Journal of Digital Imaging

Functional Cluster Analysis of CT Perfusion Maps: A New Tool for Diagnosis of Acute Stroke?

Christian Baumgartner, Ph.D.,[1] Kurt Gautsch, M.D.,[2] Christian Böhm, Ph.D.,[3] and Stephan Felber, M.D.[2]

CT perfusion imaging constitutes an important contribution to the early diagnosis of acute stroke. Cerebral blood flow (CBF), cerebral blood volume (CBV) and time-to-peak (TTP) maps are used to estimate the severity of cerebral damage after acute ischemia. We introduce functional cluster analysis as a new tool to evaluate CT perfusion in order to identify normal brain, ischemic tissue and large vessels. CBF, CBV and TTP maps represent the basis for cluster analysis applying a partitioning (k-means) and density-based (density-based spatial clustering of applications with noise, DBSCAN) paradigm. In patients with transient ischemic attack and stroke, cluster analysis identified brain areas with distinct hemodynamic properties (gray and white matter) and segmented territorial ischemia. CBF, CBV and TTP values of each detected cluster were displayed. Our preliminary results indicate that functional cluster analysis of CT perfusion maps may become a helpful tool for the interpretation of perfusion maps and provide a rapid means for the segmentation of ischemic tissue.

KEY WORDS: Computed tomography, perfusion imaging, brain infarction, cluster analysis

INTRODUCTION

Stroke constitutes the third most frequent cause of death and disability in industrialized countries. Examination of cerebral perfusion using computed tomography (CT) has become an accepted tool to assess functional properties of ischemic brain tissues.[1–6] Under normal conditions, the mean global cerebral blood flow (CBF) is about 50 ml/100 g/min. CBF in gray matter (40–60 ml/100 g/min) is twice to three times higher compared to white matter (20–25 ml/100 g/min) and decreases in older people. Regional CBF values lower than 20 or 15 ml/100 g/min can be observed in cerebral ischemic events. Below 15 ml/100 g/min, irreversible damage occurs.

The combined interpretation of CBF, cerebral blood volume (CBV) and time-to-peak (TTP) maps via visual analysis is most commonly used in the clinical situation. Manual extraction of defined cerebral regions may help to estimate the degree of hemodynamic alteration but relies on a tedious and observer-dependent process of segmentation.

Our purpose was to employ *functional cluster analysis* to facilitate a computer-assisted extraction of abnormal brain perfusion in acute stroke. We applied a partitioning (*k*-means) and a density-based (density-based spatial clustering of applications with noise, DBSCAN) clustering algorithm to CBF, CBV and TTP maps in order to (i) identify and segment clusters of normal and apparently ischemic parenchyma by combining hemodynamic alterations of all three parameters into a single map

[1]*From the Research Group for Biomedical Data Mining, Institute for Information Systems, University for Health Sciences, Medical Informatics and Technology, Eduard Wallnöfer Zentrum 1, A-6060 Hall in Tirol, Austria.*

[2]*From the Department for Radiology II, Innsbruck Medical University, Anichstrasse 35, A-6020 Innsbruck, Austria.*

[3]*From the Institute for Computer Science, University of Munich, Oettingenstrasse 67, D-80538 Munich, Germany.*

Correspondence to: Christian Baumgartner, Ph.D., Research Group for Biomedical Data Mining, Institute for Information Systems, University for Health Sciences, Medical Informatics and Technology, Eduard Wallnöfer Zentrum 1, A-6060 Hall in Tirol, Austria; tel: +43-50-86483827; fax: +43-50-8648673827; e-mail: christian.baumgartner@umit.at

Online publication 26 January 2005

doi: 10.1007/s10278-004-1048-9

and to (ii) estimate absolute values of each detected cerebral cluster area.[7,8]

METHODS

CT Examination Protocol

The acquisition procedure for CT perfusion application consisted of repetitive scanning through a defined "region of interest" (ROI) after injection of a contrast medium bolus using a last generation multi slice scanner (Somatom Sensation 16, Siemens, Erlangen, Germany). Two slices (slice thickness 12 mm) defined according to the clinical deficit were imaged with a time resolution of 0.5 s (110 mAs, 120 kV) for a period of 40 s. 40 ml of a non-ionic contrast medium (Ultravist 370 Schering, Berlin, Germany) was injected at a flow rate of 5 ml/s.

