspect of CTP and the limited coverage of brain volume in CTP examination. For modern CT scanner settings with increased coverage and decreased slice thickness, the latter is no longer an issue. This now allows for combining all CTP time frames into a single CTA image that displays the maximum
of the contrast enhancement over time in each voxel, a process referred to as timing-invariant CTA (tiCTA) \(^{59}\). TiCTA could provide more information since the CTP source images cover the whole time period of contrast flow, in contrast to the single time-frame conventional CTA image. TiCTA may therefore provide better predictors of clinical patient outcome. To test this idea, it is important to evaluate the functionality of tiCTA in clinical research settings. Several studies confirmed the usability of TiCTA in some clinical research applications: measuring clot burden \(^{63}\), large vessel occlusion detection \(^{61}\), arterial visualization \(^{64}\), artery-vein separation \(^{62}\) and also collateral flow analysis \(^{60}\).

A final issue in the application of CTP and tiCTA is the translation of the images and summary maps to a score for stroke severity. A common strategy is the ASPECTS (Alberta Stroke Program Early CT Score). This is a quantitative 10-point region-based score, identifying areas in the middle cerebral artery perfusion territory for possible early ischemic changes\(^{65}\). ASPECTS is conventionally applied to non contrast CT and furthermore developed for CTA image and CTP maps. While the scoring seems robust and useful, automated rather than manual scoring is strongly needed in order to avoid interobserver variability, standardize the procedure and reduce handing time. This holds for CTP as well as tiCTA.

**Outline of the Thesis**

In this thesis, several topics in CTP imaging for acute ischemic stroke are discussed. The first topic is to study and in particular quantitate the pitfalls that arise from the use of CTP. We conducted studies related to two issues: lack of standardization (chapter 2) and motion during acquisition (chapter 3 and chapter 4).

In chapter 2, we study the quantitative differences between summary maps generated with two commercially available software packages for CTP analysis, using identical CTP source images. These two software packages represent the two mainstream algorithms: delay sensitive and insensitive \(^{50}\); deconvolution and non-deconvolution.

In chapter 3 we qualitatively and quantitatively assess the head movement during CTP acquisition. We analyze and quantify the extent, frequency and severity of head movement during CTP acquisition in a population of patients suspected of acute ischemic stroke. This chapter also discusses the relation between the severity of head movement and
the neurological condition of patients at admission, as expressed by the baseline characteristics: the National Institute of Health Stroke Scale (NIHSS) score, age and gender.

To get a better understanding of the effect of head movement on the accuracy of CTP analysis, a study using a digital head phantom CTP dataset is discussed in Chapter 4. This dataset allows simulation of translation and rotation to various degrees. We evaluate the effects of such movement on predicted summary maps and quantitate the degree of overlap with the known ground truth. We also determine the limits of movement that can still be corrected by the in-built registration algorithms.

The second topic concerns solutions for compensating head movement during CTP acquisition. Two methods are proposed: automatic selection of unsuitable CTP data with excessive movement and 3D movement correction based on registration with non contrast CT.

In chapter 5, we propose an automated selection of unsuitable CTP data with excessive movement. This method utilizes an image registration based technique to quantify the extent and range of head movement. The 3D image-registration of CTP data with non-contrast CT provides transformation parameters that identify rotation and translation. The results of the phantom study in chapter 4 are then used to define threshold values above which unacceptable deviations of perfusion analysis results occurred. The quantified transformation parameters are then compared to thresholds to come to an automated selection of CTP data that are unsuitable for analysis.

In chapter 6, we validate a correction method to compensate the head movement during CTP acquisition by again using the 3D registration of the CTP dataset with NCCT data. Improvements of the CTP result were compared to the result of 2D registration method available in the commercial software package.

The above strategies for head movement compensation allow the better use of time-invariant CTA derived from CTP datasets. The third topic discusses the usability of tiCTA for clinical applications. We specifically study the advantage of using tiCTA for automatic ASPECT Score analysis. In chapter 7, the use of the automatic ASPECT score application is broadly discussed while the benefit of using tiCTA data is highlighted.

Chapter 8 provides a general discussion of the thesis with recommendations for future research and clinical application of the current findings.
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Chapter 2

Differences in CT Perfusion Summary Maps for Acute Ischemic Stroke Patients Generated by Two Software Packages


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Abstract

**Background and Purpose:** Although CT Perfusion is a promising tool to support treatment decision of acute ischemic stroke patients, it still lacks a standardized method for CTP analysis. The purpose of this study was to assess the variability of area of infarct core and penumbra as presented in summary maps produced by two different software packages.

**Methods:** Forty-one CTP image datasets of 26 consecutive patients who presented with acute ischemic stroke were retrospectively evaluated. Identical image datasets were analyzed using two different commercially available CTP analysis software packages, each representing a mainstream of widely used algorithms: delay sensitive and delay insensitive. Bland-Altman analyses were performed to evaluate the level of agreement between the two methods in determining the area of infarct core and penumbra area in the summary maps.

**Results:** There was a statistically significant difference in infarct core area (\(-23.6, \text{SD}=25.6 \text{ cm}^2\)) and penumbra area (15.8, \text{SD}=25.3 \text{ cm}^2) between the two software packages. For all the areas presented in the summary maps the Bland-Altman interval limit of agreement was larger than 100 cm².

**Conclusion:** The infarct core and penumbra area of CTP summary maps generated by two commonly used software packages were significantly different, emphasizing the need for standardization and validation of CTP analysis before it can be applied for patient management in clinical practice.

**Abbreviations:** AIF=arterial input function; CBF = cerebral blood flow; CBV = cerebral blood volume; CTP = CT Perfusion; DWI = Diffusion Weighted Imaging; MTT = mean transit time; NVT = non viable tissue; SD = Standard Deviation; TAR = tissue at risk; TTP = time to peak; VOF= venous output function
Introduction

Stroke is the 3rd most common cause of death and most common cause of disability in the western world. CTP is emerging as a promising diagnostic tool for initial evaluation of acute ischemic stroke patients (1). In CTP images, areas with perfusion defects can be detected immediately after the onset of clinical symptoms.

CTP analysis results in brain perfusion maps indicating several parameters: CBV, CBF, MTT, and TTP. These parameters are combined in a summary map to quantitatively determine the area of infarct core (sometimes referred to as NVT) and the area of penumbra (sometimes referred to as TAR) (2, 3). Previous studies have shown that the estimation of the size of infarct core and penumbra area is valuable information for predicting the benefit of treatment (3). However, before such a new analysis is adapted in clinical practice, sufficient evidence of its robustness and accuracy should be provided. The CTP analysis might be influenced by both vendor specific hardware for CTP image acquisition and software CTP analysis settings and algorithms.

With the increasing availability of quantitative CTP analysis software, it becomes important to understand the potential pitfalls. It has been shown that differences in CTP hardware and software can affect the results (4-6). Additional known pitfalls of CTP analysis include incorrect placement of the perfusion volume, incorrect selection and variability of the AIF and VOF, chance of missing small infarcts due to the low resolution of CTP analysis, and changes in perfusion due to extracranial and intracranial stenosis (7). On the other hand, it has recently been shown that, despite the general believe, the order of scanning (CTA before or after CTP) has no significant influence on quantitative CTP parameters (8).

Although commercial software packages for CTP analysis are widely available, there is currently no standardized method for the analysis. Several algorithms have been developed applying different perfusion models (9, 10). Kudo et al demonstrated in 10 patient image data sets that brain perfusion maps resulting from CTP analysis of five different commercial software packages (GE, Philips, Siemens, Toshiba, and Hitachi) may vary considerably (11). The algorithms of these software packages were categorized into two groups based on the applied model and the effect of delay of bolus tracer: delay sensitive and delay insensitive (12). A more recent study showed that inter-vendor differences constituted the primary cause of the variability in CTP analysis results in a population of 11 patients (13).
In this study, we assessed quantitative differences in CTP summary maps between two software packages analyzing identical CTP source images. These two software packages represent the two mainstream algorithms: delay sensitive and delay insensitive. We compared CTP analysis results produced by (A) Philips Extended Brilliance Workspace, which represents the delay sensitive algorithm and (B) Siemens Syngo, which represents the delay insensitive algorithm (12).

To our knowledge, this is the first study that studies the variability of CTP summary maps of commercially available software packages. A summary map utilizes CBV, CBF, and MTT maps into single depiction that quantitatively describes both infarct core and penumbra area. Such summary maps are now commonly presented in commercial software packages. These summary maps, rather than the primary perfusion parameters, have the potential to become a major determinant of stroke management. Based on a larger patient population than was analyzed in previous studies, we additionally calculated the correlation of infarct core and penumbra area estimated between the two algorithms.

**Methods**

**Patient population**

CTP image data of patients suspected of acute ischemic stroke were retrospectively collected from February 2010 until March 2011. All datasets of patients with a slice thickness of 9.6 mm were included. Exclusion criteria were: severe motion artifacts, patients with previous craniotomy, and patients with poor cardiac function. Permission of the medical ethics committee was given for this retrospective analysis of anonymous patient data. Informed consent was waived because no diagnostic tests other than routine clinical imaging were used in this study. Because the results of the evaluation of the images for the purpose of the current study were performed retrospectively, they could not influence clinical decisions.

**Imaging Protocols**

All scans were performed on a 64 slice Siemens scanner (Somatom Sensation 64, Siemens Medical Systems, Erlangen Germany). Forty ml Ultravist 320 was infused at 4 ml/s using an 18G canula in the right antecubital vein. Acquisition and reconstruction parameters were as
follows: 80 kV tube voltage, 150 mAs, collimation 24x1.2 mm, FOV 300 mm, reconstructed slice width of 9.6 mm. At the level of the third ventricle, every 1.5 sec images were acquired for first 50 sec, followed by a 4 minute lasting image acquisition every 30 sec. Subsequently, at the level of the roof of the lateral ventricles, only a 50 sec lasting acquisition with imaging every 1.5 sec was performed.

**CT Perfusion Analysis**

The CTP image data were analyzed by a single trained author (F.F) blinded from all clinical data using two software packages; A: Philips Extended Brilliance Workspace 4535 674 25061 version 3.5, Brain CT Perfusion Package (Philips Healthcare, Cleveland, OH) and B: Siemens Syngo version CT 2007A, Neuro Perfusion CT Package (Siemens Healthcare, Forchheim, Germany).

The post-processing steps conducted for both software packages in the process of registration, segmentation, and perfusion parameter definition were inspected by an experienced radiologist (L.B) to ensure identical input parameters for CTP analysis. The input parameters included the AIF, VOF, hematocrit, CBV threshold, CBF threshold, and relative MTT threshold. The arterial input function is required to perform a deconvolution with the time-intensity curves of the brain tissue. The venous output function is required to correct the arterial input for volume averaging effects. The hematocrit is the ratio of red blood cells volume to the total volume of blood. This factor is used to convert contrast enhancement information (in HU) to CBV in ml/100g of tissue. It should not be adjusted without actually measuring the patient’s hematocrit, and accordingly was set at the default value of 0.45. Software package A selects the whole ischemic area on the basis of a relative MTT threshold, defined as the area in which the MTT is increased 1.5 times compared to the contralateral side. Software B uses the CBF threshold to identify the areas of perfusion abnormality. Both software packages use the CBV threshold to identify what part of the area of perfusion abnormality is salvageable (penumbra) or not (infarct core).

Both software packages include automatic registration of the images, which was not manually modified. By default, cerebral segmentation was also automatically performed in both software packages with vendor’s default threshold values. If a manually generated mask was required, a similar cerebral area was generated for both software packages.
Because the AIF and VOF are generated semi-automatically in software package B, this analysis was performed first. Most commonly, the AIF was determined in an anterior cerebral artery. The VOF was generally determined in the superior sagittal sinus (3, 14). For software package A, the same region of interest was chosen for the AIF and VOF generation as in software package B. The maximum intensity in Hounsfield Unit (HU) and time to peak of the AIF and VOF were inspected to ensure similarity. The midlines were manually set to be the same for both packages. Subsequently, the summary maps were generated using the same settings, a hematocrit of 0.45, and vessel removal at the threshold value of 9 ml/100 gr in the CBV map.

![Figure 1. Example of CTP analysis results as presented by the two software packages. Above: Software package A. On the left CBF, CBV, TTP, and MTT maps are displayed; on the right the summary map is depicted: Red represents the infarct core area and green represents penumbra area; Below: Perfusion analysis result of Software package B. On the left CBF, CBV, and TTP maps are displayed. The summary map is displayed on the right. In this summary map red is used for infarct core area and yellow for penumbra area.](image)
The labeling of the voxels as infarct core and penumbra was performed using the factory settings of the thresholds. In software package A, the infarct core was defined as pixels with a measured relative MTT > 1.5 and measured CBV < 2.0 ml/100 gr, and the area of penumbra defined with a measured relative MTT > 1.5 and measured CBV > 2.0 ml/100 gr. In software package B, the infarct core is called NVT and was defined with a measured CBF < 20 ml/100 gr/minute and a measured CBV < 2.0 ml/100 gr. The equivalent of the penumbra, TAR was defined with a measured CBF < 20 ml/100 gr/minute and a measured CBV > 2.0 ml/100 gr. From this point, NVT and TAR are referred to as infarct core and penumbra respectively. In the summary maps, the infarct core was presented in red. The penumbra was displayed in green and in yellow for software package A and B respectively (Figure 1).

To study whether potential differences are caused by using the MTT threshold versus the CBF threshold, we also analyzed the summed area of infarct core and penumbra. We defined this summed area as area of perfusion abnormality. For software package A, this is equal to the area of relative MTT > 1.5, for package B this is the area with a CBF < 20 ml/100 gr/minute.

**Statistical Analysis**

Means and SD of absolute and relative differences of the area of infarct core, penumbra, and perfusion abnormality as determined by the two software packages were calculated. The relative difference of the measured area was defined as the ratio of the difference in area to the average area, and was represented as a percentage. The relation between the measurements based on both software packages was assessed with scatter plots and with the calculation of linear regression lines. Correlation between the values was evaluated by calculating Pearson's correlation. Agreement between the two software packages was tested by calculating the systemic error (bias), and the 95% limits of agreement, defined as the bias ± 1.96 SD of the individual differences, as part of a Bland-Altman analysis. The dependency between the two methods was tested by linear regression of differences as shown in the Bland Altman plots. If the two methods are equally variable, the slope of this linear regression line would equal zero. P values smaller than 0.05 were considered statistically significant.
Results
From the 30 consecutive patients, 26 patients were included and 41 generated image data sets were used. As part of the protocol of the multi-center Dutch Acute Stroke Trial (DUST), some patients have had follow up CTP. One patient was excluded because of craniotomy, 3 patients were excluded because of severe motion artifacts. Of the 26 patients, the average age was 58 years ranging from 26 to 91 years, 16 were male.

Figure 2. CTP analysis result of a 40 years old female patient with infarct in the left hemisphere. Both summary maps were generated from the same patient at the same height. The difference in appearance of the grey-image results from default setting in visualization of the summary map of the two software analysis packages. Software A displays a slice and software B displays a time-MIP image and removed the skull. The summary map from software package A (A) shows a smaller infarct core and larger penumbra compared to software package B (B). The total area of perfusion abnormality is similar.

Figure 2 shows a typical example of a summary map from identical patient data generated by the two packages. This figure shows a similar area of perfusion abnormalities, but a different size of infarct core and penumbra. Table 1 shows the average of the absolute differences in area measurements by the two software packages. There was a significant absolute difference in the area of infarct core and penumbra between the two packages. The relative difference in infarct core and perfusion abnormality was also significant. The
scatter plots of the area of infarct core, penumbra, and perfusion abnormality of the summary maps are shown in Figure 3. The correlation coefficient of the area of infarct core between the software packages was \( r=0.62 \) (\( p<0.001 \)), the regression resulted in a slope of 0.78 (\( p<0.001 \)). For the area of the penumbra the correlation coefficient was \( r=0.28 \) (\( p=0.07 \)), the slope of the regression line was 1.26 (\( p=0.07 \)). The area of perfusion abnormality had a better correlation coefficient of \( r=0.70 \) (\( p<0.001 \)). The linear regression generated from this relation had slope of 1.02 (\( p<0.01 \)).

