CT perfusion-based prediction of final tissue status in cerebral ischemia

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June 04, 2014

***Abstract*—CT Perfusion offers us some great diagnostic features for neuroimaging and has great potential in the field of acute ischemic strokes. Over the last few years more research is being conducted regarding the prediction of final tissue status in cerebral ischemia. The goal of this research is to automatically or semi-automatically differentiate between infarct core lesion and ischemic penumbra. Some commercially available packages already provide such features, but are not always as accurate. Much research is ongoing in more specialized institutes featuring different methods like thresholding, functional clustering and more advanced methods such as the use of artificial neural networks. Results look promising but we should remain critical before applying it in clinical settings due to the fact that most current research is being conducted on homogeneous data sets and is not clinically validated.**

***Index Terms*—CT Perfusion, stroke, ischemia, thresholding, infarct core, penumbra, prediction**

I. Introduction

STROKES have been one of the major causes of death for years now. The most common type of stroke contributing to this is the ischemic stroke, where the brain does not receive enough oxygen and other required nutrients which can lead to permanent brain damage. Ischemic stroke occurs when a blood clot forms that will block blood flow to a certain part of the brain. When brain tissue is deprived from oxygen or nutrients for too long, cell death will occur. This area of the brain where cell death has occurred is in a state of irreversible damage and is referred to as the ischemic lesion core or the infarct core. In a situation where the blood flow is less badly disrupted or the supply towards the brain tissue has only been disrupted for a short amount of time, the tissue affected still has a chance for recovery. This mostly depends on how fast the blood flow will be restored. This tissue, which is potentially reversibly damaged, mostly surrounds the infarct core and is referred to as the ischemic penumbra. Being able to always salvage as much of this penumbra as possible has always been the main target of stroke related research.

In order to salvage as much ischemic penumbra time is key. The main treatment for stroke patients is to unblock the clotted artery in order to prevent more brain tissue to prevent both the infarct core and the ischemic penumbra to expand. To be able to treat effectively and salvage as many brain tissue as possible, there is a need for an effective method which we can use in order to make an accurate prediction regarding the final tissue status after an ischemic stroke. Such a method is to determine whether tissue is still salvageable and belongs to the penumbra, or whether it belongs to the infarct core. The first imaging method to be able to show penumbra was proton emission tomography (PET), where both infarct core and ischemic penumbra showed low blood flow, but the penumbra still had an ongoing glucose metabolism showing possibly reversible damage.

Although PET seemed like a good solution for the problem it has some major downsides. The technique is not widely available and is not always as practical as it is required to be used in acute stroke. A more widely available and more practical method to use in acute stroke management is CT Perfusion. CT Perfusion is able to give reliable quantitative measurements of cerebral tissue properties trough image processing. Research has primarily been focused on being able to define accurate relative thresholds to decide whether or not tissue is salvageable based on different CT perfusion parameters. These relative thresholds are defined by setting a percentage of the contralateral measurements. It requires a lot of different approaches to find an accurate method. First we will need to achieve a good and accurate segmentation of the ischemic area. Most of these segmentations do not take into account whether the ischemic tissue is reversibly or irreversibly damaged. This is where we can make use of prediction to determine the status of the tissue taking into account different perfusion parameters, mostly using thresholding or more advanced prediction models. Research is also available on dynamic evolution models in which the dynamic progression of the infarct core and evolution of the penumbra in stroke have been addressed. These research papers however do not contain any clinical validation and have not been applied on actual CT perfusion yet. Instead, simplified models have been used [23].

Currently most of the stroke related research is being performed on either CT perfusion or MRI. Over the past years CT perfusion imaging for stroke diagnosis has made huge technological steps, however MRI has done the same. Both CT perfusion and MRI have their own advantages and disadvantages. For the past decades probably neither ones will proceed each other and both modalities will probably remain coexisting.

In this review we will first address CT perfusion, the

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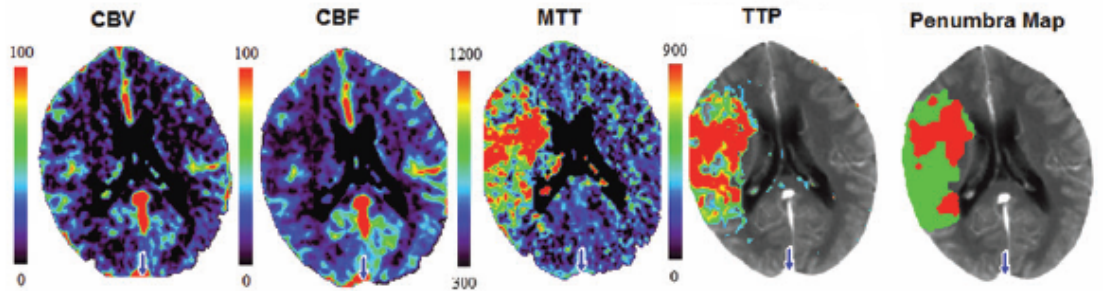