CT Perfusion

CBF, CBV and transit time maps were calculated using commercial software (Syngo®, Siemens). This software uses the so-called *maximal slope model* for determining absolute values of CBF and was initially developed for microspheres assuming that the indicator is completely extracted in the capillary network at first pass.[5,9] This model can also be applied to CT perfusion studies as follows:

$$\mathrm{CBF} = \frac{\text{maximal slope of } Q(t)}{\text{maximal height of } C_a(t)} \tag{1}$$

where $Q(t)$ designates the amount of indicator in a local vascular network and $C_a(t)$ is the arterial concentration of indicator at time t.

CBF, CBV and Transit Times

Basically, dynamic CT can be used for measurements of CBF, CBV and blood transit time through the cerebral tissue after injection of an iodinated contrast medium into a large vein, in particular, in an antecubital position.[2,5,10–12]

The theoretical basis is the indicator-dilution principle[13,14] which relates CBF, CBV and mean transit time (MTT) values in the simple relationship:

$$\mathrm{CBF} = \frac{\mathrm{CBV}}{\mathrm{MTT}} \tag{2}$$

Mean transit time (MTT) relates to the time it takes for blood to cross the local capillary network. The calculation of a CBV map necessitates knowledge of a time–concentration curve in a vascular region of interest (ROI), e.g., at the center of the superior sagittal venous sinus, devoid of a partial averaging effect:

$$\mathrm{CBV} = K\frac{\text{area under the curve in a parenchymal ROI}}{\text{area under the curve in the vascular ROI}} \tag{3}$$

where K is a proportionality constant considering the ratio of peripheral hematocrit and tissue hematocrit. Finally, the combination of CBV and MTT at each pixel gives a CBF value, as indicated by Equation 2.

Clustering Techniques

For cluster analysis, we considered (i) CBF (ml/100 g/min) as calculated from the maximal slope model, (ii) CBV (ml/100 g) using Equation 3, and (iii) TTP (time-to-peak) which is the time (seconds) it takes from injection of a contrast bolus to the maximum level of attenuation recorded in a ROI. The calculation of the MTT map is not provided in the Syngo package.

Clustering algorithms are used for the task of class identification, i.e., the grouping of "functional" pixels into meaningful subclasses scanning CBF, CBV and TTP maps. The similarity among pixels of the form $f\mathrm{Pixel} = f(\mathrm{CBF}, \mathrm{CBV}, \mathrm{TTP})$ within the transformed three-dimensional feature space $S(\mathrm{CBF}, \mathrm{CBV}, \mathrm{TTP})$ is calculated by means of a distance function, i.e., the Euclidian distance (ED):

$$\mathrm{ED}(x,y) = \sqrt{\sum_{i=1}^{n}(x_i - y_i)^2} \tag{4}$$

where $x_i = x_{\mathrm{CBF}}, x_{\mathrm{CBV}}, x_{\mathrm{TTP}}$ and $y_i = y_{\mathrm{CBF}}, y_{\mathrm{CBV}}, y_{\mathrm{TTP}}$ are two pixels in the $n = 3$ dimensional feature space. Finally, the identified clusters are retransformed from feature space back into image space by visualizing the clusters in a single map. Thereby, pixels of the same cluster, which may represent normal, abnormal (ischemic) cerebral tissue or large vessels, are characterized by maximum similarity in hemodynamic behavior; pixels of different clusters indicate maximum dissimilarity.[7,8]

For the classification of cerebral tissue, we applied two different clustering techniques, *k*-means and a density-based (DBSCAN) algorithm, and compared their clustering characteristics.

k-Means

k-Means, a partitioning paradigm, constructs a partition of the database of N pixels (= $3nm$, three maps of image size nm; n = number of pixels in rows; m = number of pixels in columns) into a set of k clusters. Each cluster is represented by the gravity center and all pixels must be assigned to a cluster.[8,15] The algorithm is briefly sketched as follows:

(i) Initialization (arbitrary assignment of the ith pixel to the i modulo k th class).
(ii) Start loop until termination condition is met:

Each pixel in the image is assigned to a class such that the distance (= Euclidean distance, which is the square root of the componentwise square of the difference between the pixel and the class, see Eq 4) from this pixel to the center of that class is minimized.
Means of each class are recalculated on the pixels that belong to that class.