**Table 1. Statistical Analysis of the area of infarct core, penumbra, and perfusion abnormality for two CTP analysis software packages.**

<table>
<thead>
<tr>
<th></th>
<th>Average difference ± SD in cm(^2)</th>
<th>Relative difference ± SD (%)</th>
<th>Bland-Altman limits of agreement (cm(^3))</th>
<th>Pearson’s correlation coefficient (P-value)</th>
<th>Slope of regression line (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infarct core</td>
<td>-23.6 ± 25.6 (( P &lt; 0.001 ))</td>
<td>-114±94 (( P &lt; 0.001 ))</td>
<td>[-74.8, 27.6]</td>
<td>0.62 (&lt; 0.001)</td>
<td>0.78 (&lt; 0.001)</td>
</tr>
<tr>
<td>Penumbra</td>
<td>15.8 ± 25.3 (( P &lt; 0.001 ))</td>
<td>31±143 (( P = 0.16 ))</td>
<td>[-34.7, 66.3]</td>
<td>0.28 (0.07)</td>
<td>1.28 (0.07)</td>
</tr>
<tr>
<td>Perfusion Abnormality</td>
<td>-7.81 ± 29.6 (( P = 0.10 ))</td>
<td>56±98 (( P &lt; 0.001 ))</td>
<td>[-67.0, 51.4]</td>
<td>0.70 (&lt; 0.001)</td>
<td>1.02 (&lt; 0.001)</td>
</tr>
</tbody>
</table>
Figure 3. Scatter plots and regression lines of area of infarct core (A), penumbra (B), and perfusion abnormality (C) for the two software packages.
Figure 4. Bland-Altman plot including the limits of agreement between the two software packages in (A) Infarct Core, (B) penumbra, and (C) area of perfusion abnormality. For Bland-Altman plots, only the significant linear regression lines are shown, for the penumbra area the slope is 1.62 ($p<0.001$), for the area of perfusion abnormality the slope is 0.43 ($p<0.001$).
Figure 4 illustrates the Bland-Altman analysis for the area measurements. A statistically significant regression line was observed only for the penumbra area and area of perfusion abnormality. The limits of agreement for each measurement of the infarct core, penumbra, and perfusion abnormality area are shown in Figure 4 and given in Table 1. The Bland-Altman limits of agreement were -74.8 to 27.6 cm² for the infarct core area, -34.7 to 66.3 cm² for penumbra area, and -67.0 to 51.4 cm² for perfusion abnormality area.

**Discussion**

We found large differences in estimated infarct core and penumbra areas resulting from the two perfusion CT software packages. The Bland-Altman analysis showed severe lack of agreement reflected by the large intervals of agreement for each measurement, with discrepancies of more than 100 cm².

In general, analysis with software package A resulted in larger penumbra areas and analysis with software package B in larger infarct core areas. There were many cases for which software package A estimated a small area of infarct core (smaller than 10 cm²), and software package B estimated a large infarct core (up to 80 cm², Fig 3A). On average, the infarct core area was 30% smaller for software package A, and the penumbra area was approximately 30% larger. The average area of perfusion abnormalities was not significantly different but there was a large spread of the differences. This was also illustrated in the typical example of a difference in infarct core and penumbra area with a similar area of perfusion abnormality (Fig 2).

The correlation between both software packages for the penumbra area was especially weak. A higher correlation coefficient was observed in the area of perfusion abnormality. The linear correlation for both the penumbra area and perfusion abnormality area in the Bland-Altman analysis of Fig 4 revealed a dependency between the difference of the two methods and their average. Such a dependency is probably due to a systematic difference between these methods.

The two software packages use a different algorithm for the CTP analysis. Software package A uses a delay sensitive algorithm and package B a delay insensitive algorithm (6). These different mathematical methods for CTP analysis were described by Wintermark et al. (9). One approach uses a deconvolution model; the other uses a non-deconvolution maximum slope model. In software package A, CBV, CBF, and MTT maps were calculated
using a deconvolution algorithm. Deconvolution is a mathematic process that compensates the effects of the AIF on time-density curve to calculate the perfusion parameters. In software package B, the maximum slope technique was used, which takes the slope of bolus arrival time and maximum value of time-density curve into account, and therefore is considered delay-insensitive. Therefore, CTP parameters based on both methods may have the same name, but are actually defined and calculated quite differently. Kudo et al (11) have already shown that these differences in the CTP parameter maps are considerable. This difference in algorithm used in both software packages is crucial in generating the CTP maps of CBV, CBF and MTT/TTP (11). Furthermore, there is also a difference in the way both software packages define the infarct core and penumbra based upon generated CTP maps. In software package A, the infarct core is defined as the area with a relative MTT value 50% higher than the other hemisphere (i.e. relative MTT > 1.5) and CBV value lower than 2.0 ml/100 gr. If the CBV value is larger than this threshold, the area is defined as penumbra. Software package B defines infarct core as the area with CBF value below 20 ml/100 gr/min and CBV value below 2.0 ml/100 gr. If the CBV value is larger than this threshold the area is defined as penumbra. We suspected that this difference in definition also contributes to the large differences in area estimated in this study.

For decades, reduced CBF has been associated with ischemia. Since the flow cannot be directly measured from CTP data, it has to be estimated using dynamic parameters such as MTT, which also represent flow defects since it equals volume/flow by definition. However, both parameters have different dimensions and scaling. The concern is how to estimate MTT as well as to estimate CBF. Both vendors use algorithms for this that lead to quite different results. This does not disqualify contrast dynamics techniques, but should inspire us to identify optimal ways to estimate local perfusion.

Our findings agree with Kudo et al (11, 12) who studied 5 commercially available software packages and classified these into 2 groups based on differences in tracer-delay sensitivity. These authors have found that CTP maps correlated well within the classified groups but not across them. The packages used in the current study are from these two separate groups. They showed that a delay-sensitive algorithm has the tendency to produce substantial differences in CBF and MTT, with a decrease in CBF and increase in MTT for positive delays, and vice versa for negative delays. This affected the estimation of infarct core and penumbra area (12, 15). Another study showed that delay-sensitive algorithms
may overestimate CBV values in patients with concomitant intra- or extra- cranial severe hemodynamic delays (16). Adjusting the threshold value for CBV in software package A might result in a better correspondence with software package B. A recent study reported that it is CBF - not CBV - which has highest accuracy comparing to DWI as golden standard in defining infarct core (17). In that study it was shown that adjusting the threshold value for CBF resulted in a better correlation with DWI. Yet, again, the adjustment of CBF threshold differed for each software package (17).

CTP analysis results are sensitive to several parameters. Preceding studies revealed that the CTP analysis results may also vary due to scan parameters (18), post-processing steps such as the defining of input and output function (19). Other studies also assessed the reproducibility of CTP due to inter- and intra-user variability as the result of different selection of parameters (20, 21). Even though there was a high degree of correlation between and within users in producing the CBV, CBF and MTT maps within a single analysis software package (GE), the level of agreement was considered not sufficient to allow quantitative data derived from these map for clinical decision making (21). Recently, it was shown that intra-vendor differences are the primary cause of the variability in CTP analysis (13).

In this study we have assessed the reproducibility of the CTP analysis summary maps between both methods, rather than the accuracy of either method. We, therefore, withhold ourselves from any judgment on which package is more accurate than the other. Evaluating the accuracy of the CTP (summary) maps is a difficult task. CTP results can be compared with DWI, which is the current widely accepted de facto clinical reference standard for the determination of the infarct core (22, 23). DWI is, however, not widely available in the acute setting and during the time between CTP and DWI imaging, the infarct core could increase. Furthermore, the assessment of the penumbra with DWI is more difficult. In the study of Kamalian et al (17) it was shown that the optimization of perfusion parameter thresholds to obtain the best agreement with DWI was also dependent on the analysis software package. The accuracy of the CTP summary was also addressed by Wintermark et al (24) who have compared CTP analysis with follow up CT or MR and showed that CTP-based analyses are more accurate in detecting hemispheric stroke than using admission non-enhanced CT. However, the accuracy of the actual area measurements of infarct core and penumbra was not performed in this study. Also, software packages are introduced in the market without
published clinical validations of the measurements. Often the algorithms of these packages are not published as well. As a result, physicians may view these software packages as "black boxes".

There were several limitations to this study. First, it should be noted that the summary maps that have been studied here are derived from the vendor specific CBV, CBF, MTT, and TTP estimations. It is expected that the differences in these maps will result in differences in the infarct core and penumbra area in the summary maps. Differences in CBV, CBF, and MTT have already been addressed in previous studies (11, 12) and were not subject of this study. Instead, we studied how these differences in combination with a different definition of infarct core and penumbra area result in biases of infarct core and penumbra area. Since detail of the algorithms of the software packages was restricted by the vendors, we were not able to present a detailed explanation of the origin of differences in the summary map. A second limitation is that software packages for CTP analysis may be prone to updates of the algorithms and the used packages may already have been changed resulting in different results as presented here. Finally, not all parameters were completely identical for the two software packages because it was not possible to adjust these. We tried to optimize the similarity but some processes could not be truly identical. For example, the software packages used an internal registration of the CTP images which was difficult to adjust.

We should note that we only studied the variability of CTP analysis resulting from using different software. Both vendors also provide CT scanners which may vary as well in the generation of CTP image data, either due to scanner hardware or image reconstruction parameters. Because these scanner systems are regularly calibrated, we expect that this variation is smaller than the variation due to using different software analysis packages (25). However, this was not investigated in this study. Such a comparison would require additional CT scanning of stroke patients and is therefore unethical because of an increase of radiation and contrast material and a delayed treatment.

**Conclusion**

We observed large differences in the summary maps generated by two software packages, representing the two main types of CTP analysis. In our study of 41 cases, the differences in infarct core and penumbra area were statistically significant and the degree of agreement
was not acceptable. Because of this variability, CTP summary maps should be interpreted with care. This study emphasizes the need for standardization of CTP analysis algorithms, and further research and protocol development is advocated before CTP can become a robust determinant of stroke management in clinical practice.

Acknowledgements

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Chapter 3

Head Movement
during CT Brain Perfusion Acquisition
of Patients with Suspected Acute Ischemic Stroke

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A. Riordan, Y.B. Roos, C.B. Majoie, E. vanBavel, H.A. Marquering

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Abstract

Objective: Computed Tomography Perfusion (CTP) is a promising tool to support treatment decision for acute ischemic stroke patients. However, head movement during acquisition may limit its applicability. Information of the extent of head motion is currently lacking. Our purpose is to qualitatively and quantitatively assess the extent of head movement during acquisition.

Methods: From 103 consecutive patients admitted with suspicion of acute ischemic stroke, head movement in 220 CTP datasets was qualitatively categorized by experts as none, minimal, moderate, or severe. The movement was quantified using 3D registration of CTP volume data with non-contrast CT of the same patient; yielding 6 movement parameters for each time frame. The movement categorization was correlated with National Institutes of Health Stroke Scale (NIHSS) score and baseline characteristic using multinomial logistic regression and student’s t-test respectively.

Results: Moderate and severe head movement occurred in almost 25% (25/103) of all patients with acute ischemic stroke. The registration technique quantified head movement with mean rotation angle up to $3.6^\circ$ and $14^\circ$, and mean translation up to 9.1 mm and 22.6 mm for datasets classified as moderate and severe respectively. The rotation was predominantly in the axial plane (yaw) and the main translation was in the scan direction. There was no statistically significant association between movement classification and NIHSS score and baseline characteristics.

Conclusions: Moderate or severe head movement during CTP acquisition of acute stroke patients is quite common. The presented registration technique can be used to automatically quantify the movement during acquisition, which can assist identification of CTP datasets with excessive head movement.

Keywords: Computed Tomography, Perfusion, Head Movements, Stroke
Introduction

Stroke is the 3rd most common cause of death and ranks second after ischemic heart disease as a cause of lost disability-adjusted life-years in the western world\(^1\),\(^2\). CT Brain Perfusion imaging (CTP) is a promising diagnostic tool for initial evaluation of acute ischemic stroke patients\(^3\)-\(^5\) and has been validated in some previous study\(^6\)-\(^9\). With CTP analysis, areas with brain perfusion defects can be detected after the onset of clinical symptoms, which allows the differentiation between the irreversibly damaged infarct core and the potentially reversibly damaged infarct penumbra\(^10\),\(^11\). This information is important in choosing the most suitable therapy\(^12\).

During CTP acquisition, CTP source images are acquired every 1 to 3 seconds for approximately 1 minute. Time–attenuation curves of individual voxels in these images are used to estimate local perfusion parameters such as cerebral blood volume, cerebral blood flow, and mean transit time. Using pre-defined thresholds and contra-lateral comparison, these maps are combined to create a summary map estimating the volume of infarct core and penumbra\(^3\),\(^13\). In the analysis, it is assumed that a certain position in the CTP source images is associated with a single anatomical position in each time frame. In clinical practice, this assumption may not hold due to the patient's head movement during the image acquisition.

Several approaches for reduction of head movement during image acquisition have been proposed. The most straight-forward method is to use a head restraint. Acceptable methods for use in human studies are foam headrest, molded plastic masks, tapes, orthopedic collars and straps, and vacuum-lock bags\(^14\),\(^15\). However, such methods are not able to eliminate movement entirely. The more restrictive methods may be uncomfortable, reducing their acceptability by patients and potentially even giving rise to further movement to relieve discomfort\(^16\). From Positron Emission Tomography (PET) studies it is known that even with headrests sudden or gradual head movements are frequently observed during image acquisition\(^14\),\(^17\).

Head movement during CTP image acquisition has been recognized as a source of inaccuracy in cerebral blood flow measurements\(^15\),\(^18\). CTP analysis software packages are usually capable of correcting for small head movements, but in our experience this correction is often not sufficient. Figure 1 shows an example of the impact of head movement on the perfusion parameters generated from a CTP dataset, where the time-
Minimum Intensity Projection (t-MIP) image shows a double falx cerebri and perfusion maps show a frontal left shadow with high Cerebral Blood Volume (CBV) and Cerebral Blood Flow (CBF) values. In current practice, time frames within a CTP dataset with excessive movement are commonly considered unusable and are excluded from analysis. This results in a reduction of information and an increase of uncertainties in the perfusion parameter estimation. The decision to remove these time frames is currently based on subjective interpretation of radiologists or technicians.

Figure 1. Examples of a perfusion map disturbed by head movement CBF (a), CBV (b), MTT (c), TTP (d), and Summary Map (e).

Up to now, head movement has not yet been studied quantitatively. The goal of this study is to analyze and quantify the extent, frequency and severity of head movement during CTP acquisition in a population of patients suspected of acute ischemic stroke. Furthermore, we studied the relation between the severity of head movement with the neurological condition of patients at admission, as expressed by the National Institute of Health Stroke Scale (NIHSS) score and with the baseline characteristics: age and gender.

Materials and Methods

Patient population
We retrospectively included all patients admitted to our medical center between January 2010 and February 2012, who were suspected of acute ischemic stroke and underwent CTP. Non-contrast CT (ncCT) was performed on all patients suspected of ischemic stroke. If intracranial hemorrhage was ruled out, CTP was performed. Exclusion criteria for this study
were: patients with previous craniotomy and patients with poor cardiac function. A flow diagram to sum up patient population is shown in figure 2. The NIHSS score of the patients was retrieved from our neurology stroke database. Permission of the medical ethics committee was given for this retrospective analysis of anonymous patient data. Informed consent was waived because no diagnostic tests other than routine clinical imaging were used in this study.

**Figure 2. Flow chart of the study population**

**CT data acquisition**

All CT image acquisitions were performed on a sliding gantry 64 slice Siemens scanner (Somatom Sensation 64, Siemens Medical Systems, Erlangen Germany) in the emergency room. The ncCT scan of the brain was acquired at admission using 120 kV and 300-375 mAs, slice thickness was 5mm. In case head movement occurred during ncCT scanning, this CT was repeated. For each series of CTP acquisition, 40 ml iopromide (Ultravist 320; Bayer HealthCare Pharmaceuticals, Pine Brook, New Jersey) was infused at 4 ml/s using an 18
gauge canula in the right antecubital vein followed by 40 ml NaCl 0.9% bolus. Acquisition and reconstruction parameters were: 80 kV tube voltage, 150 mAs, collimation 24x1.2 mm, FOV 300 mm, reconstructed slice width of 4.8 mm. Each volume consisted of 6 slices with total coverage up to 3 cm in the -z direction. In two series, images were acquired for the duration of 50 sec at 2 sec intervals, first at the level of the third ventricle and second after approximately 3 minutes at the level of the roof of the lateral ventricles, each resulting in 25 time frame CTP volumes.

During acquisition, a standard foam headrest was used to provide patient with comfortable position and to minimize the head movement. For some patients, a follow-up CTP was taken within 2-3 days after the baseline CTP study if it is considered necessary.

**Qualitative Score**
A consensus reading was conducted by two experienced radiologists (LB and CM), both with more than 10 years experiences, to qualitatively grade the severity of the patient’s head movement in all CTP datasets in one of 4 categories. Group 0 (no movement) was considered to be free from head movement; group 1 (minimal movement) contained CTP datasets with only slight movements that, as judged by the observers, could be corrected by the image registration available in CTP software packages. Group 2 (moderate movement) consisted of CTP datasets with head movement and were considered too large to be corrected by the registration available in the CTP analysis software. Group 3 (severe movement) consisted of CTP datasets with severe movement that was expected to affect the CTP analysis in a major part of the brain. The categorization was presented for every CTP dataset as well as for every patient in separate analysis. The patient was categorized according to its most severe CTP dataset.

**Head Movement Quantification**
For all CTP datasets, the range and direction of head movement were quantified by 3D registration of every time frame within the CTP data set with the ncCT admission image data of the same patient. An ncCT scan is always performed for patients suspected of stroke\(^{19,20}\). Therefore, no additional scan was required for the movement quantification. The ncCT is scanned in a much shorter time period than the CTP acquisition. Therefore no, or only minimal, head movement is expected during the ncCT acquisition. It covers a larger volume
Head Movement during CT Perfusion Acquisition

than the CTP, thus it is suitable as a target for registration. The registration was performed using Elastix\textsuperscript{21} with the normalized correlation coefficient as a similarity measure and gradient descent algorithm to solve the optimization problem. The rigid registration was described with 6 motion parameters: three angles of rotations: pitch (Rx), roll (Ry), and yaw (Rz); and three spatial translations in the x- (Tx), y- (Ty) and z-direction (Tz) (Figure 3). The extent of movement was determined for each time frame separately, providing 25x6 temporal motion parameter values for each CTP data set, comparing to first time frame as a reference. The range of each motion parameter was defined as the largest value subtracted by the smallest value for the whole CTP acquisition. The speed of head movement during acquisition was estimated as the difference in motion parameters in consecutive time steps divided by the time between the 2 acquisitions (2 seconds).