Fig. 1. CT Perfusion maps: CBV, CBF, MTT and TTP. The penumbra map is a prediction map showing in red the estimated ischemic core and in green the estimated penumbra. Source: Bivard *et al.* [2]

viability, different parameters and the techniques being used in acute stroke. The main focus will be on prediction in order to identify both the infarct core and the penumbral area as accurate as possible. Different methods for prediction will be compared and discussed within this paper.

II. CT Perfusion

CT is currently the standard imaging modality for therapy decision in acute stroke thanks to the fact that it has a lot of advantages. These advantages include low costs, wide availability, speed and ease of patient monitoring [14]. Although MRI is more sensitive to early changes of infarction, the major advantages of CT Perfusion over MRI are the availability and the possibility to obtain similar information but more rapidly. In the past it was required to make use of a delayed steady-state phase of contrast fluids for a good measurement. Recent studies however have shown us that it is possible to obtain accurate measurements making use of first-pass CT instead of using delayed image acquisition [19]. Making use of first-pass acquisition, not only scanning time can be lowered, but exposure to radiation can also be minimized. Thanks to these properties, in addition to the wide availability, Perfusion has shown a lot of potential compared to other imaging modalities regarding the selection of patients who can benefit from treatment with thrombolysis [20].

In clinical practice radiologists make use of software which give a quantitative estimation of the Cerebral Blood Flow (CBF), Cerebral Blood Volume (CBV) and the Mean Transit Time (MTT). In addition to that kinetic parameters are being calculated such as the time-to-peak and the time of onset. The main difficulty regarding these different parameters is that each of them will give us a different size of penumbra or infarct core. therefore it is important to study these and determine which parameter is most reliable. Figure 1 illustrates some of these CT perfusion maps.

A. CBV

The Cerebral Blood Volume describes the volume of flowing blood flowing through the cerebral vasculature. Looking at it for a region of interest we can describe this as the total volume of blood in a given volume of the brain. This does not only include the blood in the capillaries, but also the large vessels such as the arteries and veins. CBV has units of ml of blood per 100g of brain tissue. In acute ischemic stroke there will be a decrease in CBV. This parameter is often used to identify the core of infarcted tissue.

B. TTP

The time-to-peak is described as the time it takes from the start of the scan until maximum attenuation occurs. In early studies this parameter was found potentially useful to facilitate the detection of acute cerebral ischemia before morphological changes are visible on regular CT scans [22]. However, in more recent literature this parameter is no longer used very much as the other options show to be more accurate.

C. MTT

The Mean Transit Time describes the amount of time the blood needs to pass through the tissue. The amount of time needed varies depending on the distance traveled between arterial inflow and venous outflow. In acute ischemic stroke we mostly see an increase in MTT. This can be used to identify penumbra.

D. CBF

The Cerebral Blood Flow describes the flow rate of volume of blood through cerebral vasculature, also described as the blood supply to the brain in a given time. CBF stands in relation with CBV and MTT through the following equation: CBF = CBV/MTT. This relationship is also referred to as the central volume principle. CBF has units of ml of blood per 100g of brain tissue per minute. In CT Perfusion this is mostly recognized to be the most important parameter as results are most accurate. This parameter can also be used to identify penumbra and will show decreased measurements in acute ischemic stroke.

E. CT Perfusion in research

The need for CT Perfusion for providing additional and critical information regarding cerebral tissue status for

clinical application has been emphasized already [11]. An early study was performed on a subset of 38 patients of a clinical stroke study in order to investigate the power of CBF values to predict whether tissue belongs to a definite infarction or ischemic penumbra. The results were compared with follow-up CT and MRI data. For 19 patients who received heparin, an injectable anticoagulant, the mean relative CBF values were 19% and 62% for respectively infarct core and penumbra regions. The 19 other patients received intra-arterial fibrinolysis had mean relative CBF values of 18% and 57% and the difference between the CBF in the penumbra or infarct core was highly significant in both groups. Penumbra was not found with a relative CBF value of $< 20\%$, however in tissue with a relative CBF value of between 20% and 35% only 25% survived in the heparin group, compared to 61% from the group of patients who received fibrinolysis. The study concluded that a relative CBF of 20% is probably the definite lower limit for ischemic tissue to survive. It also shows that CT Perfusion provides very important additional information with regards to selecting the best treatment strategies for patients with an acute ischemic stroke to prevent as much damage to the tissue as possible.