(iii) End loop.

Theoretically, *k*-means should terminate when no more pixels change classes. This relies on the fact that both steps of *k*-means (assign pixels to nearest centers, move centers to cluster centroids) reduce variance. Running to completion (no pixels

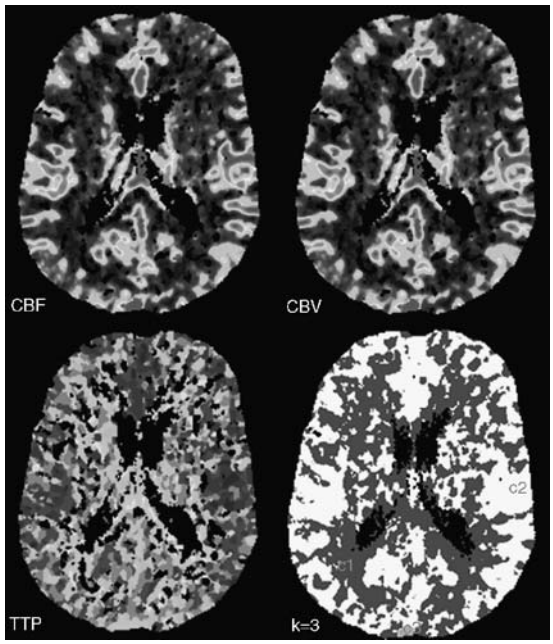

Fig 1. Cerebral blood flow (CBF), cerebral blood volume (CBV) and time-to-peak (TTP) maps of a 66-year-old male patient (patient 1) with aphasia and moderate hemiparesis. Clusters identified applying *k*-means (*k* = 3) are shown. Clusters c1 and c2 represent gray and white matter, cluster c3 depicts a large venous vessel.

changing classes) may require a large number of iterations, so we terminated after 50 iterations.

For the application of *k*-means on perfusion maps, the user needs to know the "natural" number of clusters (k = expected number of cerebral structures) in the image data which is the only input parameter of the paradigm. The limited spatial resolution of the functional maps provided enables primarily the classification of normal parenchyma (gray and white matter), abnormal ischemic parenchyma and large vessels. Therefore, we suggested a k-value of 3 for the segmentation of gray and white matter as well as large vessels in normal brain perfusion or reversible ischemia (e.g., TIA), a k-value > 3, if additionally, ischemic parenchyma was visualized in perfusion maps.

DBSCAN

The key idea of density-based clustering is that for each pixel of a cluster the neighborhood of a given radius ε has to contain at least a minimum number of pixels MinPts. The algorithm DBSCAN (density-based spatial clustering of applications with noise), which discovers clusters and noise in a database, is based on the fact that a cluster is equivalent to the set of all pixels which are density-reachable from an arbitrary core pixel in the cluster.[16]

To find a cluster, DBSCAN starts with an arbitrary pixel in the database and checks the ε-neighborhood of each pixel in the database. If the ε-neighborhood $N_\varepsilon(p)$ of a pixel p has more than MinPts pixels, a new cluster C containing the pixels in $N_\varepsilon(p)$ is created. Then, the ε-neighborhood of all pixels q in C which have not yet been processed is checked. If $N_\varepsilon(q)$ contains more than MinPts pixels, the neighbors of q which are not already contained in C are added to the cluster and their ε-neighborhood is checked in the next step. This procedure is repeated until no new point can be added to the current cluster C. DBSCAN uses MinPts and ε-neighborhood as global input parameters specifying the lowest density not considered to be noise. MinPts is recommended to be >3.[16] We used MinPts = 5. An ε-neighborhood of 0.1 was determined empirically from prior experiments.