![Figure 3. Different types of head rotation](image)

From PET studies it is known that head movement occurs more frequently as scanning time progresses\textsuperscript{15}. To study whether such an effect is also present in the CTP acquisitions, the average motion parameters for all patient data sets as a function of time were determined.

Since it is expected that CTP analyses are accurate for all CTP datasets in category 0 and 1 (no or minimal head movement), the quantitative analysis was only performed for data sets in category 2 and 3 (moderate or severe head movement).
Statistical Analysis

Means and SD of the range of the motion parameters and velocity were calculated for the two categories. The relationship between head movement and the NIHSS score was studied using a multinomial logistic regression. The significance test with the final model chi-square and the Wald test was our statistical evidence of the overall relationship between NIHSS score and movement categorization, as well as to evaluate whether or not the NIHSS score is statistically significant in differentiating between patient groups of movement. Student’s unpaired t-test was used to compare patients’ baseline characteristic (age and gender) between groups of head movement.

Results

A total of 220 CTP datasets of 103 patients were included. For most patients (89/103), the CTP study consisted of two CTP series at two brain levels. For 14 patients, CTP data were only available for one series at a single level. We also included 15 follow-up CTP study available (13 patients with two series, 2 patients with only one). Sixty-five patients (62.5%) were male. The average age was 62 years, ranging from 19 to 90 years. Detail of patient’s characteristic is listed in Table 1.

Table 1. Patient Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Movement 0-1</th>
<th>Movement 2-3</th>
</tr>
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<tbody>
<tr>
<td>ΣPatients</td>
<td>103</td>
<td>78 (76%)</td>
<td>25 (24%)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>38 (37%)</td>
<td>28 (36%)</td>
<td>10 (40%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62±16</td>
<td>61±15</td>
<td>64±15</td>
</tr>
<tr>
<td>NIHSS</td>
<td>10.7±7.42</td>
<td>10.2±7.63</td>
<td>13.1±5.91</td>
</tr>
</tbody>
</table>

Thirty-five out of 220 CTP datasets (16%) were categorized as moderate or severe head movement (groups 2 and 3) (Figure 4). Twenty-five patients of 103 (24%) had at least one CTP dataset with moderate or severe movement with 15 of 103 patients (14%) having severe movement during CTP acquisition.
Head movement occurred in both baseline and follow-up CTP study: from the 15 patients, 33% of baseline study and 20% of follow up study was classified as having moderate or severe movement (Figure 4).

![Pie charts proportions of movement severity classifications for all datasets (a) and all patients (b). The lower pie charts show the movement classification of patients with follow-up CTP for admission CTP, baseline (c) and the follow-up study (d).](image-url)
Figure 5. Movement categorization plotted against the NIHSS scores.

In Figure 5, the movement classification is plotted against the NIHSS scores. This figure shows that the head movement was almost equal for all NIHSS scores. In the multinomial logistic regression analysis, the probability of the model chi-square (2.5) was 0.47 (P>0.05), indicating that there was overall no relationship between NIHSS score and movement categorization. In the comparison to group 3 (severe movement), the probability of the Wald statistic for group 0, 1, and 2 was (0.96) 0.43, (0.93) 0.15, and (0.93) 0.24 respectively (all P-values >0.05), resulting in a statistically not significant difference of NIHSS score between each groups compared to group 3.

There was no statistically significant difference in age and gender in between the groups. The average age was 61±15 year for patients in groups 0 and 1 and 63±15 year for groups 2 and 3 (P=0.5). Within groups with moderate and severe head movement, the ratio between male and female was equally distributed, 60% and 40% respectively, and for the group with none and minimal movement the ratio was 64% and 36% respectively (P=0.4).

Quantitative result
The range of motion parameters for all CTP series classified as moderate and severe movement is summarized in Table 2 and Figure 6. As expected, the quantitative assessment reveals larger rotational and translational movement for data sets categorized in group 3.
than in group 2. The mean value of the rotation angles in group 2 was $2.3^\circ$, $2.0^\circ$ and $3.6^\circ$ for roll, pitch and yaw respectively. For group 3, mean value of the rotation angles were $5.7^\circ$, $8.3^\circ$ and $14^\circ$ for roll, pitch and yaw respectively. The mean speed of rotation ranged from $0.04^\circ$/s to $0.8^\circ$/s in group 2 and from $2.17^\circ$/s to $5.46^\circ$/s in group 3 (Table 3). In both groups, the largest rotation was in-plane (yaw).

![Box plots showing range of head movement and speed of head movement for groups 2 and 3.](image)

**Figure 6** Range of head movement (a) and speed of head movement (b), group 2 (left) and group 3 (right). Note the different y-axis ranges for group 2 and 3. (*) express the highest outlier value.

**Table 2.** Range of head movement parameters. $R_x$, $R_y$, and $R_z$ are the rotation angles around the x-, y-, and z-axis. $T_x$, $T_y$, and $T_z$ are the translation in x-, y-, and z-direction.

<table>
<thead>
<tr>
<th></th>
<th>Group 2 (28 CTP series)</th>
<th></th>
<th>Group 3 (27 CTP series)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rotation (degree)</strong></td>
<td>$R_x$</td>
<td>$R_y$</td>
<td>$R_z$</td>
</tr>
<tr>
<td>Max</td>
<td>5.56</td>
<td>5.55</td>
<td>14.4</td>
</tr>
<tr>
<td>Mean</td>
<td>2.30</td>
<td>1.97</td>
<td>3.55</td>
</tr>
<tr>
<td>±SD</td>
<td>±1.35</td>
<td>±1.51</td>
<td>±3.54</td>
</tr>
</tbody>
</table>
Table 3. Speed of head movement parameters. $R_x$, $R_y$, and $R_z$ are the rotation angles around the x-, y-, and z-axis. $T_x$, $T_y$, and $T_z$ are the translation in x-, y-, and z- direction.

<table>
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<th>Group 2 (28 CTP series)</th>
<th>Group 3 (27 CTP series)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Rotation (degree/s)</td>
<td>Translation (mm/s)</td>
</tr>
<tr>
<td>Max</td>
<td>1.49</td>
<td>3.13</td>
</tr>
<tr>
<td>Mean</td>
<td>0.43</td>
<td>0.83</td>
</tr>
<tr>
<td>±SD</td>
<td>±0.48</td>
<td>±0.89</td>
</tr>
</tbody>
</table>

Figure 7 shows two examples presenting the dynamic behavior of motion parameters for each time-frame. Figure 7a is an example of data set classified as group 2 (moderate) and figure 7b classified as group 3 (severe). In Figure 8, the average movement as a function of time is shown for all data sets of the group 2 and 3 categories. This figure shows a slight increase around 1/4 and 3/4 of the scanning time period. Nevertheless, head movement seems to occur during the whole period of acquisition.
Figure 7. Example of CTP image data of group 2 (a) and group 3 (b). Graphs on the right show related motion parameters. Rotation angle and translation parameters are presented for -x axis (blue line), -y axis (red line) and -z axis (green line) for each time step.
Discussion

In this study we have shown that in patients with acute ischemic stroke, moderate and severe head movement during CTP acquisition is rather common. In our population of 103 patients who presented with a suspicion of ischemic stroke, 24% had at least one CTP dataset showing moderate to severe head movement. Since CTP analysis assumes that a specific location in each time frame is associated with a single anatomical position, movement of the head alters time-attenuation curves and as such CTP analysis results.

In general, rotation was more severe within the axial plane (yaw/Rz), and translation occurred predominantly in the longitudinal z-direction (Tz, scan direction). The quantitative movement assessment showed larger values for all motion parameters for CTP datasets that were qualitatively categorized as severe (group 3), than for the CTP datasets that were categorized as moderate (group 2).

We presented a method to quantify head movement during CTP acquisition based on a 3D registration technique utilizing the ncCT data. To our knowledge, this is the first
study that quantifies head movement during CTP acquisition using available image data only. This method allows an objective detection of movement that may exceed specific thresholds and that should therefore be excluded from the CTP analysis.

Using the quantification of head movement during CTP acquisition, we were also able to estimate the speed of head movement by calculating the difference of motion parameters between time steps. Previous studies on general axial CT scanning emphasized that the velocity of motion rather than the range of the movement is crucial, even though the study investigated single-frame image quality and related parameters such as blurring, rather than dynamic sequences. Estimating the speed of movement during acquisition will give additional information in predicting flaws in CTP datasets.

Since CTP analysis is based upon the interpretation of time-intensity curves, it can be expected that head movement occurring early during the acquisition influences the analysis differently from movement late during the acquisition. We did not observe a strong dependence of head movement on the time point in the enhancement curve: movement was observed in all time frames. This observation is in contrast to PET studies, in which more movement was observed at the end of the acquisition. However, we need to emphasize that the duration of a CTP acquisition is much shorter than PET acquisition.

From a limited number of follow-up CTP study (15 datasets), there was no difference regarding occurrences of head movement in follow-up compared to base line acquisitions, indicating that this problem may arise also in a more stable condition of patients.

We found no statistically significant correlation between the NIHSS score and the movement categories. With increasing NIHSS, we observed a small increase in probability of movement during scanning. However, the odd-ratios were close to 1 indicating that the difference is small and clinically insignificant. As such this study suggests that the NIHSS score cannot be used as a predictor for head movement during CTP acquisition. It was also shown that there was no significant difference in distribution of age and gender between groups with and without head movement.

In our experience, the current registration techniques available in CTP analysis software are in many cases not sufficient to correct patient’s head movement. The proposed quantification method allows identification of datasets with excessive movement which unsuitable for accurate CTP analysis and therefore should be excluded. This technique provides also a base for a more advanced registration to correct this head movement. We
suggest the correction of movement of should be performed by the 3D registration of CTP dataset with ncCT data to improve the reliability of core and penumbra estimations in CTP analysis.

Our study has some limitations. First, we could not quantitatively assess the accuracy of the registration technique. The Elastix software had been used in variety application using different modality like MR, CT and Ultrasound. Several publications provided accuracy measurement of Elastix and it is increasingly used as benchmark\textsuperscript{21, 24, 25}. In our study, visual assessment of the registration showed a good correspondence of the ncCT scans with the registered CTP source images. Second, for every patient 1 to 4 datasets were included in our population. As a result, not all datasets were independent. This was neglected in our statistical analysis. Each CTP dataset was acquired separately and therefore we treated these multiple dataset as independent data. As an addition, we included also the patient-based analysis in this study. Third, we did not evaluate the precise effects of head movement on the result of CTP analysis, although impact of head movement on perfusion maps can obviously be observed as in Figure 1. An intrinsic difficulty of such an analysis is the absence of a ground-truth reference standard. The effects of head movement on CTP analysis results should be studied further in future studies.

Conclusion

We have shown that head movement during CTP acquisition is common in our population of patients with acute ischemic stroke. Motion occurs during the whole acquisition period and is independent of the neurological condition. Almost a quarter of all patients showed moderate or severe head movement during CTP acquisition and therefore the CTP dataset was considered unsuitable for accurate CTP analysis. We presented a technique to quantify head movement with a good correlation with the qualitative classification.

Acknowledgements

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Conflict of Interest Statement

All authors declare that there is no potential conflict of interest including any financial, personal or other relationships with other people or organizations within three (3) years of beginning the work submitted that could inappropriately influence (bias) the work.

References


Chapter 4

The Effect of Head Movement
on CT Perfusion Summary Maps:
Simulations with CT Hybrid Phantom Data

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Abstract

Head movement is common during CT Brain Perfusion (CTP) acquisition of patients with acute ischemic stroke. The effects of this movement on the accuracy of CTP analysis has not been studied previously. The purpose of this study was to quantify the effects of head movement on CTP analysis summary maps using simulated phantom data. A dynamic digital CTP phantom dataset of 25 time-frames with a simulated infarct volume was generated. Head movement was simulated by specific translations and rotations of the phantom data. Summary maps from this transformed phantom data were compared to the original data using the volumetric Dice Similarity Coefficient (DSC). DSC for both penumbra and core strongly decreased for rotation angles larger than approximately 1°, 2°, and 7° for respectively pitch, roll and yaw. The accuracy is also sensitive for small translations in the z-direction only. Sudden movements introduced larger errors than gradual movement. These results indicate that CTP summary maps are sensitive to head movement, even for small rotations and translations. CTP scans with head movement larger than the presented values should be interpreted with extra care.

Keywords: CT perfusion, head movements
Introduction

CT Brain Perfusion imaging (CTP) is emerging as a promising diagnostic tool for initial evaluation of acute ischemic stroke patients [1-3]. In CTP images, areas of the brain with perfusion defects can be detected after the onset of clinical symptoms and it facilitates the distinction between the irreversibly damaged infarct core and the salvageable damaged infarct penumbra, which is important in choosing the most suitable therapy [3-5].

Perfusion images are obtained by monitoring the dynamic passage of an iodinated contrast agent bolus through the cerebral vasculature and tissue. The perfusion analysis is based on local time-attenuation curves during contrast in- and outflow. The analysis provides estimation for local perfusion parameters such as Cerebral Blood Volume (CBV), Cerebral Blood Flow (CBF), and Mean Transit Time (MTT). Using pre-defined thresholds and contra-lateral comparison, these maps are combined in a summary map estimating the volume of infarct core and penumbra [6,7].

CTP analysis assumes that a specific location in the images is associated with a single anatomical position, ignoring the possibility of head movement. However, previous study revealed that 24% of acute ischemic stroke patients had considerable or severe head movement during CTP acquisition. As a result, almost 16% of CTP source data sets were judged unsuitable for accurate CTP analysis by experienced radiologists [8]. It is currently not clear to what extent the patients' head movement actually affects the CTP analysis. The aim of this study was to quantify the relationship between the extent of rotation and translation to alternations in CTP summary maps using a digital dynamic head phantom.

Methods

Digital Phantom Data

All simulated CTP datasets were generated from a digital hybrid phantom, which was based on a combination of CT images of an anthropomorphic head phantom with clinically acquired MRI brain images to quantify the different tissues. These data were combined with processed high resolution 7T clinical MRI images to include healthy and diseased brain parenchyma, as well as the cerebral vascular system. Time attenuation curves emulating contrast bolus passage based on perfusion as observed in clinical studies were added. This resulted in a dynamic 3D, noise-free, non contrast-enhanced CT volume of 104 thin slices.
(0.8mm), 25 time-frames with a 2 seconds interval [9]. Noise was not added to the images in order to study the effects of the movement solely.

Infarct and penumbra volume was designated according to clinical experiences. The infarct volume used in this study was positioned at the right part of the brain. The volume of infarct core and penumbra were created proportionally by applying mask to the digital hybrid phantom data. The imposed size and location of infarct volume will be used as ground truth for further analysis.

Fig. 1 Types of head rotation and translation.

To simulate head movement, the CTP phantom data were rotated and translated using Transformix an accompanying toolbox in Elastix [10]. Translations and rotations were performed along and around each coordinate axis (Fig. 1). The ranges of the motion parameters applied in the simulations were based on a previous study that quantified the patients’ head movement during clinical CTP acquisition [8]. Based on these observations, the simulated rotation angles were set from -10 to +10 degrees around the z-axis (yaw), and -5 to +5 degree for the x-axis (pitch) and y- axis (roll), with steps of one degree. The translations were set from -10 to +10 mm for all three axes. The head movement was simulated in the time frames 8 to 20.

We simulated both sudden and gradual movement by applying different speeds of movement: gradual movements with rotation angle of 0.5°/s (pitch and roll) and 1°/s (yaw)
and sudden movement with rotation angle up to 2°/s (pitch and roll) and 3.5°/s (yaw). These movement profiles are illustrated in Fig. 2.

**Fig. 2** Sudden vs Gradual Movement, for 7 degree yaw rotation.

### CTP perfusion analysis

The thin slice CTP phantom data volume was averaged along the z-direction to generate 6 slices of 4.8 mm thickness, representing the slice thickness that is used in most clinical practices. The original and transformed CTP datasets were processed by a trained operator using Philips Extended Brilliance Workspace version 3.5 Brain CT Perfusion Package (Philips Healthcare, Cleveland, OH).

The standard clinical procedure was used to produce the CTP summary maps. The arterial input function (AIF) and venous output function (VOF) regions were confirmed by an experienced radiologist. The classification of infarct core and penumbra was performed using default software settings: the infarct core was defined as pixels with a relative MTT > 1.5 and CBV<2.0 ml/100gr, and the area of penumbra defined based on a relative MTT > 1.5 and CBV>2.0 ml/100gr [11]. The image registration of the software package was applied if it produced a better match between successive frames, and skipped otherwise.

### Volume Similarity Measurement

The effects of head movement in CTP analysis was determined by comparing volumes of core, penumbra and total infarct presented in summary maps generated from both original and transformed CTP phantom data. We calculated the volume similarity and the spatial agreement using the Dice Similarity Coefficient (DSC). DSC is a measurement of spatial overlap of volumes, widely used for comparing segmentation results [12]. The DSC, ranging
from 0 to 1, is defined as two times the volume of the intersection divided by the union of the two volumes.

**Results**

The summary map of the original CTP phantom data is shown in Fig. 3. The regions of artificial infarct core (red) and penumbra (green) are shown in the left part of the image.