Prior study has shown that CBV has the highest specificity of the four perfusion parameters regarding the infarct core, but has a low sensitivity. MTT and TTP on the other hand have a high sensitivity, but suffer from a low specificity. CBF is in between the CBV and the MTT/TTP with regards to sensitivity and specificity [15][16]. A study from Kheradmand et al. [10] looked into the predictive value of both the MTT and the TTP. CT Perfusion data were being analyzed using deconvolution software by Philips Medical Systems. Deconvolution removes or reduces the effect of system response on a signal. The size of these lesions were calculated using MTT and TTP values. This study concludes that widely accepted MTT thresholds used to define ischemic penumbra often overestimate. The correlation coefficients were calculated for both TTP/infarct lesions and MTT/infarct lesions and were respectively 0,95 and 0,66. In this setting the TTP variable with a relative threshold of TTP $> 113\%$ is a better predictor of infarct tissue in patients with an acute ischemic stroke.

III. Prediction methods

Making use of CT perfusion parameters there is a wide variety of methods in order to make an accurate prediction of the final tissue status in cerebral ischemia. In addition to this ongoing research, which is mostly conducted in-house, there are also commercial software packages available which are based on prognostic maps. Most of the in-house developed prediction methods are also strongly based on thresholding, either absolute or relative. Some research has been done towards finding more advanced prediction methods such as the use of functional clustering or neural networks. Although this field of research has been around for some time now, there are still a lot of options which can be explored in order to develop the most accurate method for the prediction of final tissue status, which results much ongoing research.

For these methods to become clinically relevant they do not only require to be as accurate as possible, but also as fast as possible. Because most initial studies have been performed on either small or homogeneous data sets, or on phantoms of the human brain, current methods are being more thoroughly tested with the use of more heterogeneous data sets. As a result of this development there is also a lot of ongoing research towards the improvement and further development of earlier described methods.

Some commercial software is used to predict whether brain tissue is part of the infarct core or the ischemic penumbra has already been released. Recently Huisa *et al.* [9] investigated one of these software packages for its ability to predict final tissue state. The study included 165 patients with clinical symptoms suggestive of an acute ischemic stroke. Each of these patients received an initial non-contrast head CT, CT perfusion, CT Angiogram and a follow-up Brain MRI. CT Perfusion images were processed by making use of the commercially available CT Perfusion v3 software by GE Healthcare. CBV, MTT and Diffusion-Weighted Imaging (DWI), commonly performed in MRI imaging for evaluation of an acute ischemic stroke, lesion volumes were calculated and afterwards statistical analysis was performed. Initial CBV and MTT had missed over half the strokes that were later identified by brain MRI. MTT was found to be the most successful with a high specificity (91,8%), but a very poor sensitivity (40,0%). There are a few reasons which could explain the low sensitivity in this study. The first being the large and heterogeneous set of patient data on which this study was performed. Prior studies had often only included people with large strokes. A second reason being that DWI was not used as the gold standard, but the images were delineated by vascular neurologists in order to simulate for real-world application. Using the DWI as a gold standard however, has improved both the specificity and sensitivity to respectively 91% and 81%. As the clinical diagnosis of acute ischemic stroke is estimated to have a sensitivity of 80% to 90% [13], new methods must at least match or improve this sensitivity. This means with regards to real-world use the prediction of stroke or DWI lesions was not accurate enough and the researchers argue against the use of CT perfusion for screening acute ischemic stroke patients until real-world implementations match the accuracy which have been reported by specialized research centers.

Another recent study by Ho *et al.* [7] has been performed making use of the Extend Brilliance Workstation CT Perfusion package by Philips Healthcare for post-processing. Sixty-five patients, presenting stroke-like symptoms, were included. CBF, CBV, MTT and TTP maps were obtained. Combining these data lesion-maps were generated. The computer generated lesion-maps generated by this software package showed very low specificity (21%) and a high sensitivity (83%). Compared to qualitative analysis with a specificity of 69% and a sensitivity of 70% the specificity

resulting from the computer generated lesion-maps is very low. As a result of combining both the computer generated lesion-maps the specificity increases towards 80%, however the sensitivity drops towards 67%. A positive predictive value, the probability that a positive result is actually correct, of 29% compared to respectively 50% and 61% from either quantitative analysis or qualitative analysis combined with computer generated lesion-maps is also very low. The authors of this article therefore concluded that, however these computer generated lesion-maps are a very sensitive tool for the prediction of acute ischemic stroke, it lacks with regards to specificity and positive predictive value.