Image Pre- and Post-Processing

Our calculations were performed on a software tool which has been developed at our institutions implementing *k*-means and DBSCAN. It is easy to handle so that cluster analysis can be performed by physicians or CT technologists during clinical routine.

For cluster analysis, input image data was generated routinely in a 12-bit grayscale format (Monochrome2) from Siemens Syngo software. Syngo already segments cerebral tissue so that the processed matrix size can be reduced from originally 512 × 512 to approximately 300 × 350 (depending on the patient's head size and the imaged topographic level). This reduction is helpful in shortening the runtime of the cluster algorithms, because pixels outside the skull contain no information that could change clustering outcome. The segmented areas of the ventricle system and background pixels were set to zero by default. However, the pre-segmented maps contained the absolute CBF, CBV and TTP values added to an offset of 2^{10} (= 1024) counts, which had to be subtracted before the algorithm was started. These offset-corrected maps were then normalized to $\mu = 0$ and $\sigma^2 = 1$, which is an essential condition for calculating the Euclidian distance function (Eq 4) in a meaningful way.

Functional maps were also available in RGB format, which were preferably used for clinical decision making (see Figs 1 and 2a), but were not appropriate for cluster analysis. After each analytic run, all clusters identified were retransformed from feature space into a single 8-bit grayscale image (TIFF), visualizing the clustered cerebral regions and displaying CBF, CBV and TTP values of each cluster detected. Currently, our software runs on a PC (Pentium IV, 500 MB RAM, 2 GHz) computing cluster results <10 min when applying *k*-means and <2 min when using DBSCAN supported by an index structure.

Quality of Clustering

Between-cluster and within-cluster variance measurements for each *k*-level were performed using *F*-tests. In this test, the ratio of two variances was calculated. If the two variances were not significantly different ($P > 0.05$), their ratio would be close to 1. This measure constitutes a way to test whether the use of $k + 1$ clusters instead of k clusters adds any significant information. Student's *t*-tests were considered to compare the mean CBF, CBV or TTP values between clusters. A *P*-value less than 0.05 indicated two significantly different means.