![Summary map of the original CTP hybrid phantom data. Perfusion abnormalities (infarct core-red and penumbra-green) can be seen in the right side of the brain.](image)

Fig. 3 Summary map of the original CTP hybrid phantom data. Perfusion abnormalities (infarct core-red and penumbra-green) can be seen in the right side of the brain.

The size of core, penumbra and total infarct, is plotted in Fig. 4. For pitch and roll rotations (Fig. 4 a-b), errors in volume estimations fluctuated strongly. For positive pitch rotations, an increase in infarct volume is accompanied with a decrease in penumbra. In roll rotation the size of penumbra decreased compared to the penumbra of original phantom data while the size of core increased.

For yaw rotation (Fig. 4 c), the estimated total infarct volume was nearly constant between +/- 7°. In this range, the size of penumbra was overestimated by 20-25%, while the
core volume was underestimated by 30-35%. For rotation angles beyond this range, the total infarct volume decreased rapidly.

Translation in the x- and y- direction for a range of 0 to 10 mm did not have a noticeable effect on the calculated volumes and are therefore not plotted in this figure. Positive translations in the z-direction had large effects on the infarct size estimates (Fig. 4d).

The DSC values are shown in Fig. 5. This figure shows that the DSC were nearly constant within narrow ranges of rotation (-7° to 7° for yaw, -1° to 1° for pitch, and -2° to 2° for roll). The DSCs for positive translations in the x- and y-direction were all close to 1. For translation in z- direction, DSC values dropped even for small translations of 2 mm.

The comparison of the DSC for gradual and sudden movements is shown in Fig. 6. This figure shows that there is no large difference between the DSC values for gradual and sudden movement.
Fig. 5 DSC value of the infarct core, penumbra and total infarct volume; plotted for every simulated rotation angle (a-c), and translation in the z-direction (d).
Fig. 6 Comparison of DSC for gradual and sudden head movement for + and - 4 degrees pitch (a), + and - 4 degrees roll (b), and + and - 7 degrees yaw (c).
Discussion

This study showed that simulated head movement has strong effects on the summary map of brain perfusion CT with inaccurate classifications of size and location of core and penumbra, even for small rotation and or translation.

Restricting head movement during CTP acquisition would be part of the solution. Several methods to minimize head movement include foam headrest, molded plastic masks, tapes, orthopedic collars- straps, and vacuum-lock bags [13,14]. However, restrictions that limit the rotation and translation are not trivial to implement and would have a risk of inducing further movement problems [15,16].

Our previous study revealed that head movement in patients with acute ischemic stroke is quite common (about a quarter of all clinical patients during CTP acquisitions), with a range of rotations between 2.0°-3.5° for moderate and 5.6°-14° for severe movement [8]. This study emphasizes the importance of the severe effects that this range of movement can have on CTP analysis.

Out of plane movement such as pitch, roll, and translation in z direction, deteriorated the summary maps more than in plane movement (yaw and translation in x and y direction). The image registration function available in the software package is only able to correct the in plane motion, but not the out of plane movement. As a result, the out of plane movement causes large error in estimating infarct volume and its spatial location.

Nevertheless, it is somewhat surprising that in plane movement also contributes to inaccuracies in infarct volume and location in CTP analysis. Our results suggest a limitation of the available registration of yaw rotation more than 7° for example. This finding suggests that even for in plane head movement, the CTP analysis should be carried out with care.

Previous studies on general axial CT scanning showed that the speed of movement instead of the range of the movement was also crucial [17]. The effects of rotation might also depend on the dynamics of such movement, sudden or immediate movements tend to cause larger mismatches on the summary map. In this study we showed that for the total infarct area there was a larger mismatch for sudden movement than for gradual movement, for all rotations. However, both the accuracy of the core and penumbra estimation was less sensitive to the speed of the movement.

Core and penumbra classification is performed using estimations of relative MTT, CBV, and CBF values in combination with estimations of the arterial input function and
venous output function. Head movement was expected to alter AIF, VOF and local attenuation curves and therefore produced error in estimations of core and penumbra. Fig. 7 shows examples of how different movement patterns can alter the AIF and VOF curves. However, it was beyond the scope of this study to evaluate the effects of different movement patterns on local attenuation curves.

Fig. 7 AIF -VOF of original phantom data (a), and transformed phantom data: with 4 degrees pitch (b), 5 degrees roll (c), and 7 degrees yaw (d). AIF was selected at Anterior Communicating Artery (ACA) and VOF at Superior Sagital Sinus (SSS).

The current study has not addressed movement in a real patient population. However, the limits of movement were derived from a previous study in a population of 103 patients with ischemic stroke. The current study estimates the effects of movement on the
summary maps and may be used in clinical practice to select image datasets that potentially deteriorate CTP analysis results. However, this would require a quantification of the movement, which is something that is not commonly available in clinical practice. Currently, the evaluation of suspicious movement is performed by visual inspection. This study shows the added value of a quantitative assessment of head movement to help radiologists identifying unsuitable CTP image data for the CTP analysis.

The effects of head motions are expected to be dependent on the scanner type, scanning protocol, and dedicated analysis software. To the best of our knowledge, similar studies have not been performed for other settings. However, the extent and poor predictability of these artifacts suggest that also in many other cases, head movement severely affects proper estimation of core and penumbra size and location.

This study has some limitations. The simulation was done separately for individual rotations and translations. Moreover, motion was simulated as a single gradual or sudden event only, with return to baseline. Actual movement in stroke patients is far more complicated, with coupled rotation and translation in multiple directions at various times during the procedure [8]. Such complex movement could even result in less accurate infarct volume estimations. We chose to perform the analysis for various movement parameters separately to quantify the effect of each transform parameter. We generated 6 slices of 4.8 mm thickness for this study. The use of thinner slices could make the CTP analysis more robust against small head movement, but this issue was not addressed in this study. In the simulation, we only use one model of CTP phantom data with specified size and location of infarct. The DSC value of core and penumbra with smaller volume can be worse due to lack of overlap. This study utilized 2D registration function available in the software package that is only able to handle in plane movement. This way, we can never be really sure what precisely the effect of out of plane head movement to the summary map. However this was the best approach we can do, as in our knowledge 3D registration is not yet available for CTP application.

Based on the presented simulations, this study suggests that head movement can be dealt with for only a small range of movement. The head movement, even for small rotation angles and z-axis displacements, strongly alters size and position of infarct core and penumbra in the CTP analysis. The range of movement parameters for which an accurate CTP analysis result can be expected differ for the different parameters: (-1°, 1°) for pitch, (-
2°, 2°) for roll and (-7°, 7°) for yaw and a translation in z-axis less than 2mm. This study suggests that CTP scans with a rotation angle larger than the limits should be interpreted with extra care.

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References


Chapter 5

Automatic Selection of CT Perfusion Datasets

Unsuitable for CTP Analysis due to Head Movement of Acute Ischemic Stroke Patients

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ABSTRACT

CT Brain Perfusion (CTP) datasets with severe head movement can deteriorate accurate perfusion analysis on acute ischemic stroke patients. We developed an automated selection of unsuitable CTP data with excessive movement. A 3D image-registration of the dynamic CTP data with non-contrast CT data provides transformation parameters. When these parameters exceeded threshold values, the data set was rejected for perfusion analysis. Threshold values were derived using controlled CTP phantom experiments. The automatic selection was compared to manual selection of unsuitable data by 2 experienced radiologists. ROC characteristics were calculated to determine the optimal threshold. In 114 CTP datasets, the optimal threshold was 1.0°, 2.8° and 6.9° for pitch, roll and yaw limit, and 2.8mm for z-axis translation. This resulted in a sensitivity and specificity of 91.4% and 82.3%. We conclude that registration of CTP datasets allows an automated and accurate selection of CTP datasets that should be removed from perfusion analysis.

Keywords—CT Brain Perfusion, Computer Aided System, Ischemic Stroke, ROC
INTRODUCTION

CT Brain Perfusion imaging (CTP) is evolving towards a promising diagnostic tool for initial evaluation of acute ischemic stroke patients [1-4]. In CTP images, areas with brain perfusion defects can be detected after the onset of clinical symptoms and can facilitate the differentiation between the irreversibly damaged infarct core and the potentially reversibly damaged infarct penumbra[5-9], which is important in choosing the most suitable therapy[10-12].

The patient's head movement during scanning, however, limits the applicability of CTP. Since CTP analysis assumes that a specific location in the images is associated with a single anatomical position [13, 14], it is likely that head movement deteriorates CTP analysis results, as shown in an example in Figure 1. While it is indeed well recognized that head movement is a common problem during CTP acquisition of stroke patients [15-17], automated procedures for exclusion of unsuited CTP data are lacking, requiring substantial manual work by radiologists.

Figure 1. Example of summary map in CTP analysis, disturbed by head movement: the red arrows point out double falx cerebri due to moderate head movement (A); deformation of brain images due to severe head movement (B).

Thus, in clinical practice, a radiologist must first visually check the CTP datasets to conclude whether it is affected by head movement, and to decide whether the data set is suitable for accurate perfusion analysis. If the data set is approved, registration, commonly available in software analysis packages, is applied to correct for small motion. Alternatively, certain time frames of the CTP acquisition that could disturb the perfusion analysis can be
removed. The visual inspection is performed for all 25-30 time frames and is commonly conducted in 2D maximum intensity projections. Next to being time consuming, the selection of out-of-plane head movement acquisitions with this method is sometimes difficult. Furthermore, it relies on the subjective interpretation whether CTP data sets are considered suitable for analysis.

The goal of this study is to develop and validate an automatic selection for unsuitable CTP data subject to excessive head movement. To this end, we used an image registration based technique to quantify the head motion. We utilized our previous phantom study to estimate threshold values of the head motion parameters beyond which unacceptable deviations of perfusion analysis results occurred. These threshold parameters were combined with the quantified motion parameters to come to an automated selection of CTP data unsuitable for analysis.

METHODS

CTP Data Acquisition

We collected 114 CTP data set from 100 patients who were suspected of acute ischemic stroke and underwent non-contrast CT and CTP in our medical centre (AMC) during 2010-2012. All CT image acquisitions were performed on a sliding gantry 64 slice Siemens scanner (Somatom Sensation 64, Siemens Medical Systems, Erlangen Germany) in the emergency room. Permission of the medical ethics committee was given for this retrospective analysis of anonymous patient data. Informed consent was waived because no diagnostic tests other than routine clinical imaging were used in this study. Because the results of the evaluation of the images for the purpose of the current study were performed retrospectively, they could not influence clinical decisions.

For the CTP acquisition, 40 ml iopromide (Ultravist 320; Bayer HealthCare Pharmaceuticals, Pine Brook, New Jersey) was infused at 4 ml/s using an 18 gauge canula in the right antecubital vein followed by 40 ml NaCl 0.9% bolus. Acquisition and reconstruction parameters were: 80 kV tube voltage, 150 mAs, collimation 24x1.2 mm, FOV 300 mm, reconstructed slice width of 4.8 mm. During acquisition, a standard foam headrest was used to provide patient with comfortable position and to minimize the head movement.
An ncCT scan is always present for patients suspected of stroke; therefore no additional scan was required [2, 18, 19]. The ncCT scan of the brain was acquired at admission using 120 kV and 300-375 mAs, with a reconstructed slice thickness of 5mm. The ncCT is scanned in a much shorter time period than the CTP acquisition. Therefore no, or only minimal, image degradation due to head movement is expected during the ncCT acquisition. In case severe head movement occurred during ncCT scanning and this was noticed by a technician, this ncCT was repeated.

**Quantification of Head Movement**

The range and direction of head movement were quantified by the 3D registration of every time frame in the CTP data set with the ncCT image data of the same patient. Because the ncCT covers a larger volume than the CTP time frames, it is suitable as target for 3D registration.

The rigid registration resulted in 6 motion parameters: three angles of rotations: pitch (Rx), roll (Ry), and yaw (Rz); and three spatial translations in the x-, y- and z-direction (Tx, Ty, and Tz) (Figure 2). The registration was performed using Elastix [20, 21], with the normalized correlation coefficient as a similarity measure and the use of the gradient descent algorithm to solve the optimization.

The extent of movement was determined for each time frame, providing 25x6 temporal motion parameter values, using the first time frame as a reference.

![Figure 2. Head movement parameters. Rx is the rotation around the x-axis (pitch), Ry is the rotation around the y-axis (roll), and Rz is the rotation around the z-axis (yaw).](image_url)
Estimation of Threshold Values with Phantom Experiment

Small movement is not expected to deteriorate the CTP analysis result. To define the threshold values for which we expect serious effects, we investigated the effect of head movement on CTP analysis result (Fahmi et al; submitted for publication, 2013) using CTP phantom data [22].

To simulate head movement, the CTP phantom data were rotated and translated using Transformix, a companion tools of Elastix [20]. Controlled translations and rotations were performed along and around each coordinate axis. The simulated rotation angles were set from -10 to +10 degrees around the z-axis (yaw), and from -5 to +5 degree around the x-axis (pitch) and y-axis (roll), with steps of one degree. The translations were set from -10 to +10 mm for all three axes.

The original and transformed CTP datasets were processed using Philips Extended Brilliance Workspace version 3.5, Brain CT Perfusion Package (Philips Healthcare, Cleveland, OH) to obtain the perfusion maps. We calculated the volume similarity and the spatial agreement between summary maps generated from the original and rotated phantom data. The agreement was expressed with the Dice Similarity Coefficient (DSC) [23, 24], expressing agreement not only for size but also location of infarct core and penumbra in between summary maps. The DSC, which value is ranging from 0 to 1, is defined as twice the volume of the intersection divided by the sum of the two volumes.

Rotation angles and translations related to given DSC values were used as thresholds. We explored DSC values ranging from 0.4 to 0.8 to obtain candidate threshold parameter sets for our automated motion detection. In our experiments we excluded the in-plane translations in x- and y-direction because the experiments showed that the CTP analysis software can correct these translations, and these translations do not have an effect on the analysis results. A set of threshold values therefore consists of roll, pitch and yaw rotation angle, and translation in z-axis.

Automated Selection

The decision to reject or accept a CTP dataset was based on the comparison of quantified motion parameters resulting from the registration with the threshold values that is associated with given DSC values resulting from the CTP phantom data experiments. If one
or more of these 4 movement parameters exceeded the threshold values, it was rejected; otherwise the CTP dataset was accepted.

**Manual Selection**

Two radiologists (CM and LFB, both with more than 10 years experiences) qualitatively graded the severity of the patient’s head movement in CTP data as “Accepted”; CTP data with no or minor head movement that could be corrected by the CTP analysis software registration, or as “Rejected”; when the CTP datasets showed severe movement that was expected to affect the CTP analysis and as such should be excluded. This manual selection of CTP data was used as ground truth for the validation of the automatic selection.

**Statistical Analysis**

We use a binomial classification test in the comparison of the automatic selection result with the manual selection to evaluate the performance of this method. True positive rate, false positive rate, true negative rate, and false negative rate were determined. Diagnostic accuracy, sensitivity and specificity of the automatic method were calculated for each set of threshold values with 95% confident interval. Furthermore, receiver-operating characteristics (ROC) for the different threshold values were calculated. The area under the ROC curve was also determined.

**RESULTS**

In total, 114 CTP datasets from 100 patients were included in the analysis. During visual inspection, the radiologists rejected 35 CTP dataset because of severe movement and accepted the remaining 79 CTP datasets.

**Motion parameters**

The mean value of the rotation angles of all CTP datasets was $1.7^0 \pm 3.0^0$, $2.1^0 \pm 6.2^0$ and $3.3^0 \pm 7.7^0$ for roll, pitch, and yaw respectively. The mean value of the translation was $2.2 \pm 4.1$ mm, $1.2 \pm 2.0$ mm and $1.6 \pm 2.2$ mm for translation in x, y and z direction. The largest rotation recorded was in-plane (yaw) movement with maximum rotation angles up to $61.3^0$. Figure 3 shows an example presenting the dynamic behavior of motion parameters profiles for each time frame during CTP acquisition.
Figure 3. Examples of the six movement parameters (rotation on the left, translations on the right) for 25 time frames as a result of the head movement quantification. This figure indicates that there is a large yaw rotation and z-translation around the 17th time frame.

Defining Threshold Values

The deterioration of CTP analysis results is illustrated by plotting DSC as a function of motion parameters. We derived 5 sets of threshold values at DSC of 0.4, 0.5, 0.6, 0.7, and 0.8 (Figure 4). This figure shows that the direction of movement is also important for the accuracy of the perfusion analysis result. For example, this figure shows that for an in plane rotation of more than 6 degrees there is only a small deviation resulting in a DSC value, whereas a pitch rotation of 1 degree has a large effect as expressed with a DSC value of 0.5.
Figure 4. DSC graph resulting from phantom study indicating the accuracy of the CTP analysis when CTP data from a moved phantom is analyzed. The red line describes the accuracy of the infarct core volume estimations, the green line for the accuracy of the infarct penumbra (adapted from Fahmi et al; submitted for publication, 2013) The yellow dots represent interpolation for given DSC values. The x-values of these dots represent the threshold values for roll (A), pitch (B) and yaw(C) rotation angle, and the translation in the z-direction (D) used in the automated selection procedure.