A report by Zhao *et al.* [25] two years earlier also making use of the Extend Brilliance Workstation CT Perfusion package by Philips Healthcare for post-processing has clearly spoken against the clinical use of this software package to predict reversible and irreversible neurological damage. The aim of the study was to evaluate the predictive value of this commercially available CT perfusion software package by Philips. The study was performed on patients who had received early and full tissue repurfusion. To determine irreversible damage, a CBV threshold of $<$ 2ml/100g has been used. To determine whether the tissue was salvageable a relative MTT threshold of $>$145% has been used. During this study only 42% of irreversibly damaged areas was correctly identified and only 56% of the salvageable tissue has been predicted correctly. Due to the low accuracy achieved by this method the authors conclude that the use of these CT perfusion Prognostic maps for prediction of irreversibly or reversibly lost neurological functions was not sufficient. What is seen in this study however is that for the determination of irreversibly damaged tissue, an absolute threshold has been used. More recent studies however making use of relative thresholds improve results and would most likely also improve accuracy achieved using this prediction methods.

Above findings are in large contrast with an earlier conducted study by Rai *et al.* [21] including a total amount of 422 patients. In this study a very high specificity was reached of 100%, due to the fact that none of the 265 patients who did not have an acute ischemic stroke showed any abnormality on their CT perfusion parameters. Including all patient data a sensitivity of 49,7% for CBF/MTT was achieved and 42,7% for CBV. However after excluding all acute ischemic strokes with a volume of less than 5 cc, which are considered relatively small, abnormal CBF/MTT was found in 71 of the 77 of these larger strokes, resulting in a sensitivity of 92,2%. An abnormal CBV was found in 64 out of 77 patients which resulted in a sensitivity of 83,1%. From this data we can conclude that this software package is rather promising, however it is only effective for larger acute ischemic strokes. In real-world applications where there is a large variety in types and sizes of these strokes, the technique lacks sensitivity.

In a study from 2011 by Bivard *et al.* [3] more parameters were included to help with the prediction of final tissue state. The CT Perfusion maps were calculated by the commercially available MIStar (Apollo Medical Imaging Technology). Alongside with the more conventional parameters delay time maps were constructed and were taken into account. Comparison of both the absolute and the relative delay time gave AUC values of respectively 0,83 and 0,86. The absolute delay time had a sensitivity of 82% and a specificity of 83%. The relative delay time had a sensitivity of 82% and a specificity of 90%. Furthermore the best result defining the infarct core in combination with the relative delay time for predicting the total lesion was a relative CBF threshold of $<$ 40% which gave an AUC value of 0,86. Although a relative CBF threshold of $<$ 50% yields the same AUC value, the sensitivity and specificity of 96% and 62% compared to a sensitivity and specificity of 93% and 78% were worse overall. According to this study, the most accurate prediction of final tissue status in cerebral ischemia can be achieved by making use of both the relative delay time and a relative CBF threshold of $<$ 40%. In comparison to the other commercially available software packages this method does show to be more promising for clinical use as it is more accurate. Certain assumptions were made however that have to be taken into account such as the fact that the patient groups were cut off into 'pure' reperfusion and no reperfusion groups.

In 2013 the same authors performed a new study [2] in which they included data of 314 patients in order to compare six different post-processing techniques. The goal was to compare the accuracy of all commonly used CT Perfusion data post-processing methods to define infarct core and penumbra in acute ischemic stroke. The six post-processing techniques are: maximum slope, partial deconvolution, singular value decomposition (SVD), SVD with delay correction, block-circulant deconvolution and stroke-stenosis. Separate CT Perfusion maps were generated using these techniques. Afterwards pixel-based analysis was performed on each of these maps in order to calculate the sensitivity and specificity for different CT perfusion thresholds. Follow-up DWI was used as the gold standard for this study. ROC curves were plotted and AUC analysis was performed to then find the most optimal thresholds. The best results were obtained using SVD with delay correction as post-processing method. The perfusion lesion was defined with an AUC value of 0,86 making use of a delay time $>$ 2s threshold. The sensitivity for this perfusion lesion detection was 83% and the specificity was 82%. The most accurate results for defining core were obtained using using a double core threshold of CBF $<$ 40% and delay time $>$ 2s. This also gave an AUC value of 0,86. The sensitivity using the double core threshold was 73% and the specificity was 93%. The maximum slope post-processing method performed the worst and the other methods performed about equal. The study has been performed on a large data set and considerable variation in the perfusion threshold was found. SVD with delay-correction has shown to be the best, most accurate, post-processing method quite consistently. This was also confirmed by volumetric analysis. The results from this study seem very promising. What is highlighted by the

authors however, is the need for standardization of image acquisition to define infarct core and penumbra in acute ischemic stroke to provide generalization results.