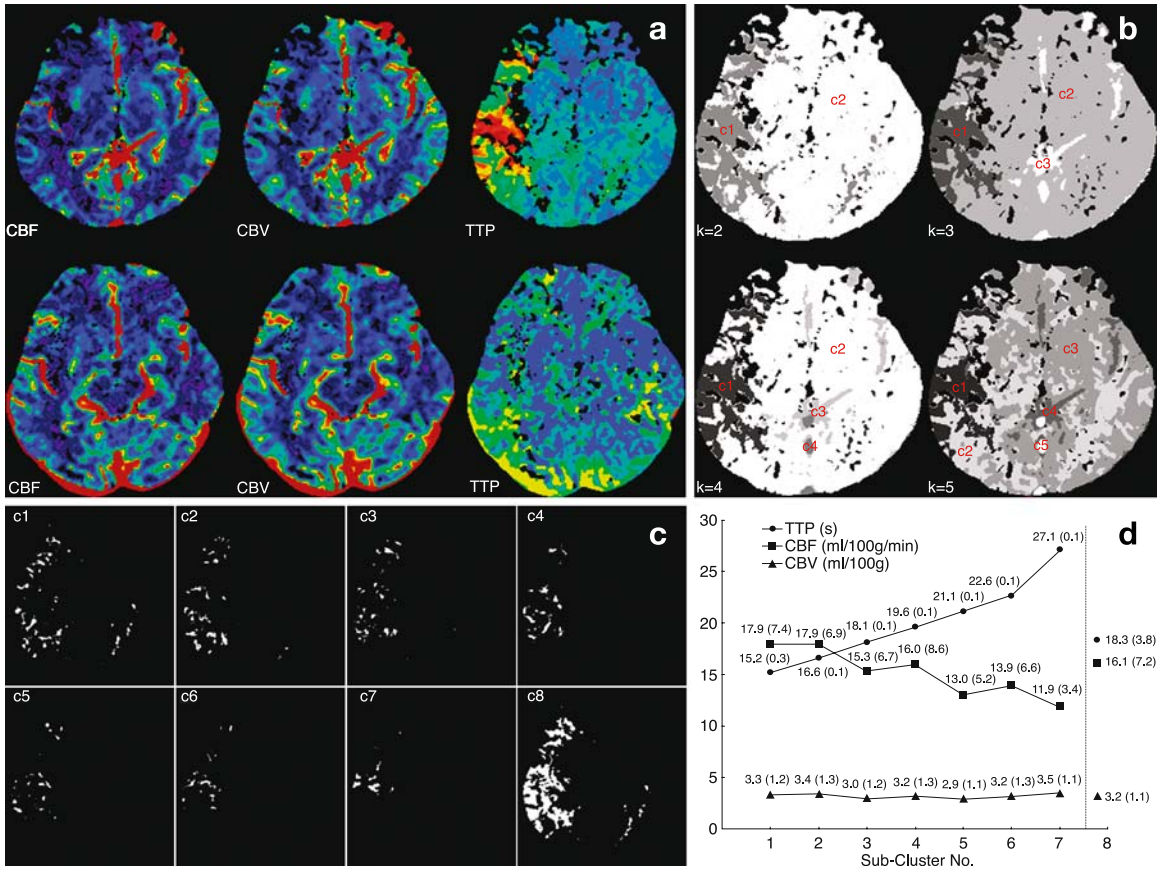

Fig 2. (a) Cerebral blood flow (CBF), cerebral blood volume (CBV) and time-to-peak (TTP) maps of a 40-year-old male patient (patient 2) at acute stroke (left-sided hemiparesis, occlusion of the right MCA, first line) and 24 h after thrombolytic therapy (second line). (b) Clusters identified applying *k*-means at acute stroke are depicted for $k = 2$, 3, 4 and 5 (clusters c2–c5). Cluster analysis 24 h after thrombolytic therapy with $k = 3$ showed symmetric cluster patterns for both hemispheres, as illustrated in patient 1 (maps not shown, absolute CBF, CBV and TTP values see Table 2). (c) Sub-clusters identified (c1–c7) in the global ischemic region using density-based clustering (DBSCAN, MinPts = 5 and ε-neighborhood = 0.1) are shown. Sub-clusters c1–c7 are ordered by increasing TTP. Sub-cluster c8 represents the accumulated cluster of all seven sub-clusters $\left(c8 = \sum_{i=1}^{7} ci\right)$. (d) CBF, CBV and TTP values of sub-clusters c1–c7 and accumulated cluster c8 are displayed as means (SD).

Clinical Examples

Cluster analysis was applied to CBF, CBV and TTP maps of two patients who had undergone a CT perfusion examination within 2 and 3 h after onset of symptoms as part of their routine diagnostic workup. Patient data was anonymized before transfer to an external workstation where cluster analysis was performed.

Patient 1 (male, 66 years) was presented with aphasia and moderate hemiparesis on admission, which resolved completely over the following hours. CT, CT angiography and CT perfusion maps were normal (Fig 1). Patient 2 (male, 40 years) showed a left-sided hemiparesis. CT angiography revealed an occlusion of the right middle cerebral artery (MCA). On CT perfusion maps, there was a marked prolongation of TTP over the right MCA territory. Decrease in CBF and CBV was less prominent (Fig 2a, first line). He received thrombolytic therapy (rTPA 47.7 mg, i.v.). Follow-up examination after 24 h showed normalized perfusion parameters and recanalization of the MCA, the neurologic deficit resolved (Fig 2a, second line).