A list of the rotation and translation thresholds for each DSC value is listed in Table 1. The translations in the x- and y-direction are here omitted because the CTP analysis software is insensitive to in-plane movement.
Table 1. Threshold values of the motion parameters associated with DSC values derived from the phantom experiments.

<table>
<thead>
<tr>
<th>DSC value</th>
<th>Rx [deg]</th>
<th>Ry [deg]</th>
<th>Rz [deg]</th>
<th>Tz [mm]</th>
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<tr>
<td>0.4</td>
<td>1.97</td>
<td>5.01</td>
<td>7.15</td>
<td>8.14</td>
</tr>
<tr>
<td>0.5</td>
<td>1.04</td>
<td>2.80</td>
<td>6.99</td>
<td>6.14</td>
</tr>
<tr>
<td>0.6</td>
<td>0.83</td>
<td>1.85</td>
<td>6.83</td>
<td>3.34</td>
</tr>
<tr>
<td>0.7</td>
<td>0.62</td>
<td>1.39</td>
<td>6.68</td>
<td>1.93</td>
</tr>
<tr>
<td>0.8</td>
<td>0.42</td>
<td>0.92</td>
<td>6.52</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Accuracy

For each DSC value, the automated selection was performed and compared with the manual classifications, as shown in Table 2. In this comparison the manual selection was used as ground truth. The diagnostic accuracy was calculated for 5 sets of motion thresholds associated with the DSC values presented in this table (see Table 1 for the specific motion thresholds).

The ROC curve is shown in Figure 5 with an area under curve of 0.94. The optimal threshold was for DSC value of 0.5 (predictive power 0.79) with a diagnostic accuracy of 85.1% (95%CI: 78.6%-91.6%), sensitivity of 91.4% (95%CI: 86.3%-96.5%) and a specificity of 82.3% (95%CI: 75.3%-89.3%).

Table 2. Diagnostic accuracy of the automated selection of CTP datasets for different DSC value.

<table>
<thead>
<tr>
<th>DSC value</th>
<th>TP*</th>
<th>TN†</th>
<th>FP‡</th>
<th>FN§</th>
<th>PPV§</th>
<th>NPV§</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
<th>PP**</th>
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<tr>
<td>0.4</td>
<td>24</td>
<td>76</td>
<td>3</td>
<td>11</td>
<td>89%</td>
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<td>68.6%</td>
<td>96%</td>
<td>88%</td>
<td>0.77</td>
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<td>0.5</td>
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<td>65</td>
<td>14</td>
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<td>70%</td>
<td>96%</td>
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<td>54</td>
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<td>0</td>
<td>58%</td>
<td>100%</td>
<td>100%</td>
<td>68%</td>
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<tr>
<td>0.8</td>
<td>35</td>
<td>28</td>
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<td>0</td>
<td>41%</td>
<td>100%</td>
<td>100%</td>
<td>35%</td>
<td>55%</td>
<td>0.58</td>
</tr>
</tbody>
</table>

*TP/TN = True Positive/Negative, †FP/FN= False Positive/Negative, §PPV/NPV = Positive/Negative Predictive Value, **PP = Predictive Power
DISCUSSION

We presented a method for automatic selection of unsuitable CTP data sets based on the quantification of motion between the time frames. These motion parameters were compared to threshold values based on simulations of CT perfusion analysis with a CTP phantom. Performance of this automatic selection method, as evaluated by comparison with manual qualitative classification of head movement severity by radiologists, was high. To our knowledge, this is the first study that quantitatively analyzes head movement during CTP acquisition using available image data only.

Based on simulations with the digital hybrid phantom, it was shown that head movement can only be corrected by the standard CTP analysis software when the range of movement is limited. We have shown in our previous study that head movement strongly alters estimated size and position of infarct core and penumbra in the CTP analysis. The range of movement parameters for which an accurate CTP analysis result can be expected with DSC value 0.5 were 1.0° for pitch, 2.8° for roll and 6.9° for yaw; and also 2.8mm
translation in z-axis. These values were defined as threshold values to accept or reject CTP data, and might be different for other software packages. Individual phantom studies should therefore also be conducted for other software packages in order to allow adequate automatic selection of motion-affected CTP analyses.

The ROC analysis provided an optimal threshold for DSC value of 0.5. The sensitivity of the proposed method with this threshold values is high, while the specificity is somewhat lower. This characteristic is more preferable for such a computer aided system where the radiologists are expected to check the suspected CTP data. It was shown that for this DSC value, the automatic detection of suspicious data sets resulted in a rejection of more data than the selection of the radiologists. For a higher DSC value of 0.6 the sensitivity of the automated selection could be set to 100% at the cost of a specificity decrease to 68%. The threshold values used in this study could be optimized for other CTP methods and scanners. However, this was beyond the scope of this study.

This study has some limitations. First, the required computational time needed for the automatic selection is currently too large for introduction in clinical practice. Time constraint is an important issue especially for hyper acute stroke patient situation [25-27]. The main time consuming process of this study was the simulation of CTP phantom data in order to derive the threshold values for the motion parameters. Once the threshold values defined, it requires only single rigid registrations of a CTP dataset with ncCT image. This process could be computationally fast with adequate computer resources. Another limitation of this study is that the used motion threshold values were derived from CTP phantom instead of using large clinical patient data. A difficulty of such the latter analysis is the absence of a ground truth for the CTP analysis result, which is important in deriving the threshold values. The use of CTP phantom data for this purpose is the more suitable. Head movement parameters measured in this study consider only motion between time frames and ignore the motion occurred during the acquisition of a single time frame. Therefore, only deterioration due to this kind of movement that can be minimized with automatic selection of CTP dataset, and artifacts due to motion during acquisition of single frame was beyond the scope of this study.

The presented method has the potential to be integrated in clinical practice such that any movement during CTP acquisition will be automatically detected allowing radiologists to remove suspicious image data from the CTP analysis.
CONCLUSIONS

We presented a method that automatically selects CTP datasets that are subject to excessive head movement. The accuracy of the method was 85.1% with a high sensitivity (91.4%) and good specificity (82.3%). It supports the accuracy of CTP analysis and assures that clinical decision is not based upon faulty image data due to excessive head movement.

ACKNOWLEDGEMENT

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CONFLICT OF INTEREST

- Mr. Fahmi reports other grant from DIKTI Scholarship, Ministry of National Education, Government of Republic of Indonesia, outside the submitted work.
- Dr. Marquering has nothing to disclose.
- Dr. Streekstra has nothing to disclose.
- Dr. Beenen has nothing to disclose.
- Ms. Janssen has nothing to disclose.
- Prof. Dr. Majoie has nothing to disclose.
- Prof. Dr. van Bavel has nothing to disclose.

All authors declare that there is no potential conflict of interest including any financial, personal or other relationships with other people or organizations that could inappropriately influence (bias) the work.

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Chapter 6

3D Movement Correction of CT Brain Perfusion Image Data of Patients with Acute Ischemic Stroke

on behalf of the DUST study

Published in:
Neuroradiology (NEURORAD)
2014, 56: 445-452
ABSTRACT

Introduction: Head movement during CT brain Perfusion (CTP) acquisition can deteriorate the accuracy of CTP analysis. Most CTP software packages can only correct in-plane movement and are limited to small ranges. The purpose of this study is to validate a novel 3D correction method for head movement during CTP acquisition.

Methods: Thirty-five CTP datasets that were classified as defective due to head movement were included in this study. All CTP time-frames were registered with non-contrast CT data using a 3D rigid registration method. Location and appearance of ischemic area in summary maps derived from original and registered CTP datasets were qualitative compared with follow-up non-contrast CT; A quality score (QS) of 0 to 3 was used to express the degree of agreement. Furthermore, experts compared the quality of both summary maps and assigned the improvement score (IS) of the CTP analysis, ranging from -2 (much worse) to 2 (much better).

Results: Summary maps generated from corrected CTP significantly agreed better with appearance of infarct on follow up CT with mean QS 2.3 versus mean QS 1.8 for summary maps from original CTP (p=0.024). In comparison to original CTP data, correction resulted in a quality improvement with average IS 0.8: 17% worsened (IS= -2, -1), 20% remained unchanged (IS=0) and 63% improved (IS=+1, +2).

Conclusion: The proposed 3D movement correction improves the summary map quality for CTP datasets with severe head movement.

Keywords: Computed Tomography, Stroke, Perfusion imaging
Introduction

CT Brain Perfusion (CTP) enables the depiction of irreversibly damaged ischemic core and salvageable ischemic penumbra in the initial evaluation of patients with acute ischemic stroke [1-3]. The size of the ischemic core and penumbra are considered to be important determinants of clinical outcome and may add relevant clinical information compared to traditional stroke CT workup, including only non-contrast CT (NCCT) and CT Angiography (CTA) [4].

Perfusion analysis with CTP is performed by monitoring the dynamic behavior of iodinated contrast agent through the cerebral vasculature and tissue. Time–attenuation curves of individual voxel in the image are generated to estimate local perfusion parameters such as cerebral blood volume, cerebral blood flow, and mean transit time. Using pre-defined thresholds and contra-lateral comparison, these parameters are combined to create a summary map estimating the volume and location of the ischemic core and penumbra [5,6].

In CTP analysis, it is assumed that a certain position in the CTP source images is associated with a single anatomical position for each time frame. In clinical practice, this assumption may not hold due to patient’s head movement during CTP acquisition. Head movement may deteriorate time attenuation curves and cause the analysis to be inaccurate. The pattern and severity of head movement during CTP acquisition have been described previously, showing variation in timing, magnitude, and direction[7].

Head movement during CTP acquisition can partly be limited by a foam headrest that provides the patient with a comfortable position [8,9]. However, despite these precautions, sudden or gradual head motion is frequently observed during image acquisition [10,11]. About 25% of acute ischemic stroke patients experience quite severe head movement during CTP acquisition[7], and result in CTP datasets that do not allow accurate perfusion analysis.

In clinical practice, a radiologist or a specialized technician inspects the CTP datasets to ensure that it is not affected by severe head movement, and decides whether the data set is suitable for accurate perfusion analysis. In some cases, certain time frames of the CTP acquisition that could disturb the perfusion analysis can be removed. The inspection for all 25-50 time frames is performed visually and sometimes 2D maximum intensity projection is
used. The selection of out-of-plane head movement acquisitions with this method is difficult, and relies on the subjective interpretation. A previous study proposed an automatic detection of unsuitable CTP data due to head movement[12]. Nevertheless, rejecting valuable patient data should be avoided if possible, and correction of the motion would be the preferred solution to deal with head movement.

Most CTP analysis software packages provide an option for image registration to correct for movement. However, current registration techniques can only correct in a limited range of movement and can only deal with in-plane movement only. A previous study showed that a commercially available software package only allowed for adequate correction of rotational movements when the rotational angles were below a mere 1°, 2°, and 7° degree for respectively pitch, roll and yaw movement, and that larger rotation caused major flaws in the CTP analysis[13].

The purpose of this study is to introduce a new approach to correct for head movement during CTP acquisition by 3D registration of the CTP dataset with NCCT data, and to evaluate its performance compared to currently available registration methods.

**Materials and Methods**

**Patient Population**

CTP datasets from patients suspected of acute ischemic stroke were collected from a multi-center national trial: the DUST (DUTch acute Stroke Trial, ClinicalTrials.gov NCT00880113, [14]), between 2011 and 2012. All DUST patients underwent CT-scanning with non-contrast CT (NCCT), CT angiography (CTA), and CTP within nine hours after onset of suspected ischemic stroke. Inclusion criteria for the current study were whole brain coverage CTP datasets (6cm or more) defective due to head movement. Only CTP datasets with follow up CT were included. Based on inspection of the source data, CTP datasets with image quality defects due to other problems than head movement were excluded. These included incomplete CTP datasets, part of brain out of field of view, and low contrast to noise ratio (CNR). This resulted in a total of 35 datasets available for this study (Figure 1). All patients or legal representatives signed informed consent and permission of the medical ethics committee was obtained.
CT Acquisition
Out of 35 CTP datasets, 27 were acquired with a Philips scanner (iCT256, Philips Medical System, Best, The Netherlands) and 8 with a Toshiba scanner (Acquilion One 320, Toshiba Medical System, Tokyo, Japan). All included CTP datasets consisted of at least 25 time frames with 12 to 32 slices of 5 mm thickness with a whole brain coverage ranging from 6 to 16 cm in the z-direction. During acquisition, a standard foam headrest was used to provide the patient with a comfortable position and to minimize head movements. An admission NCCT scan was conducted as part of the standard stroke CT workup. The follow-up NCCT of the patients was performed within 1-5 days after admission.

Head Movement Correction
The proposed method to correct for head motion is based on 3D registration of each CTP time frame to the NCCT of the same patient. The registration is performed using Elastix[15].
with the normalized correlation coefficient as a similarity measurement and a gradient
descent algorithm to solve the optimization problem. The rigid registration yields 6 motion
parameters: three angles of rotations: pitch, roll, and yaw; and three translations in the x-, y-
and z-direction. These motion parameters are subsequently used to align all frames using
transformix, a toolbox included in the Elastix software. All aligned time frames are
subsequently combined into a complete CTP dataset ready to be used for CTP analysis. An
illustration of the head movement correction procedure is shown in Figure 2.

\begin{figure}
\centering
\includegraphics[width=0.8\textwidth]{fig2.png}
\caption{Proposed method: start with 3D rigid registration between CTP dataset with NCCT.
The registration processes are applied for each time-frame volume set and produce n x 6
transformation parameters (by Elastix). Correction step: Transforming all CTP volume for
each time frame using inverse transformation parameters (by Transformix). All
corrected volume set are then combined into a corrected CTP dataset for further CTP
analysis}
\end{figure}

CTP Analysis
Both original and corrected datasets were processed using dedicated software: Philips
Extended Brilliance Workspace version 3.5, Brain CT Perfusion Package (Philips Healthcare,
Cleveland, OH). The built-in registration function was switched off for the corrected CTP
dataset and used only for the uncorrected image data.
The perfusion analysis was performed by a single trained author (FF) and checked by experienced radiologists (LB & CM) to ensure accurate analysis. The midlines were set manually, as input parameters, the arterial input function was mostly defined in the anterior cerebral artery, the venous output function was mostly defined in the superior sagittal sinus, and a hematocrit factor of 0.45 was used. The labeling of the voxels as ischemic core and penumbra was performed using the factory settings: Cerebral Blood Volume (CBV) threshold 2 ml/gr and relative Mean Transit Time (MTT) threshold value of 1.5. The ischemic core was defined as pixels with a measured relative MTT > 1.5 and measured CBV<2.0 ml/100 gr, and the ischemic penumbra defined with a measured relative MTT > 1.5 and measured CBV>2.0 ml/100 gr [16]. Ischemic volumes for both the original and the corrected summary maps were recorded for comparison.

Validation

We conducted a quantitative analysis comparing the estimated size of ischemic core and penumbra in both summary maps to assess any differences. The size of ischemic core was measured from the red labeled area and ischemic penumbra size was measured from the green labeled area on the summary map. Both ischemic core and penumbra together constitute the total ischemic defect.

To validate the motion correction method, appearance and location of ischemic area in both summary maps resulting from the original and corrected CTP datasets were qualitatively compared with follow-up NCCT. A consensus reading was performed by two experienced radiologists (both with more than 10 years experience) to grade the agreement of the summary maps with the ischemic area on the follow up study. The quality grade was also based on other characteristics of the analysis map such as the completeness of Arterial Input Function (AIF) and Venous Output Function (VOF) and the validity of the ischemic core and penumbra labeled in the summary maps. Both observers were blinded for information indicating which summary map was from the original or the corrected CTP dataset. A quality score (QS) of 0 to 3 was used to express the degree of agreement of the CTP analysis result with the follow up study: QS=0 indicated no relation, QS=1 indicated a poor match, QS=2 indicated a moderate match, and a QS=3 indicated a good matching of ischemic area between the summary map and the appearance on the follow up study.
Furthermore, in different sessions, the experts also graded the improvement of the adjustment resulting from the 3D registration. The Improvement Score (IS) ranged from -2 to 2; with IS=2 representing a much better quality of the summary map using corrected CTP data compared to using the original CTP data, IS=1 for some improvement (better), IS=0 reflecting equal quality, IS=-1 for worse, and IS=-2 for much worse quality. Also for this analysis, observers were blinded from information on the kind of CTP data that was used (original or corrected data).

**Statistical Analysis**

Means and Standard Deviation of the ischemic size from both summary maps consisting of the core, penumbra and total ischemic defect, were calculated. The difference was calculated by subtracting the ischemic size in the corrected dataset from the original. A Wilcoxon signed rank test was used to test whether the difference between two summary maps was significant.

We compared the QS for both summary maps. A Wilcoxon signed-ranked test was used to test the statistical significance of the difference in QS values between original and corrected CTP data. Kruskal-Wallis and Jonckheere-Terpstra tests were used to explore the relation of improvement score (IS) with the initial quality (QS) of the perfusion maps of the original CT image data. A P-value <0.05 was considered to indicate statistical significance.

**Results**

Thirty-five CTP datasets were included. Nearly 75% of the patients (26/35) were male, and the average age was 63 years, ranging from 27 to 93 years. Average head movement of these CTP datasets was $2.3^\circ\pm2.5^\circ$, $1.3^\circ\pm1.6^\circ$, $3.2^\circ\pm5.2^\circ$ for pitch, roll and yaw respectively, and $1.5\pm2.3$ mm, $0.8\pm1.2$ mm and $10\pm12$ mm for translation in the x-, y- and z- direction. The maximum rotations were $11^\circ$, $7.1^\circ$ and $20^\circ$ for pitch, roll and yaw respectively. Maximum translations were $10$ mm, $5.6$ mm and $44$ mm in the x-, y-, and z- direction. Although the average values may seem quite low, maximal movement in some cases was much higher, precluding movement correction with the currently available registration.