Looking back at the studies mentioned above we can see that there is a huge trade-off between specificity and sensitivity for most the commercially available methods. What we can see by comparing the results is that often the specificity is very high, but the sensitivity is still too low to make these methods of any use in real-world clinical applications. One exception is however MIStar as reported by Bivard *et al.* [3]. Accurate results acquired on a large data set show this package to be more promising for real-world clinical use.

A. Scientific methods

One of the more popular methods in defining ischemic penumbra and infarct core is thresholding. In an early study by Koenig *et al.* [12], the authors already explored the use of CT Perfusion parameters into creating thresholds for this cause. CT Perfusion data was acquired from 34 patients with acute ischemic stroke <6 hours after onset. CBF, CBV and TTP values were obtained from both infarcted and healthy tissue and were used to find the most optimal thresholds. This showed a significant difference in CBF and CBV values between infarct core and penumbra, but no differences for the TTP. In this study relative CBV $< 60\%$ and CBF $< 48\%$ thresholds were found to be most accurate. The CBV threshold had a sensitivity of 80,4% and a specificity of 86,5%. The CBF threshold had a sensitivity of 76,1% and a specificity of 73%. This study shows that in this setting the CBV threshold is more accurate than the CBF threshold. Combining multiple parameters did not give more accurate results.

In 2010 a study was done by Sun *et al.* [26] in which the authors made use of monkey stroke models. The middle cerebral artery occlusion (MCAO) method was used to compare the accuracy of prediction of ischemic penumbra in CT perfusion compared to follow-up DWI. An ROC curve was constructed as to find the most suitable ischemic penumbra thresholds and the most suitable parameter to use. A relative threshold using CBF <0,20 was found to be the most accurate with an AUC value of 0,97 and a sensitivity and specificity of respectively 83,3% and 98,5%. A relative CBV threshold of <0,48 followed with a AUC value of 0,92 and a sensitivity and specificity of respectively 79,2% and 86,4%. MTT scored a lot lower with a AUC value of 0,43. The authors suggest that the relative CBF method is the most accurate method for estimating the ischemic penumbra. There are however significant differences between the human brain and monkey brain with regards to the fact how long ischemic penumbra may be present. Clinical studies should be performed to validate the conclusion of these authors.

Three years later a study by McLeod *et al.* [18] based on rat stroke models showed that CT Perfusion is a good and stable method for defining the volume of infarct core and ischemic penumbra making use of relative CBF thresholds which were defined at different points in time within the first two hours. Within one hour of MCAO a relative CBF threshold of $< 75\%$ resulted into an area under the curve (AUC) of 0,66. For CBV $< 75\%$ this AUC was 0,63 and for MTT $> 120\%$ the AUC was 0,60. After two hours of middle cerebral artery occlusion new measurements were performed and this resulted into a AUC of 0,66 for CBF $< 75\%$, 0,62 for CBF $< 75\%$ and 0,57 for MTT $> 140\%$ for the prediction of the stroke lesion. Prediction of the infarct core resulted into AUC of 0,77 for CBF $< 55\%$, 0,69 for CBV $< 75\%$ and 0,60 for MTT $> 130\%$ after one hour after the occlusion. After two hours after the occlusion this resulted into AUC of 0,69 for CBF $< 55\%$, 0,71 for CBV $< 70\%$ and 0,55 for MTT $> 145\%$. In this model the CT perfusion parameter that most accurately predicted the infarct core and penumbra was the relative CBF. Relative CBF thresholds of $< 75\%$ and < 55 % most accurately predicted the penumbra and the infarct core, respectively, within the first two hours of acute ischemic stroke. This result correlates with the findings of Sun *et al.* [26] on monkey models described previously. One shortcoming of this study was the fact that the different parameters were not combined in order to obtain a prediction map. Another shortcoming is the fact that the animal data was very homogeneous, the infarcts were all very similar.

In a recent study by Maija *et al.* [17] the authors used a similar approach with human patient data to determine optimal thresholds to predict whether the ischemic tissue is salvageable or not. CT Perfusion images were obtained and post-processing was applied by the means of semi-automated deconvolution. Regions of interest were systematically drawn to define values for potentially salvageable penumbra and infarct core. Non-parametric T-tests showed that there was no significant difference between core and penumbra with regards to MTT, there were however statistically significant differences with regards to the CBV and the CBF. Making use of contralateral measurements, thresholds have been calculated. The most accurate threshold for defining the ischemic lesion was found to be MTT $> 190\%$ and the most accurate threshold for defining the infarct core was CBF <30-40% and CBV <40%. The accuracy achieved with these thresholds was however not reported in this article. However, compared to the study on rat stroke models, we can conclude that the relative threshold values are different for humans.