RESULTS

Functional Clusters Identified by *k*-Means

Functional clusters identified by scanning CBF, CBV and TTP maps are summarized in Figure 1 (Patient 1, $k = 3$) and Figure 2b (Patient 2, $k = 2$ to $k = 5$). Mean (SD) cluster values of CBF, CBV and TTP are shown in Tables 1 and 2. Choosing $k = 1$, the mean global CBF, CBV and TTP values

Table 1. Absolute functional values of clusters identified in patient 1

k-Value	Cluster no.	CBF (ml/100 g/min)	CBV (ml/100 g)	TTP (s)	Area (cm^2)
At acute TIA					
$k = 1$		23.2 (25.1)	4.2 (4.4)	11.2 (2.1)	121.7
$k = 2$	c1	13.7 (8.5)	2.7 (1.7)	12.7 (1.9)	64.3
	c2	33.8 (32.3)	5.8 (5.8)	10.0 (1.2)	57.4
$k = 3$	c1	13.5 (8.6)	2.7 (1.8)	12.8 (1.9)	60.92
	c2	31.2 (16.3)	5.3 (2.8)	10.0 (1.2)	60.49
	c3	412.6 (78.9)	74.1 (14.6)	14.4 (0.4)	0.29

CBF, CBV and TTP values of each cluster are given as means (SD) using *k*-means. $k = 1$ represents the mean global functional values of the examined CT level. TIA is transient ischemic attack. All differences in CBF, CBV and TTP cluster values (c1–c2 for $k = 2$ and c1–c2, c1–c3 and c2–c3 for $k = 3$) show statistical significance ($P < 0.001$). Changing the *k*-value from 2 to 3, cluster c2 (gray matter + large vessels) is separated into c2 (gray matter only) and new c3 (vessels only). *F*-tests for c1 between $k = 2$ and $k = 3$ indicate that both variances CBF ($F = 3.93$) and CBV ($F = 4.29$) are significantly different ($P < 0.001$). However, TTP reveals an *F*-value close to 1, showing no significant changes.

were determined. The high standard deviations of accumulated CBF and CBV can be explained by the large differences of these parameters in white and gray matter and large vessels, respectively. TTP yielded more homogenous values. In Patient 1, three clusters representing white matter (cluster

Table 2. Absolute functional values of clusters identified in patient 2

k-Value	Cluster no.	CBF (ml/100 g/min)	CBV (ml/100 g)	TTP (s)	Area (cm^2)
At acute stroke					
$k = 1$		29.5 (41.5)	5.2 (6.4)	11.0 (3.4)	134.11
$k = 2$	c1	15.9 (13.4)	3.3 (2.2)	17.0 (4.1)	22.72
	c2	32.2 (44.7)	5.6 (6.9)	9.8 (1.4)	111.39
$k = 3$	c1	15.1 (10.4)	3.3 (1.9)	18.9 (3.6)	15.20
	c2	22.7 (15.1)	4.1 (2.4)	10.0 (1.6)	111.48
	c3	161.9 (94.0)	26.1 (13.3)	9.8 (2.2)	7.43
$k = 4$	c1	15.0 (10.0)	3.3 (1.8)	19.0 (3.6)	15.19
	c2	21.3 (12.3)	3.8 (1.9)	10.1 (1.6)	108.74
	c3	112.8 (36.4)	17.7 (5.7)	9.6 (2.1)	8.91
	c4	322.2 (124.4)	48.9 (17.1)	11.9 (1.7)	1.28
$k = 5$	c1	14.7 (10.5)$^{\#}$	3.3 (1.9)	20.2 (3.3)	11.46
	c2	14.8 (9.1)$^{\#}$	2.9 (1.5)	11.8 (1.4)	47.96
	c3	26.4 (13.1)	4.6 (2.1)	9.1 (1.0)	65.42
	c4	121.3 (33.3)	20.1 (6.0)	9.6 (2.1)	8.31
	c5	357.1 (123.3)	53.7 (16.8)	12.4 (10.1)	0.97
24 h after therapy					
$k = 1$		47.9 (64.3)	8.2 (10.2)	9.1 (3.1)	164.56
$k = 2$	c1*	37.4 (19.7)	5.4 (3.2)	7.5 (1.6)	117.58
	c2*	85.7 (108.6)	15.5 (6.9)	12.8 (16.5)	46.98
$k = 3$	c1*	23.3 (15.4)	4.8 (3.3)	11.3 (2.3)	74.75
	c2*	40.2 (23.7)	6.5 (4.0)	6.6 (1.0)	77.02
	c3*	234.9 (103.5)	39.5 (11.8)	11.0 (3.7)	12.79