Examples of summary maps generated from CTP dataset with and without correction are shown in Figure 3. Both summary maps provided a different estimation of the ischemic
core and penumbra as shown in Figure 3a. Quality improvement was obvious in Figure 3b where the movement was too large to be corrected by the available registration techniques.

![Fig.3 Two examples of summary maps with ischemic core (red) and ischemic penumbra (green) generated from original CTP dataset (left) and corrected CTP dataset (middle). The follow up NCCT from the same patient is provided (right). Summary maps from original and corrected CTP show different size of ischemic core and ischemic penumbra in example (a). Quality improvement is clearly noticed in example (b).](image)

The comparison of the ischemic size, quantified from both corrected and original summary maps, is shown in Figure 4. Differences of size estimation have an average value of $-4.3 \pm 22.0 \text{ cm}^3$ for ischemic core ($P=0.25$), $-11.2 \pm 28.6 \text{ cm}^3$ for penumbra ($P=0.02$) and $-15.3 \pm 31.2 \text{ cm}^3$ for total ischemic defect ($P=0.01$). Moreover, the correction resulted in significantly smaller ischemic core size estimation. Detailed results on ischemic size estimation from all summary maps and their differences are shown in Table 1.
Fig. 4 Comparison of ischemic size, quantified from summary maps in both original and corrected CTP dataset

Table 1 Comparison of infarct size for summary map from original and corrected CTP data

<table>
<thead>
<tr>
<th></th>
<th>Original (Mean± SD, cm³)</th>
<th>Corrected (Mean± SD, cm³)</th>
<th>Differences (Original – Corrected) (Mean±SD, cm³), (95%CI, cm³), P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core</td>
<td>23.56 ± 37.73</td>
<td>19.26 ± 32.42</td>
<td>-4.31 ± 22.0, (-26.3, 17.7), P=0.25</td>
</tr>
<tr>
<td>Penumbra</td>
<td>29.67 ± 45.98</td>
<td>18.64 ± 25.81</td>
<td>-11.2 ± 28.6, (-39.8, 17.4), P=0.02</td>
</tr>
<tr>
<td>Total ischemic defect</td>
<td>53.23 ± 66.12</td>
<td>37.91 ± 48.24</td>
<td>-15.3 ± 31.2, (-46.5, 15.9), P=0.01</td>
</tr>
</tbody>
</table>

Distribution of quality scores of summary maps obtained from the original and corrected CTP data are presented in Table 2. The average quality score using the original CTP dataset was QS=1.8 (range 0-3) and the average quality score for using the corrected CTP was QS=2.3 (range 0-3), which was a statistically significant difference (p=0.025).
Table 2: Quality score for original and corrected CTP data

<table>
<thead>
<tr>
<th>Quality Score (QS)</th>
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<th>1</th>
<th>2</th>
<th>3</th>
<th>Total Score / Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original CTP</td>
<td>5/30</td>
<td>4/30</td>
<td>11/30</td>
<td>10/30</td>
<td>56 / 1.8</td>
</tr>
<tr>
<td>Corrected CTP</td>
<td>0/30</td>
<td>4/30</td>
<td>12/30</td>
<td>14/30</td>
<td>70 / 2.3</td>
</tr>
</tbody>
</table>

Figure 5 shows the association between the maximum motion parameters (rotation and translation) and the quality score (QS) for the original and corrected datasets. There was no statistically significant relation between the extent of head movement and quality improvement provided by the correction method. Although, in some cases with higher range of movement, the corrected method was able to provide a good quality score (QS=2).

The average improvement IS score was 0.8 (range -2 to 2). Of the 35 CTP datasets, 5 were considered unsuitable for comparison due to unaccepted AIF and VOF, truncated curves and a different location of brain ischemic core shown at both summary maps. In 12 cases (40%) the summary maps from the corrected CTP data were considered of much better quality than the ones from the original CTP data (IS=2), in 7 cases (23%) the experts gave a score of IS=1 (better), in 6 cases (20%) both summary maps were of equal quality (IS=0), and in 5 cases the summary maps from the corrected CTP data were considered worse than the original CTP datasets (17%, IS=-1 or IS=-2). A summary of the improvement score analysis is shown in Figure 6.
The Kruskal-Wallis test indicated that the IS was dependent on the initial QS (p=0.014), where IS was highest for low initial QS scores. However, the Jonckheere-Terpstra test showed that there is no statistically significant trend between IS and initial QS (p=0.162).

**Discussion**

The motion correction method proposed in this study resulted in improved CTP analysis summary maps for most patients with movement during image acquisition. The ischemic area in the summary maps using corrected CTP data matched significantly better with follow up imaging (QS=2.3) than using original CTP data (QS=1.8, P=0.025). In a direct comparison of summary maps with and without correction, 83% of the maps using corrected CTP data had a better or equal quality.

In cases where severe head movement occurred, the correction method was still able to provide good quality summary map (Figure 5), even though there was no statistical significant relation between the severeness of head movement and the quality score provided by the correction method. In all cases with a very low initial quality (QS=0), the correction resulted in considerable improvement (IS=2).
The proposed correction method requires the CTP volume to have large whole brain coverage to compensate the motion properly, especially for the out-of-plane movement. The effectiveness of this method therefore depends on the availability of data beyond the region of interest, required in the transformation process. The more severe the head movement, the greater the need for ‘extra-space’ required in the correction method. Location of the ischemic core can also influence the success of this correction technique. Acquiring a larger volume with more coverage area will be advantageous when adopting this method. The CTP acquisition protocol should cover at least 6 cm or more, to allow the method to be effective for large head movements as in this study.

Although the corrected summary maps were of better quality, this does not indicate that the correction leads to a closer approximation of the true size and location of the ischemic core and penumbra. Therefore we did not use the follow-up NCCT at day 1-5 as the gold standard for a quantitative comparison because in the early stage infarct size may increase in the time period between the moments of CTP scanning and follow-up CT scanning.

In 17% of the datasets (5/30), correction worsened the quality of the summary map (IS= -1 and -2). This may be caused by cropping maps due to lack of space for correction regarding the position and extent of head movement. In other cases, streak artifacts were enhanced, since the registration strongly depends on the high intensity of the brain skull. However, in all these cases, the corrected summary maps were still considered as in good quality (QS=+1 and +2)

Our method is in line with other developments in the field of CT perfusion. The importance of alignment of the time frames in 3D images has been acknowledged in other studies [17,18]. Most of the 3D registration techniques use the first time frame of the CTP dataset as reference to aligned subsequent time frames. In contrast, the basic concept of our proposed method is to register 3-dimensionally the CTP dataset with the NCCT as a reference frame. This has the advantage of the large volume that NCCT covers; making it is more suitable for the registration of the CTP source data. By registering CTP data to NCCT volume, we have the ability to identify the head movement and correct out-of-plane head movement. No extra scan is required as the NCCT scan is always present as part of the general work-up of patients suspected of acute ischemic stroke [19,20].
This study has several limitations. First, our study was based on only expert qualitative grading and may have lead to subjectivity of the evaluation. The scoring systems used (quality score-QS and improvement score-IS) have not been validated nor used in other studies. This scoring method assessed the quality of summary maps by visual evaluation of the ischemic area compared to the appearance of infarct as present in follow up NCCT. Despite that it is known that infarct may grow in time, the use of follow-up CT as reference standard is commonly used in various studies, beside the MRI-DWI and follow-up MRI [21]. Second, we did not assess the accuracy of the registration technique used as part of the correction technique. However, the Elastix software had been used in a variety of applications using different modalities. Several publications provide accuracy measurements of Elastix for specific purposes and this software is increasingly used as a benchmark [15,22].

The correction method is fully automated without user intervention. The transformation for correction requires less than a minute. However, the current implementation of the 3D registration requires quite some time: 25-30 minutes on a regular desktop. It should be noted that the aim of this study was to provide a proof of concept rather than a clinical application. Computation time optimization should be considered before implementing this method in clinical practice.

Previously, the same registration method was applied to automatically detect CTP datasets that were unsuitable for accurate analysis due to head movement[12]. This approach could be used to remove culprit time frames before the analysis. Considering the limitations of the current correction method, the best solution might be to combine these 2 approaches in a single strategy. Ideally, the CTP datasets should first be checked automatically to remove any time frames with excessive head movement, followed by the correction method proposed in this study. However, it is still not clear to what extent frames can be removed without severely affecting the CTP analysis. Future work is needed to clarify this issue.

**Conclusion**

The proposed 3D movement correction method using a 3D registration of CTP dataset with NCCT images generally improves the quality of summary maps generated from CTP datasets with head movement.
Acknowledgements

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Conflict of Interest

We declare that we have no conflict of interest.

References


Chapter 7

Automatic ASPECTS Analysis in Time-Invariant CTA of Acute Ischemic Stroke Patients

F. Fahmi, G.J. Streekstra, N.J. Janssen, O.Berkhemer, B.C. Stoel, M. Starling, M. van Walderveen, E. vanBavel, C.B. Majoie, H.A. Marquering on behalf of the MRCLEAN researchers

Submitted for Publication
ABSTRACT

Introduction: In patients with acute ischemic stroke, time invariant CTA (tiCTA) has benefits because of its insensitivity of delayed contrast arrival. The ASPECTS method for assessing early ischemic changes was found superior when applied to contrast-based image modalities. We hypothesize that ASPECTS as determined on tiCTA has an improved association with neurological scores compared to ASPECTS as determined on CTA.

Method: TiCTAs were generated from 25 CTP datasets. An automated ASPECTS method was applied to both standard CTA and tiCTA. The scores were compared with each other and with manual ASPECTS, in terms of total ASPECTS, dichotomized ASPECTS (≤7 and >7), and per ASPECTS region. Statistical analysis using Intra-class Correlation Coefficient (ICC), percentage of agreement and Bland-Altman analysis was calculated. Furthermore, the association of all ASPECTS scores with NIH Stroke Scale (NIHSS), final infarct size, and modified Rank Scale (mRS) was determined using the calculation of the Spearman correlation coefficient.

Results: The agreement of the automated ASPECTS on CTA and tiCTA with manual ASPECTS on CTA provided an ICC of 0.2-0.5 and 0.1-0.3 respectively. This was in the range of ICC of 0.3 for the interobserver CTA ASPECTS. The automated ASPECTS scores for CTA and tiCTA were identical for 40% of the patients, and 60% in dichotomized ASPECTS. The tiCTA ASPECTS correlated slightly better with final infarct size and mRS score compared to standard CTA but this difference was statistically not significant (p=0.18).

Conclusion: While all ASPECTS scores have a limited association with outcome, our study illustrates non-inferiority of tiCTA compared to CTA, allowing simplifying the CT workflow for acute ischemic stroke patients.

Keywords. Computed Tomography, Stroke, Perfusion Imaging
Introduction

Neuroimaging plays a crucial role in the evaluation and management of patients suspected for acute ischemic stroke management. Typically there are 3 admission CT examinations for acute ischemic stroke patients: Non contrast CT (NCCT) to rule out hemorrhage, CT Angiography (CTA) for visualization and analysis of the patency of vessels and CT brain perfusion (CTP) for cerebral perfusion analysis. To simplify the workup of patients suspected of acute ischemic stroke, it has been suggested to conduct only 2 series of image acquisition: one without and one with contrast. This has advantages not only in the reduction of radiation dose and contrast medium load to patients, but also in a reduction in image acquisition time, which is important in the acute setting.

In this scenario, a CTA image could be generated from CTP images. This is possible since CTP acquisitions on modern multi-slice CT scanners can be considered as multi-time frame CTA. The result of this technique is sometimes referred to as timing-invariant CTA (tiCTA).

Compared to CTA, tiCTA has the advantage that it is independent of contrast arrival time, which makes it insensitive to any delay in contrast delivery. This delay insensitiveness of tiCTA is achieved by using the whole period from contrast inflow to outflow to find the maximum intensity for each voxel within the acquisition time interval. Smit et al have shown that this property of tiCTA provides a better visualization of slow collateral filling compared to standard CTA. This potentially facilitates judgment of the volume of brain tissue that can be rescued.

The Alberta Stroke Program Early CT Score (ASPECTS) is a semi-quantitative method for description of early ischemic changes. This score is well established in the neuroimaging workup of patients suspected of acute ischemic stroke. ASPECTS quantifies early ischemic changes in specific areas supplied by the Middle Cerebral Artery (MCA), and is associated with functional outcome of acute ischemic stroke patients. In clinical research, it is applied on NCCT as well as on CTA. ASPECTS on NCCT assesses hypo attenuation due to formation of cytotoxic edema, while on CTA it determines hypo attenuation due to reduction of cerebral blood volume. ASPECTS on CTA has greater sensitivity to ischemic changes and is more accurate in identifying infarct volume compared to NCCT. The
ASPECTS with contrast-based imaging modalities in general has better inter-observer variability compared to non-contrast imaging. Because of the advantage of tiCTA in visualizing delayed collateral filling close to the critical underperfused area, we hypothesize that ASPECTS obtained from tiCTA provides a better correlation with patient outcome than ASPECTS obtained from standard CTA.

**Material & Methods**

We determined ASPECTS on both CTA and tiCTA in patients with acute ischemic stroke using an automated approach. The automated ASPECTS was compared to manual ASPECTS on CTA to assess the accuracy of this method. Subsequently, automated and manual ASPECTS on CTA and automated ASPECTS on tiCTA were associated with baseline neurological score (National Institutes of Health Stroke Scale (NIHSS)) and patient outcome represented by final infarct volume and modified Rankin Scale (mRS).

**Patient Selection**

The study included patients suspected with acute ischemic stroke as registered in Dutch multi-center image database of the MR CLEAN clinical trial (Registries: NTR1804/ISRCTN10888758; protocol available at [www.mrclean-trial.org](http://www.mrclean-trial.org)). Upon admission, patients were subjected to a set of routine CT-examinations (i.e. NCCT, CTA and CTP) within 6 hours after onset of suspected ischemic stroke. Only datasets with thin slices (<0.5mm) and large axial coverage (at least 16 cm) were included. Patients with datasets with less than 25 time frames, patients with a hemorrhage, and with a CTA that does not cover the whole MCA territory were excluded. In total, 25 patient dataset were included. The evaluation of the neurologic deficit performed upon admission was quantified according to NIHSS. Functional outcome was examining using mRS, a ranking scale system for measuring patient outcome based on patient’s dependency in daily life at three months follow up. All patient records, information and images were anonymized and de-identified prior to analysis. All patients or legal representatives signed informed consent.
CT Acquisitions
All image acquisitions were performed on a Toshiba scanner (Acquillon One 320, Toshiba Medical System, Tokyo, Japan). All CTP datasets consisted of 25 time frames with 320 slices of 0.5 mm thickness with brain coverage of 16 cm in the z-direction. Admission NCCT was conducted as part of the standard workup. A follow up NCCT was performed within 1 - 5 days after admission.

Time Invariant CTA
The tiCTA images were reconstructed from full CTP datasets. First, all time frames of the CTP acquisition were registered to NCCT to correct for head movement during acquisition. The tiCTA was subsequently generated from the registered CTP time frames by determining the maximal contrast enhancement over time for each voxel. A 3D spatial and temporal averaging filter was applied to reduce noise.

Manual CTA ASPECTS
Two experienced radiologists independently determined the ASPECTS score on CTA images. The ASPECTS method is based on the analysis of brain part that is supplied from blood by the MCA, divided into 10 regions (Figure 1), by comparing the left and right hemisphere. For manual ASPECTS, the image is viewed at the optimal window and level setting that support the maximum contrast between normal and ischemic area. If an ASPECTS region with diminished contrast enhancement compared to the contralateral hemisphere is scored as abnormal, one point is subtracted from a maximal score of ten. Therefore, a score of ten reflects normal brain parenchyma whereas a score of 0 indicates ischemia throughout the complete MCA territory.
**Fig 1.** ASPECTS region (adapted from Barber et al\textsuperscript{7}) A=anterior circulation; P=posterior circulation; C=Nucleus Caudatus; L=Nucleus Lentiformis; IC=Internal Capsule; I=Insular Ribbon; M1=anterior MCA cortex; M2=MCA cortex lateral to insular ribbon; M3=posterior MCA cortex; M4, M5, and M6 are anterior, lateral, and posterior MCA territories immediately superior to M1, M2, and M3, rostral to basal ganglia. Subcortical structures are allotted 3 points (C, L, and IC). MCA cortex is allotted 7 points (insular cortex, M1, M2, M3, M4, M5, and M6)

**Automated ASPECTS**

The automated ASPECTS method was originally developed for NCCT by Stoel et al\textsuperscript{15}, Yao et al\textsuperscript{16}, followed by application to CTA\textsuperscript{17}. Based on this method we employed an atlas based approach to segment the MCA territory automatically into ten ASPECT regions per hemisphere. The atlas image consisted of an NCCT image of a healthy person without pathologies and image artifacts. Furthermore, a label image was created based on this atlas image contained all delineated ASPECT regions that were manually drawn and verified for correct anatomical locations.