B. Source Images

One of the less explored options is the use of source images to identify infarct core and penumbra, however a study by Wang *et al.* [24] has been performed on this subject. The purpose of this study was to develop and determine the value of CT perfusion Source Imaging in the venous and arterial phase and then compare its efficacy with the more conventional CBV and CBF variables. During this study 42 patients received a CT examination. From this patient data the Albera Stroke Program Early

CT Score (ASPECTS), a 10-point quantitative CT score, was determined for the venous and arterial CTP-SI phases and then compared with the ASPECTS score for the CBF and CBV. This study showed that the ASPECTS on the arterial CTP-SI phase was strongly correlated with the ASPECTS on the CBF and the ASPECTS on the venous CTP-SI phase was strongly correlated with the ASPECTS on the CBV. Another result is the fact that there is a mismatch between both the venous CTP-SI phase and the arterial CTP-SI phase, as well as a mismatch between CBV and CBF. Within this mismatch model the infarct core was shown as a hypo-attenuated area on the venous phase of the CTP-SI. Penumbra on the other hand was represented by a mismatch between both phases of the CTP-SI. This study shows that there is a stronger relation between CTP-SI derived information and patient outcome than for deconvolution based methodology. This gives clear evidence that there might be more useful parameters or methodologies that should be further explored into the prediction of final tissue status. This CTP-SI mismatch model could possibly be applied but should still be tested in a larger randomized trial to determine whether it is actually able to improve clinical outcome. The ASPECTS score however, is evaluated by radiologists. Therefor this method is not suitable for any form of fully-automatic prediction.

C. Advanced classification

One of the earlier studies from Baumgartner *et al.* [1] was done by functional clustering of CBF, CBV and TTP maps representing the basis for the analysis to estimate the severity of cerebral damage after an acute ischemic stroke. A partitioning algorithm (k-means) and a density based (DBSCAN) algorithm were used on the CBV, CBF and TTP maps in order to identify and segment clusters of normal and possibly ischemic tissue combining the three parameters. The second purpose of this method was to estimate absolute values for each cerebral area. As one of the results of this research, large standard deviations were found for both the accumulated CBF and CBV. This can be explained by the large difference of these parameters in grey matter, white matter and large blood-vessels. The TTP values however were more homogeneous. This form of functional clustering gives us a way to identify and segment cerebral tissue with similar hemodynamic properties. This is achieved as a result of combining all three parameters. The authors conclude that functional cluster analysis is a promising method for the identification of acute cerebral ischemia. Next to segmenting tissue at risk, this method can also differentiate between different severity of ischemia. This is however, far from clinically applicable. Studies should still be performed to correlate the functional clusters with clinical outcome. It does however present us with different insights on how to incorporate functional clustering into a predictive tool.

One of the ultimate goals into developing prediction methods to determine final tissue state in ischemic penumbra would be to develop a fully automatic Computer-Aided Diagnosis (CAD) system to improve clinical outcome for acute ischemic stroke patients. In 2011 such a study was performed by Hachaj *et al.* [5] and a CAD system for the analysis of perfusion maps, CBV and CBF was developed. The purpose of this research was to develop a CAD system which could do both quantitative and qualitative analysis. The quantitative analysis was aimed at the detection of potential lesions or asymmetries making use of a brain anatomy atlas. The qualitative analysis was done by means of semantic interpretation to decide whether the stroke was ischemic or hemorrhagic and whether brain tissue was at risk of infarction. This semantic analysis was done by a cognitive interference process used for reasoning based on specialist image knowledge. Relative thresholds of CBF $<48\%$ were used to determine whether tissue was part of infarct core or not. For fully automatic detection the the sensitivity was 33,33% and the specificity was 66,67%. This outcome might be caused by the fact that the detection algorithm does not take noise and possible other imaging artifacts into account which reduces the overall accuracy. Semi-automatic detection by presenting the found lesions to radiologists yielded a higher sensitivity of 72,73% and a specificity of 80,95%. The authors plan to improve this system by including better image registration methods, incorporate MRI images for better accuracy and create a more precise brain atlas averaged from CT images created from a larger group of patients. Using a more precise brain anatomy atlas, better labeling of brain structures can be done.