CBF, CBV and TTP values of each cluster are given as means (SD) using *k*-means. $k = 1$ represents the mean global functional values of the examined CT level. The asterisk (*) indicates clusters identified after thrombolytic therapy. Differences in CBF, CBV and TTP cluster values show statistical significance ($P < 0.001$) by testing all combinations of clusters c*X* within each *k*-level at acute stroke and after therapy. Only mean CBF values between c1 (ischemic parenchyma) and c2 (normal tissue) at $k = 5$ (see symbol $^{\#}$) are not significantly different ($P = 0.387$). However, increased CBV and prolonged TTP in ischemic cluster c1 differ significantly from c2. *F*-tests indicate similar results as presented in Patient 1 (cf. Table 1). The area of ischemic cluster c1 decreases by raising the *k*-value from 2 to 5 which is affected by the partitioning concept of *k*-means. These changes thus lead to little alterations of mean CBF (↓) and TTP values (↑).

c1: CBF = 13.5 ml/100 g/min, CBV = 2.7 ml/100 g, TTP = 12.8 s), gray matter (cluster c2: CBF = 31.2 ml/100 g/min, CBV = 5.3 ml/100 g, TTP = 10.0 s) and large vessels (cluster c3, see Fig 1 bottom right and Table 1) were identified at a *k*-level of 3. Mean CBF, CBV and TTP values between white and gray matter and vessels differed significantly ($P < 0.001$).

Patient 2 revealed a diminished mean global CBF of 29.5 ml/100 g/min ($k = 1$) compared to the 24 h follow-up examination (47.9 ml/100 g/min, $P < 0.001$, Table 2). Similar results were obtained with CBV and TTP ($P < 0.001$). By increasing the value of *k*, clustering yielded more clusters with altered hemodynamic patterns (Fig 2b). A *k*-value of 2 identified the apparent territory of the occluded right MCA with a decrease in CBF (15.9 ml/100 g/min vs. 32.2 ml/100 g/min in normal brain tissue of cluster c2, $P < 0.001$), CBV (3.3 ml/100 g vs. 5.6 ml/100 g in normal brain tissue, $P < 0.001$) and prolonged TTP (17 vs. 9.8 s in normal brain tissue, $P < 0.001$). Increasing *k* up to 3, the areas of high blood flow (predominately large vessels) were separated. At $k = 4$, arterial and venous vessels may be distinguished (arterial TTP = 9.6 s, venous TTP = 11.9 s, $P < 0.001$). At a *k*-value of 5, two low-perfused areas, c1 (ischemic parenchyma) and c2 (normal tissue), were clustered, showing the same CBF of approximately 15 ml/100 g/min ($P = 0.387$) but different CBV and TTP values ($P < 0.001$).

Comparing cluster results from admission to the 24-h follow-up examination after therapy, improvement in global CBF, CBV and normalization of TTP were observed (Table 2). On follow-up, cluster c1 (ischemic area at the initial examination) had disappeared according to the recanalization of the MCA. At a *k*-value of 3, cluster c1* (white matter) and cluster c2* (gray matter) showed normalized values ($P < 0.001$) as well as symmetric cluster patterns for both hemispheres (maps not shown).

Functional Clusters Identified by DBSCAN

For the investigation of local hemodynamic alterations within global ischemic regions, as clustered by *k*-means in Patient 2, DBSCAN is appropriate to more sensitively distinguish regional processes (Fig 2c–d). Comparing *k*-means segmented ischemic area c1 (Fig 2b, $k = 2$) to DBSCAN, cluster c1 could be separated into seven sub-clusters with CBF values ranging from 11.9 to 17.9 ml/100 g/min, CBV values between 2.9 and 3.5 ml/100 g/min and increasing TTP values from 15.2 up to 27.1 s. Sub-cluster c7, predominantly located at the parietal lobe, indicated the core region of ischemia with lowest CBF (−35%) and maximum prolongation of TTP (+48%, $P < 0.001$) compared to c8, the accumulated sub-clusters c1–c7 (c8 corresponds to the above-mentioned *k*-means cluster c1, $k = 2$).