The classification of the ASPECTS regions in patient CTA and tiCTA data was performed in a two-step approach. First, we registered the atlas image to the CTA/tiCTA image, which resulted in a set of transformation parameters. The rigid, affine and non-rigid registration were performed using open source software package Elastix\textsuperscript{18}. These
parameters were used to transform the label image to delineate each ASPECTS region in the CTA and tiCTA images. This resulted in 20 patient-specific labels representing the 10 ASPECTS regions for each hemisphere (Fig 2B).

To increase the accuracy of the registration, a brain mask was used to align only structures within the brain. Labeled voxels overlapping with ventricles or skull were also excluded by using ventricle and skull masks. These masks were semi-automatically generated based on region-growing and morphological operations.

Density values expressed in Hounsfield Units (HUs) of all voxel from specific ASPECTS regions were then collected and represented in histograms. Differences of histograms between contra-lateral hemispheres were described by 2 parameters: difference of the mean and the cross correlation function. ASPECT regions were classified as affected if one of these parameters exceeded preset threshold values.

**Fig 2.** Preparation of label image (a) Registering atlas image to the CTA image; producing transformation parameters (Tx). (b) Transforming label image using Tx; producing deformed label (c) mapping of ASPECTS region on tiCTA/CTA dataset: axial, coronal and sagittal view.
Statistical Analysis
We assessed the inter-observer agreement between manual ASPECTS on CTA image data of 2 observers by creating scatter plots, calculation of the Intra-class Correlation Coefficient (ICC) and percentage of agreement. Furthermore, Bland-Altman analysis was conducted to determine the limit of agreement.

The same methods were also used to compare the automated ASPECTS on tiCTA and CTA with the manual scores. The Wilcoxon signed rank test was used to test the significance of difference between both scores and calculation of the Spearman correlation coefficient was conducted. To compare the classification as affected or unaffected for each ASPECTS region separately, the percentage of agreement was determined.

Furthermore, the ASPECTS scores were dichotomized into the ‘uncertain and unlikely to benefit’ group (ASPECTS 0-7) and ‘likely to benefit’ group (ASPECTS 8-10) with respect to the effect of endovascular thrombolytic therapy. The agreement for this dichotomized ASPECTS (≤7 and >7) between both automated ASPECTS on tiCTA and CTA using the manual ASPECTS scores as reference value, was assessed as percentage of agreement and by kappa analysis.

Finally, we assessed the association of all ASPECTS scores with NIHSS, final infarct size, and mRS by calculation of the Spearman correlation coefficient.

Results
A dataset of 25 patients was used in this study. The average age was 64.7±11.5 years with 12 male patients. The median baseline NIHSS score was 20 (IQR 16-24), and average mRS score at 90 days was 3.8 (moderate to severe disability). The automated ASPECTS method was successfully applied to all tiCTA and CTA datasets.

The scatter plot comparing the two manual ASPECTS on CTA is shown in Figure 3. The inter-observer agreement for the manual reading had an ICC of 0.5, with a limit of agreement from -7.88 to 7.80 (average paired difference -0.04).
The ICC of the automated and manual CTA ASPECTS was 0.2 and 0.5 for observer 1 and observer 2, respectively, both with wider limit of agreement (table 1). The ICC for the automated tiCTA and manual CTA ASPECTS was lower with 0.1 and 0.3 for observer 1 and observer 2, respectively.

**Table 1. Comparison of Automated and manual ASPECTs on CTA image**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>ICC</th>
<th>Percentage of agreement</th>
<th>Bland Altman Mean Difference; Limits of Agreement*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTA_{obs1} vs CTA_{obs2}</td>
<td>0.3 (p=.21)</td>
<td>20%</td>
<td>-0.04; [-7.88, 7.80]</td>
</tr>
<tr>
<td>CTA_{auto} vs CTA_{obs1}</td>
<td>0.2 (p=.71)</td>
<td>12%</td>
<td>1.92; [-6.33, 10.1]</td>
</tr>
<tr>
<td>CTA_{auto} vs CTA_{obs2}</td>
<td>0.5 (p=.84)</td>
<td>12%</td>
<td>1.88; [-6.73, 10.5]</td>
</tr>
<tr>
<td>tiCTA_{auto} vs CTA_{obs1}</td>
<td>0.1 (p=.40)</td>
<td>16%</td>
<td>1.96; [-5.38, 9.30]</td>
</tr>
<tr>
<td>tiCTA_{auto} vs CTA_{obs2}</td>
<td>0.3 (p=.18)</td>
<td>12%</td>
<td>1.92; [-4.89, 8.73]</td>
</tr>
</tbody>
</table>

*95% Confidence Interval
Figure 4 compares the automated ASPECTS on CTA and tiCTA. The ICC for the two automated ASPECTS was 0.3 (Table 2). There was no statistically significant difference between the automated tiCTA and CTA ASPECTS (Wilcoxon signed-rank test with limited samples, p=0.83). The spearman correlation coefficient was 0.30, which indicates a fair correlation. Figure 5 shows the Bland-Altman analysis comparing automated tiCTA and CTA ASPECTS. Average paired difference was 0.04 with limit of agreement of -6.01 to 5.93. The ASPECTS score was identical for 40% of the patients.

Fig 4. Comparison of automated ASPECTS on tiCTA and CTA; dashed line indicates dichotomized ASPECTS analysis.

Table 2. Comparison of automated ASPECTS on tiCTA and CTA

<table>
<thead>
<tr>
<th>Comparison</th>
<th>ICC</th>
<th>Percentage of agreement</th>
<th>Bland Altman Limits of Agreement*</th>
</tr>
</thead>
<tbody>
<tr>
<td>tiCTA&lt;sub&gt;auto&lt;/sub&gt; vs CTA&lt;sub&gt;auto&lt;/sub&gt;</td>
<td>0.3 (p=.18)</td>
<td>40%</td>
<td>-0.04 [-6.01, 5.93]</td>
</tr>
<tr>
<td>Normal ASPECTS (1-10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dichotomized ASPECTS (0-7 vs 8-10)</td>
<td>-</td>
<td>60%</td>
<td>-</td>
</tr>
</tbody>
</table>

*95% Confidence Interval
Table 3. Percentage of Agreement between automated ASPECTS on tiCTA and CTA, by regions.

<table>
<thead>
<tr>
<th>ASPECTS Regions</th>
<th>Percentage of agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleus Caudatus</td>
<td>87.1%</td>
</tr>
<tr>
<td>Nucleus Lentiforma</td>
<td>74.2%</td>
</tr>
<tr>
<td>Capsula Interna</td>
<td>71.0%</td>
</tr>
<tr>
<td>Insular cortex</td>
<td>83.9%</td>
</tr>
<tr>
<td>M1 (anterior MCA cortex)</td>
<td>71.0%</td>
</tr>
<tr>
<td>M2 (MCA cortex lateral to insular)</td>
<td>77.4%</td>
</tr>
<tr>
<td>M3 (posterior MCA cortex)</td>
<td>67.7%</td>
</tr>
<tr>
<td>M4 (anterior MCA territory)</td>
<td>74.2%</td>
</tr>
<tr>
<td>M5 (lateral MCA territory)</td>
<td>80.7%</td>
</tr>
<tr>
<td>M6 (posterior MCA territory)</td>
<td>83.9%</td>
</tr>
</tbody>
</table>

For the comparison of separate regions, the percentage of agreement was in the range of 67% (M3) to 87% (Caudate) with average value of 77% (Table 3). For dichotomized ASPECTS, the percentage of agreement between ASPECTS on tiCTA and CTA was 60% with a κ coefficient of 0.1 (p=.69), indicating slight and statistically insignificant agreement.

Fig 5. Bland-Altman plot for automated ASPECTS of tiCTA and CTA
Figure 6 shows a scatter plot of all ASPECTS scores compared to NIHSS, final infarct size and mRS score. Compared to automated CTA ASPECTS, automated tiCTA ASPECTS correlated better with final infarct size (spearman correlation coefficients 0.22 vs 0.13) and mRS score (0.10 vs 0.04), even though these correlations were statistically insignificant, and less strong than the manual score of observer 2. The scores of observer 2 yielded correlation.
coefficients of 0.23, 0.44, and 0.48 for the relation with NIHSS, final infarct size, and mRS score respectively (Table 4).

**Discussion**

Time invariant CTA image was generated from CTP data of all patients and used for ASPECTS analysis. The automated ASPECTS method could successfully be applied to both standard CTA and tiCTA datasets. Yet, the current results revealed that there is only a fair correlation of ASPECTS scores between automated and manual approaches, as well as between CTA and tiCTA data.

The ICC of automated and manual ASPECTS was in the range of the ICC of the inter-observer agreement, indicating a good accuracy of the automated method. Previous work of Janssen et al also showed good accuracy of the automated method used compared to manual reading. Nevertheless, our result revealed several concerns that need to be resolved in order to introduce this method in clinical practice. In this study, we applied the automated method by using only a single atlas image and one label image. Combination of multiple atlas images with more label images, adapting different brain shape and structure might be a better strategy that can provide better result for ASPECTS analysis.

We found that there was only fair correlation between automated tiCTA and CTA ASPECTS. Compared to the percentage of agreement for dichotomized ASPECTS, there was a better, but still poor, correlation between CTA and tiCTA for dichotomized ASPECTS, which differentiates groups of patients that are ‘likely to benefit’ and those who are ‘unlikely to benefit’ from treatment. For our patient population, the current results thus seem to show little advantage of using tiCTA compared to standard CTA. Further work is needed to unravel the causes of variability. In addition, tiCTA remains promising for subgroups of patients, notably those who have indications for delayed contrast flow.

The automated ASPECTS scores, whether based on CTA or tiCTA, has a less strong correlation with patient outcome, compared to observer 2. Automated ASPECTS of tiCTA correlates slightly better with the final infarct volume and mRS compared to automated ASPECTS of standard CTA. However, this difference is not statistically significant. This indicates that further development of the automated ASPECTS scoring method is needed in order to come to a reliable application of automated ASPECTS scores. At the same time, the
differences between both observers indicate that an automated approach is needed. This need is further stressed by the notion that a fast and standardized workflow is needed in clinical decision making in acute stroke.

We choose time maximum intensity projection method in generating tiCTA for its simplicity and suitability with the ASPECTS method. The 3D+t median filter that we used to increase the contrast to noise ratio has been used in other studies. There are alternatives described such as the Gaussian filter to maximize CNR on circle of Willis analysis and the TIPS (Time Intensity Profile Similarity) filter.

There are also several other methods for producing tiCTA images from CTP datasets developed for other specific purposes. Proposed methods include average CTA, arterial-venous weighted CTA and dynamic 4D CTA. To our knowledge none of these methods was used to analyze the ASPECTS and its comparison to patient outcome and might be considered to improve the automated ASPECTS score analysis.

The overall process of the automated ASPECTS required less than a minute. However, the preprocessing step including registration of CTP datasets with the labeling took in average 25-30 minutes. Since in this study we focused on establishing the proof of concept, we did not optimize the method in terms of computational time.

Similar to our work, several studies confirmed the usability of tiCTA in some others clinical application beside ASPECTS. These include the use of tiCTA in measuring clot burden, detection of large vessel occlusion, arterial visualization, artery-vein separation and also collateral flow analysis. Together with our study, the simplification of the CT workflow in acute stroke setting is becoming more promising.

Conclusion

In this study we have used time invariant CTA generated from CTP datasets for automated ASPECTS analysis. This provides several advantages, with a non-inferiority compared to automated ASPECTS analysis on regular CTA. Yet, the associations with outcome were poor, requiring further improvement of the underlying algorithms. Despite this, our study emphasized the usability of tiCTA as a replacement for CTA, simplifying the workflow for acute ischemic stroke patients.
References


Chapter 8

General Discussion
General Discussion

In this thesis, several topics on CT Perfusion for patients with acute ischemic stroke have been investigated and discussed, including the lack of standardization of CTP analysis software and the influence of head movement during CTP acquisition on CTP maps. Potential solutions were developed to increase the overall accuracy of CTP analysis results. We also explored the possibility of using time-invariant CTA generated from CTP dataset for automatic ASPECTS scoring. In this chapter we will discuss the main outcomes of the underlying studies, their impact on the interpretation of brain perfusion imaging results and the new research questions raised by our work.

Standardization of CTP method

Since CTP is potentially useful to select patients for acute reperfusion, there is a need for standardization in CTP especially in relation to the core and penumbra assessment. In our study we found that there was severe lack of agreement between two commercially available analysis packages reflected by the large differences in infarct areas. We found discrepancies up to 100 cm$^2$, (equal to 48 ml of infarct core volume with 4.8mm slice thickness), which is meaningful compared to the crucial threshold of 70 cm$^3$ of infarct core as highly predictive of a poor clinical outcome as proposed by Sanek et al. These differences potentially influence treatment decision in clinical practice since the ratio of infarct core and penumbra is one of the indicators for giving further reperfusion treatment to patient.

One of the explanations for the large variations is the difference between methods used in the two investigated software packages, i.e. deconvolution versus non-deconvolution method, and sensitive versus delay insensitive methods. These differences in CTP analysis are crucial in determining the different perfusion parameter values represented in CBV, CBF and MTT/TTP maps even on the same image data.

There is also a difference in the definition of estimated infarct core and penumbra. For example, for one approach the infarct core is defined as the area with a higher relative MTT value compared to the other hemisphere (i.e. relative MTT > 1.5) and a CBV value lower than 2.0 ml/100 gr. While another approach defines an infarct core as the area with CBF value below 20 ml/100 gr/min and CBV value below 2.0 ml/100 gr. Here, reduced CBF has been associated directly with ischemia. The concern regarding the differences therefore
is how to estimate MTT as well as CBF. The difference we found therefore does not disqualify contrast dynamics techniques, but should inspire us to identify optimal ways to estimate local perfusion, and furthermore to standardize it.

Evaluating the accuracy of CTP (summary) maps is important but might be a difficult task. CTP results can be compared with MRI Diffusion weighted Imaging (DWI), which is the current widely accepted de facto clinical reference standard for the determination of the infarct core\textsuperscript{5, 6}. Recently, CTP-derived CBF was found to have the highest accuracy comparing to DWI\textsuperscript{7}. Other studies showed that CTP maps were highly correlated with DWI\textsuperscript{8-10}, but with large measurement errors due to low SNR/CNR, which limited the reliability of CTP\textsuperscript{11}.

Similar to our study, some other researchers also found that the differences in the main perfusion maps, instead of the summary map, were also considerable among different software packages\textsuperscript{4, 12-14}. Apart from the method used for CTP analysis, CTP analysis results may also vary due to variation in scan parameters\textsuperscript{15}, user-defined parameters such as those influencing the input and output function, segmentation of the brain, and mirror line definition\textsuperscript{16-18}.

**Measurement of head movement during CTP acquisition**

We presented a method to quantify head movement during CTP acquisition based on a 3D registration technique utilizing non contrast CT (NCCT) data. To our knowledge, this is the first study that quantifies head movement during CTP acquisition using available image data only. Other proposed techniques to measure head movement during acquisition use sensor tracking system\textsuperscript{19}, transducers\textsuperscript{20}, an infra red camera\textsuperscript{21} or optical markers\textsuperscript{22}, which are not suitable for acute settings. It is therefore preferable to develop an image-based method to measure the movement.

In our proposed method, the head movement was quantified by registering every time frame within the CTP data set with the NCCT admission image data of the same patient. We choose NCCT here because it is always performed for patients suspected of stroke\textsuperscript{23, 24}. Therefore no additional scan was required. Since NCCT is scanned in a much shorter time period than the CTP acquisition, none or only minimal head movement is expected during the NCCT acquisition. NCCT also covers a larger volume than the CTP, thus it is suitable as a reference for 3D registration.
We found that in patients with acute ischemic stroke, head movement during CTP acquisition is rather common (with prevalence around 24%). Head movement was more severe within the axial plane and translation occurred predominantly in the longitudinal z-direction (scan direction). Depending on the imaging plane, rotation causes in-plane and out of plane movement that is variable but generally large. For CTP datasets that were qualitatively categorized as severe, rotations can have a range up to 15 degrees. We found no statistically significant correlation between head movement and patient baseline data such as NIHSS score, age and gender. Consequently, this study suggests that the degree of head movement during CTP acquisition cannot be predicted by these parameters.

Estimating the speed of movement during acquisition is also crucial and may give additional information in predicting flaws in CTP datasets. Using the quantitative movement assessment, we were able to estimate the speed of head movement during acquisition, which can be used as an indication of imaging artifacts.

Since CTP analysis is based on the analysis of time-intensity curves of individual voxels, any motion of the head will alter these curves and thereby the CTP analysis result. We investigated this effect of head motion on CTP analysis results. We found in our study, in which we used a digital hybrid phantom data, that head movement, even for small rotation angles and z-axis displacements, strongly alters size and position of infarct core and penumbra in the CTP analysis. Out of plane movement such as pitch, roll, and translation in z direction deteriorated the summary maps more than in plane movement (yaw and translation in x and y direction). Nevertheless, it is somewhat surprising that in plane movement more than ±7° of yaw, which should be corrected properly by available 2D registration techniques, also contributes to inaccuracies in infarct volume and location in CTP analysis. This finding suggests that even for in plane head movement, the radiologist should be aware of possible errors in infarct core and penumbra size and location estimations.