A more technologically advanced method [6] from the same authors has been described making use of multilayer perception neural network module and a neural network based image processing method for CT perfusion map analysis. The aim of this study was to gain higher efficiency in the classification and detection of cerebral ischemia. The main feature was the use of self-organizing maps (SOM). These are artificial neural networks that are trained using unsupervised learning in order to produce a simplified representation of the training samples. This described method works through 4 major steps. The algorithm starts with preprocessing the CT perfusion maps with SOM. This step is intended to remove most noise and other artifacts from the CT perfusion data. Afterwards all data is being registered together. When all data is registered, the abnormality type classification starts. This step makes makes use of the neural network and contralateral data to determine whether there are any abnormalities and if so, classify them as such. Finally a prognostic map will be generated making use a relative CBF threshold of 0,48 to determine whether abnormal tissue belongs to the infarct core or the ischemic penumbra. As a part of their experiments the prediction was done on both the previous method [5], using linear preprocessing, described in the previous section and this new method. Using the linear preprocessing with the used data set the achieved sensitivity was 72,73% and the specificity was 80,95%. Using the SOM preprocessing a sensitivity of 72,73% and a specificity of 90,48% was

Paper	Basic principle	Nr of data	Reference standard	AUC	Sensitivity	Specificity
Baumgartner *et al.* (2005) [1]	K-means functional clustering	2 - human	-	-	-	-
Bivard *et al.* (2011) [3]	MISTar (Apollo M.I.T.)	314 - human	follow-up DWI	0,86	0,62	0,96
Bivard *et al.*. (2013) [2]	SVD with delay correction (MIStar)	314 - human	follow-up DWI	0,86	0,83	0,82
Hachaj *et al.* (2011) [5]	Semi-automatic CAD system	30 - human	Radiologist	-	0,73	0,81
Hachaj *et al.* (2013) [6]	SOM based neural network	30 - human	Radiologist	-	0,73	0,90
Ho *et al.* (2013) [7]	Extend Brilliance (Philips)	65 - human	follow-up DWI	-	0,83	0,21
Huisa *et al.* (2014) [9]	CT Perfusion v3 (GE Healthcare)	165 - human	Radiologist	0,66	0,40	0,92
Koenig *et al.* (2001) [12]	Relative thresholding	34 - human	follow-up DWI	-	0,80	0,87
Maija *et al.* (2013) [17]	Relative thresholding	87 - human	-	-	-	-
McLeod *et al.* (2013) [18]	Relative thresholding	6 - animal	Histology	0,69	-	-
Rai *et al.*. (2008) [21]	CT Perfusion v2 (GE Healthcare)	422 - human	follow-up DWI	-	0,50	1,00
Wang *et al.*. (2010) [24]	Source imaging	42 - human	-	-	-	-
Zhao *et al.* (2011) [25]	Extend Brilliance (Philips)	109 - human	-	-	-	-
Zhihua *et al.* (2010) [26]	Relative thresholding	7 - animal	follow-up DWI	0,97	0,83	0,99

TABLE I

This table contains a comparison of all discussed papers giving an overview of the different basic principles used and the results achieved within this article. Not all results can be accurately compared with each other, due to difference in dataset heterogeneity or the lack of an AUC value. The methods listed by Philips, MIStar and GE Healthcare are commercially available software packages.

reached. From this we can see that with the use of SOM preprocessing the sensitivity does not alter, however the specificity has been increased, making the method more accurate than using linear preprocessing. The authors show in their article the importance of preprocessing the CT perfusion data, as CT perfusion methods are generally sensitive to noise and might have asymmetries that are of not relevant. SOM is highly suitable to filter this kind of irrelevant information. The neural network method can compute tissue outcome rapidly and efficiently, but requires a large training database to be accurate. In the future this approach can be used to include not only perfusion maps, but more medically relevant data that could improve outcomes.

IV. Discussion

In this review we have discussed all current research on methods towards the prediction of final status in cerebral ischemia using CT Perfusion. The main focus of this paper has been on prediction in order to identify both the infarct core and the penumbral area as accurate as possible. Allthough progress is being made and some results look promising there are variabilities, limitations and contradictions we should pay attention to.

Studies show a variability in CT perfusion parameter choice. The fact that most of the studies are based on thresholding techniques do not always give correlating results. The study by Bivard *et al.* [2] showed that regardless of the post-processing method used that CBF is the most accurate for defining infarct core, this in contrast to earlier studies by Chemmanam *et al.* [4] and Koenig *et al.* [12] which pointed towards CBV being the more accurate parameter. The more recent studies [21][26][18] however do give correlating results with Bivard *et al.* [2] and also conclude that CBF is the most accurate parameter for predicting tissue outcome. This could possibly be caused by differences in methodology or image acquisition. From this we can argue that the use of both CBV and CBF are viable, but are situation dependent. None of the studies advocate usage of the MTT values as a predictive parameter.