**Motion compensation strategy**

The available registration techniques in CTP analysis software are in many cases not sufficient to correct patient’s head movement. We investigated two approaches to deal with this problem: detection of unsuitable CTP datasets due to excessive head movement and 3D motion correction for less severe movement.
The motion detection method allows measurement of head movement for each patient and is applied to the identification of datasets with excessive movement. We presented an automatic selection of unsuitable CTP data sets based on the quantification of motion between the time frames. These motion parameters were compared to threshold values based on simulations with digital hybrid CTP phantom data and optimized with ROC analysis. These values were defined as threshold values to accept or reject CTP data. Performance of this automatic selection method, as evaluated by comparison with manual qualitative classification by radiologists, was high (91.4% sensitivity and 82.3% specificity) and is therefore potentially a useful tool to improve the CTP analysis procedure.

The main time consuming process of this study was the simulation of CTP phantom data in order to derive the threshold values for the motion parameters. Once the threshold values were defined, it requires only rigid registrations of a CTP dataset with NCCT image for CTP data selection. This process is computationally fast with adequate computer resources to allow application of the method in an acute setting.

The optimal solution to deal with head movement is a motion correction technique. A full-fledged 3D registration method has the potential to be integrated in clinical practice such that any movement during CTP acquisition could be corrected properly. The correction method we proposed is able to improve CTP analysis summary maps with an 83% of quality improvement for most patients with head movement. This method requires the CTP volume to have large whole brain coverage to compensate the motion properly, especially for the out-of-plane movement. The effectiveness of this method therefore depends on the availability of data beyond the region of interest, required in the transformation process. The more severe the head movement, the greater the need for ‘extra-space’ required in the correction method. Therefore, acquiring a larger volume with a larger coverage will be advantageous when applying this method. In our experiments, we discovered that the CTP acquisition protocol should cover at least 6 cm or more, to allow the 3D movement correction method to be effective for large head movements. With increasing availability of faster scanners with many detector arrays the problem of limited axial coverage is expected to be less of an issue in future.

The proposed correction method is fully automated without user intervention. The transformation for correction requires less than a minute. Again, the most time consuming process is the registration, which can take more than 15 minutes to proceed. Nevertheless,
with advances in hard and software such as parallel processing, the time limitation should solvable in order to incorporate the method in the clinical workflow. In some recent commercial CTP software packages, a 3D registration technique for movement compensation has recently been incorporated.

With the two methods presented in this thesis, i.e. motion detection and motion compensation, the best solution might be to combine both in a single strategy. Ideally, the CTP datasets should first be checked automatically to remove any time frames with excessive head movement that cannot be compensated, to be followed by a 3D correction method.

**Time Invariant CTA**

To investigate the potential benefit of using CTP time series for automatic ASPECTS score estimation, we generated time invariant CTA images from CTP datasets. Generating CTA from CTP would simplify the workup of patients suspected of acute ischemic stroke by to conducting only 2 CT acquisitions instead of the current 3 examinations. This has advantages not only in the reduction of radiation dose and contrast medium load to patients, but also in a reduction in image acquisition time, which is important in the acute setting.

On the other hand, The Alberta Stroke Program Early CT Score (ASPECTS) is a semi-quantitative method that can quantify early ischemic changes in specific areas supplied by the Middle Cerebral Artery (MCA) and associated with functional outcome of acute ischemic stroke patients. In our study, an automated ASPECTS method was successfully developed and applied to CTA and tiCTA datasets. Our result revealed that there is still a large variation in the ASPECTS, both when applied with the automated and with the manual method, either using CTA or tiCTA datasets. We found no statistically significant correlation of all ASPECTS score with the NIHSS, final infarct size, as well as with mRS. Automated ASPECTS of tiCTA correlates slightly better with final infarct volume and mRS compared to standard CTA, however the additional benefit of using tiCTA is still unclear in this study. Further development is needed in order to allow reliable application of an automated ASPECTS scores.

The tiCTA might provide several advantages, while not performing ASPECTS analysis worse than analysis based on standard CTA as shown in our study. Therefore, our study
supports the usability of tiCTA as a replacement of CTA in order to simplify the workflow for acute ischemic stroke patients.

**Future research**
The future research of CTP analysis for patients with acute ischemic stroke should be in the direction of (1) standardization of CTP analysis method, (2) incorporation of fast 3D registration algorithms in CTP analysis and (3) simplification of work flow in the CT examination workflow for patients with acute ischemic stroke.

The standardization is a must before CTP analysis should be accepted and widely used in clinical routine for acute ischemic stroke patient. This is challenging considering the availability of commercial packages from different vendors that already exists in health centre around the world. Collaboration between research groups and commitment between vendors should be encouraged to solve this problem together.

The development of CT Scanners technology nowadays supports the use of our 3D registration algorithms in CTP analysis. Combined with advances in hard and software engineering e.g. parallel processing, our method will be able to help increasing the accuracy of CTP analysis in daily clinical routine.

The idea to simplify CT workflow for acute ischemic stroke patients will be the main approach in the future to answer the issue of dose and time. With a larger coverage and thinner slices, current CT scanner setting will enable the CTA-CTP combination to reduce the number of examinations conducted on patients. These advances in technology and in image processing of CT images will support clinicians to make faster, more accurate and more precise diagnoses of the status of patients with acute ischemic stroke.

**References**


Appendix
Summary

Computed Tomography Perfusion (CTP) imaging, together with non contrast CT and CTA build a CT examination workflow for acute ischemic stroke patients. In CTP analysis, areas with brain perfusion defects can be detected immediately after the onset of clinical symptoms. CTP enables the depiction of infarct core and penumbra. The location and size of infarct core and penumbra as well as the ratio of their sizes are important in choosing the most suitable therapy and provide valuable information for predicting the benefit of treatment.

The first chapter of this thesis introduces the basic principal of CT Perfusion and its role in diagnosis of acute ischemic stroke management. Then, the pitfalls are discussed that arise in the use of CTP related to two issues: lack of standardization and motion during acquisition. Possible solutions offered in this thesis are described. In addition, the use of time invariant CTA generated from CTP is introduced.

Chapter 2 addresses the consequences of poor standardization. The large significant differences of estimated infarct core and penumbra between summary maps generated from two software packages for CTP analysis, using identical CTP source images are presented. The two software packages represent the two mainstream algorithms: deconvolution versus non-deconvolution, supporting the needs for standardization of CTP methods.

Chapter 3 studies the pitfalls of CTP related to head movement during CTP acquisition. Detection of rotational and translational head movement based on image processing analysis is introduced. We qualitatively and quantitatively assessed the extent, frequency and severity of such head movement. Moderate or severe head movement was found to be quite common in a population of patients suspected of acute ischemic stroke.

Chapter 4 provides a better understanding of the effect of head movement on the accuracy of CTP analysis. A study using a digital head phantom CTP dataset is performed. Use of this phantom allows simulation of translation and rotation of the head, enabling the evaluation of its effects on summary maps. The limits of movement that can still be corrected by the in-built registration algorithms are determined.
Chapter 5 proposes an automated method for the selection of unsuitable CTP data with excessive movement in order to help radiologists making a better diagnosis. This automated method utilizes an image registration technique to quantify the extent and range of head movement. The technique was found to have high sensitivity and fair specificity compared to manual selection by expert radiologists. Using the thresholds values for movement correction that were obtained from the above phantom study, an automated selection of CTP data unsuitable for accurate analysis was accomplished.

Chapter 6 proposes a correction method for complete compensation of head movement during CTP acquisition by using 3D registration of the CTP dataset with non contrast CT data. Based on examination of the images by experienced radiologists, very large quality improvement of CTP data was found. This methods outperformed commercial software package in this respect. The above strategies for head movement compensation allow better use of CTP datasets, leading to more accurate diagnosis.

The above methods for correction of movement also allow generation of high quality time invariant CTA datasets. Chapter 7 studies the usability of tiCTA derived from CTP datasets for clinical applications such as the ASPECTS method. We specifically explore the possible advantage of using tiCTA compared to standard CTA. The additional benefits remain yet unclear. Despite large variation in the results, this study emphasizes the wide usability of tiCTA as a replacement for CTA and generates options for simplifying the CT workflow for acute ischemic stroke patient.

Chapter 8 provides a general discussion, putting the findings of the thesis in a comprehensive view. It discusses the pitfalls in CTP, the implications and the proposed solutions with the respect of head movement during CTP. Recommendations for future research and clinical application of the current findings are given.
Samenvatting

Beeldvorming van de hersenen met behulp van Computed Tomography Perfusion (CTP) vormt, samen met een non-contrast CT en een CT-angiografie (CTA), de bouwstenen van het diagnostische protocol voor patiënten met een acuut herseninfarct. Met CTP kunnen direct na het begin van de symptomen gebieden in de hersenen met een verminderte bloedvoorziening worden gedetecteerd. CTP maakt het weergeven van de infarct core en penumbra mogelijk. De infarct core is het gebied in de hersenen dat door de verminderte bloedvoorziening al zo is beschadigd dat het niet meer kan herstellen. De penumbra is een gebied met verminderde bloedstroming dat nog wel levensvatbaar is en waarvoor behandeling zin heeft. De plaats en grootte van infarct core en penumbra, maar ook de verhouding tussen beide grottes, zijn voor de behandelend arts belangrijke gegevens om de mate van succes van een behandeling in te kunnen schatten.

Het eerste hoofdstuk in dit proefschrift introduceert het basisprincipe van CTP en de rol daarvan in de diagnose van het acute herseninfarct. Vervolgens wordt een tweetal valkuilen besproken die bestaan bij het gebruik van CTP: het gebrek aan standaardisatie van analysemethoden voor bepaling van CT-perfusie gegevens en beweging tijdens het scanen. Ook wordt in dit hoofdstuk het concept van time invariant CTA geïntroduceerd.

Hoofdstuk 2 behandelt de consequenties van een gebrekkige standaardisatie van CTP analysemethoden. Dit hoofdstuk rapporteert de grote verschillen in schatting van infarct core en penumbra grootte door twee software applicaties, met dezelfde beeldeddata als input. Deze twee software applicaties representeren de twee meest gebruikte methoden: deconvolution en non-deconvolution. Deze resultaten bevestigen de noodzaak van standaardisatie van CTP analyse methoden.

Hoofdstuk 3 bestudeert de valkuilen van CTP ten gevolge van beweging van het hoofd tijdens CTP acquisitie. In dit hoofdstuk wordt een methode voor de detectie van rotatie en translatie van het hoofd op basis van CTP beelden geïntroduceerd. Hiermee werden de frequentie en ernst van dergelijke hoofdbewegingen kwalitatief en kwantitatief bepaald. Uit deze resultaten blijkt dat middelmatige en ernstige bewegingen van het hoofd geen uitzondering zijn in een populatie van patiënten met verdenking op een herseninfarct.
Hoofdstuk 4 voorziet in een beter begrip van het effect van hoofdbeweging op de nauwkeurigheid van een CTP analysemethode. In deze studie werd een digitaal hersenfantoom gebruikt waarmee CTP data kunnen worden gesimuleerd. Met behulp van dit fantoom werd het effect van translatie en rotatie van het hoofd op CTP summary maps bestudeerd. Hiermee werden de beperkingen van de in commerciële software ingebouwde methoden voor bewegingscorrectie in kaart gebracht.

Hoofdstuk 5 beschrijft een automatische methode voor de selectie van CTP data die onbruikbaar zijn door ernstige beweging van het hoofd, met als doel foute diagnoses als gevolg van bewegingsartefacten te voorkomen. Bij deze automatische methode wordt een beeldregistratietechniek gebruikt om de hoofdbeweging te detecteren. We gebruikten drempelwaarden voor de ernst van de beweging op basis van de bovengenoemde fantoomstudie om een automatische methode voor selectie van onbruikbare CTP data te realiseren. Deze selectiemethode blijkt een hoge sensitiviteit en goede specificiteit te hebben in de vergelijking met handmatige selectie door radiologen.

In hoofdstuk 6 wordt een correctiemethode geïntroduceerd voor volledige compensatie van hoofdbewegingen tijdens CTP acquisitie. We gebruikten hier 3D registratie van de CTP dataset naar een non-contrast CT. Evaluaties van de bewegingsgecompenseerde beelden door radiologen laten zien dat deze methode de beeldkwaliteit sterk verbetert. Deze correctiemethode blijkt betere resultaten op te leveren dan die van commerciële softwarepakketten en maakt daarmee een betrouwbare diagnose mogelijk.

De voornoemde methode van bewegingscorrectie maakt ook het genereren van hoge kwaliteit time invariant CTA (tiCTA) uit CTP data sets mogelijk. Hoofdstuk 7 bestudeert de bruikbaarheid van tiCTA voor klinische applicaties, zoals de bepaling van de ASPECTS score van een patiënt. We onderzochten hier specifiek het mogelijke voordeel van tiCTA in plaats van standaard CTA voor bepaling van de ASPECTS score. We vonden dat de voordelen van tiCTA ten opzichte van CTA voor bepaling van de ASPECTS score onduidelijk blijven. Ondanks dit onverwachte resultaat benadrukken we in deze studie de bruikbaarheid van tiCTA ter vervanging van de CTA. Dit kan de workflow voor herseninfarctpatiënten vereenvoudigen omdat er dan geen extra CTA meer hoeft te worden gemaakt.

Hoofdstuk 8 geeft een algemene discussie van de resultaten van dit proefschrift. In dit hoofdstuk worden de valkuilen, implicaties en de voorgestelde oplossingen
bediscussieerd. Tevens worden er aanbevelingen voor toekomstig onderzoek gedaan en klinische toepassing van de resultaten van dit proefschrift voorgesteld.
Curriculum vitae

Fahmi was born in Medan, Indonesia on the 9th December 1979. After completion of high school in 1998, he studied Electrical Engineering focusing on Biomedical Engineering at the Institute Technology of Bandung (ITB) Bandung, Indonesia. He obtained his Master Degree in 2005 on Sensor System Technology at the FH Karlsruhe Germany with a thesis titled Automatic optimum phase selection using motion map in cardiac CT Imaging. He had a chance to work in Siemens Erlangen Germany for 6 months during the thesis preparation. In 2006 he became lecturer and researcher at Department of Electrical Engineering, University of Sumatera Utara, Indonesia. He joined the Department of Biomedical Engineering and Physic at the Academic Medical Centre (AMC), University of Amsterdam in October 2010 under the supervision of Prof. Ed van Bavel and Prof. Charles Majoie, performing research on the application of CT Perfusion imaging. The results of this topic are presented in this book as a PhD thesis. At the present moment, he continues as lecturer and researcher at the University of Sumatera Utara.
List of Publications

Peer Reviewed publications


Acknowledgements

In the name of God, the One and the Only, The Most Gracious, The Most Merciful.

I would like to thank all the people who contributed directly or indirectly to the works presented in this thesis.

First, I would like to express my sincere gratitude to my supervisor, Prof. Ed vanBavel for all motivation and supports, for all discussions, suggestions and feedbacks during my PhD study. Also, thank you for the patience during the whole time, despite of long distance problems that I believe normally is not part of a supervisor responsibility. Thank you for always boosting my spirit when I am down. For me Ed, you are a true mentor.

My sincere gratitude is also for my supervisor Prof. Charles Majoie. Thank you for all discussion and suggestion especially in the clinical insight of the researches that I conducted, that make the works become more valuable.

I was fortunate to have the chance to work with my co-supervisors, dr. H.A. Marquering and dr. ir. G.J. Streekstra, who patiently guide me through all the process. Thank you Henk, Geert, for all weekly meetings, all the skype conferences. All the scratches and comments, especially exclamation marks you put in the drafts, really helpful in improving my skills that I will surely miss. Thank you for all the ideas in solving practical difficulties and help me put complicated ideas into simple solution. I gained a lot from your efficient and effective working style.

I would like to thank to all Ph.D. committee members for their willingness to join the committee: Prof. dr. Y.B.W.E.M. Roos, Prof. dr. J.A. Reekers, Prof. dr. A.J. van der Lught, Prof. dr. J. Booij, dr. H.W.A.M. de Jong, and also Prof. dr. T.L.E.R. Mengko from Indonesia.

I would also like to express my gratitude for DGHE Ministry of National Education Indonesia and LP3M USU Medan for the funding that make all these works possible and also thank you also for all those flights from Medan to Amsterdam. Special thanks to Rector of University Sumatera Utara, Director of USU Academic Hospital and Dean of Faculty Engineering for all supports and motivation.

Everything in this thesis was only possible with the help and support of members of the image processing group as well as radiologist group in AMC and UMC. Thank you Ludo,
Hugo, Jordi, Olvert, Floor, Natasja, Alan, Merel; my paronym: Emilie and Mustafa, for all the data, images, scripts, and more important for warm friendship and fun work environment. Without them, my job would have undoubtedly been more difficult.

Thanks for Jetty for all administrative arrangements and always being so helpful and friendly. BMEP members: Martin, Jasmin, Renan, Nazanin and all others that I wish we can keep in touch for years ahead. Thanks to all of member of BMEP, to make me feel at home during my stay in AMC.

Finally, I would like to thank my family. I especially thank my wife Loly for her personal support and great patience at all times, especially during my stay in Amsterdam for months. My daughters: Shasya and Keyka, the apples of my eyes. I would not have made it this far without them. I am thankful for my parents and parents in law for their support and constant love. Thank you to all relatives and friends that in any way support my PhD journey during all these years.
## PhD Portfolio

### 1. PhD Training

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Supervising

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