There is no consensus regarding an optimal threshold of perfusion values for the prediction of tissue status. A large amount of studies [11][25][26][18][17][3] have presented an optimal threshold which are all different from one another. In addition to that Bivard *et al.* [2] also report on different optimal thresholds within their paper, making use of different post-processing techniques. This is because an optimal threshold depends on technical and clinical circumstances. These findings highlight the need for large multicenter trials to find standardized infarct core and penumbra thresholds.

Small volume strokes are often missed. Although that many of the discussed techniques look promising, a number of pitfalls should be accounted for. Lui *et al.* emphasize that as calculated CT perfusion maps often have a relatively low resolution, small infarcts could be missed, even when they are in the region of interest. For this reason, studies done on animals [26][18] often use the MCAO method. In the study by Rai *et al.* [21] all acute ischemic strokes with a volume of less than 5 cc were excluded. In real-world clinical practice all sorts and sizes of acute ischemic strokes can appear so it is important to develop the method in such a way that small infarcts are not missed. A solution to this problem solution could possibly be found by increasing the resolution on the calculated CT perfusion Maps. This is important because patients who suffer from small strokes have an increased risk for major stroke in the future.

Most studies are peformed on data sets which do not represent clinical practice. Often a small group of patient data [1][5][6][12][24] is included or exclusion criteria are applied [21] which lead to a rather homogeneous data set. As a result of this, satisfying accuracy has been achieved in these studies , but this may be deceptive. In real-world applications, patient-data is rarely homogeneous. More testing has to be done on larger and more heterogeneous data sets to get comparisons on how well it would work in an actual clinical setting. Data sets should contain data

of both male and female including different locations and sizes of strokes.

Most commercially clinical software provide limited diagnostic utility. Different papers have been mentioned within this review making use of commercially available clinical software. Rai *et al.* are careful with their conclusion stating it to be a diagnostics tool that can potentially be incorporated in stroke triage and treatment decisions. Ho *et al.* [7] state that used in isolation, the computer-generated lesion maps provide limited diagnostic utility. Huisa *et al.* however clearly argue against the use of the current commercial software for screening acute ischemic stroke patients in real-world use, due to the fact that it can not predict stroke with sufficient accuracy. Bivard *et al.* [3] contradict these claims by publishing results that do show high accuracy and conclude that this software has clinical value.

Good representative results have been published by Bivard *et al.* [2]. In contrary to most studies Bivard *et al.* made use of a large and heterogeneous data set. This study by gave an interesting result pointing towards SVD with delay correction as being the best post-processing method reaching an AUC value of 0,86. Because of the heterogeneity, which gives a good representation of real-world clinical practice, this is a very promising result and an advance on current practice.

Advanced supervised qualifiers give good diagnostic utility for clinical practice. One of the more interesting researches is the neural network implementation by Hachaj *et al.* [6] Not just the fact that the current results are good, but the possibility to extend this method even further by incorporating additional data and adding more learning data makes this method very promising. In a related study Huang *et al.* [8] also applied an artificial neural network for the prediction of ischemic tissue fate in stroke imaging, but did this for MRI. This study also gave good results, which gives enough reason for further research on this method. It could also be used to be a part of a larger or more complex decision making system, however it is important that ease of use, speed and efficiency remain. Speed is essential to salvage as much tissue as possible and not waste any tissue on due to high computation times.

An accurate generalized diagnostics tool for clinical practice is not yet available. Further multicenter trials must be performed to find an optimal threshold and clinical validation must be performed. When an generalized optimal threshold is available, future research should be focused on how to use these optimal thresholds into getting towards an accurate prediction method. Taking all the discussed papers in this review into account it is recommended that for further research and development first generalized optimal thresholds must be found. Making use of the MIStar package by Apollo Medical Imaging Technology combined with the the SVD with delay correction as mentioned by Bivard *et al.* [2] as the best post-processing method found in their article it could be possible to find an accurate prediction method. Using this method towards an advanced classifier such as the artificial neural network method by Hachaj *et al.* [6] could potentially lead towards a diagnostic tool which can be applied in real-world clinical practice.

V. Conclusion

In this review we have discussed all current research on methods towards the prediction of final status in cerebral ischemia using CT Perfusion. We have seen that many different options and technologies are being explored and that some of them do offer potential for use in an acute clinical environment. When high accuracy is achieved and certain pitfalls and disadvantages are minimized or eliminated this could become reality. There is however still work to be done before we can reach the accuracy required.

Acknowledgment

The author would like to thank Dr. P.C. Vos, Image Sciences Institute, UMC Utrecht, the Netherlands, for acting as daily supervisor for this review article and providing ongoing feedback and support.

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