DISCUSSION

Diagnostic interpretation of CT perfusion integrates the information derived from CBF, CBV and TTP maps and shows limitations when performing visual analysis. The degree of hemodynamic alterations can better be analyzed quantitatively using manual segmentation of defined brain areas on single CBF, CBV and TTP maps, which can be done within minutes but is observer-dependent.

Functional cluster analysis of CBF, CBV and TTP maps facilitates the identification and segmentation of anatomic regions with inherent hemodynamic properties. Each calculated cluster represents tissue with related functional parameters by combining all three parameters into a single map, where CBF, CBV and TTP values of each voxel are simultaneously accessible. The detected clusters are automatically computed in a few analytical runs and reflect functional interactions of the measured parameters in terms of similarity operations in the three-dimensional feature space.

In normals, the segmentation of gray and white matter, as well as areas of large vessels can be obtained with the algorithm *k*-means, choosing a *k*-value of 3 by default (cf. Fig 1). *k*-Means clusters all pixels independent of the number of identified clusters and—in contrary to DBSCAN—requires the favored number of clusters as input parameter (cf. Figs 1 and 2b). However, the "natural" number of clusters is limited by $k \approx 5$ since the quality of provided functional maps enables primarily the classification of normal parenchyma (gray and white matter), abnormal infarcted parenchyma and large (arterial and venous) vessels. Therefore, a further increase in *k* is not likely

to yield meaningful results, as the number of cerebral tissues and structures with functional varying data is less than the specified number of clusters. *k*-Means also reveals a decrease in the cluster area (cf. ischemic cluster c1 of Patient 2, Table 2) after incrementing the *k*-value which is affected by the partitioning concept of *k*-means and has to be accepted.

Density-based cluster analysis using the paradigm DBSCAN is more sensitive to local hemodynamic alterations within global ischemic regions and provides an additional means to grade between ischemic core (sub-cluster c7) and adjacent ischemic tissue (sub-clusters c1–c6), as shown in Patient 2 (Fig 2c–d). DBSCAN detects a finite number of clusters and—compared to *k*-means—noise pixels which, however, are generated according to the settings of the given input parameters, MinPts and ε-neighborhood. As already mentioned, MinPts and ε-neighborhood were determined empirically for this specific case to identify hemodynamic alterations within the global ischemic cluster. However, more patients are needed to optimize parameter settings for both algorithms—these experiments are presently ongoing—and to compare cluster findings to the clinical situation.

Both algorithms showed small SDs for TTP cluster values and larger SDs for CBF and CBV values. This observation might be caused by the high dissimilarity between the examined functional parameters (TTP vs. CBF and CBV) and a correlation of CBF and CBV (cf. Eq 2), which can be easily verified using, e.g., principal component analysis. A decorrelation of the features is justified, e.g., in normal brain perfusion or reversible ischemia clustering solely CBF (or CBV) and TTP maps. However, ischemia is a complex pathophysiological condition, where CBF and CBV become important when distinguishing reversible and irreversible changes. In our approach we thus considered all three feature maps for cluster analysis in which correlation of CBF and CBV does not affect final clustering results significantly, as prior experiments showed.

TTP maps seem to represent the most sensitive parameter for the estimation of endangered brain tissue following vessel occlusion. This observation corresponds well with the result of cluster analysis in our patient who had suffered a completed stroke. The "$k = 2$" cluster map of this patient segmented an area that is comparable to the TTP map. In the clinical situation, the extension of abnormal values on TTP maps indicates the maximum amount of tissue that may be salvaged by a recanalization therapy. The extension of abnormal CBF indicates the tissue that is reached by collateral flow and may still be amenable to benefit from recanalization. CBV shows the center of ischemia with complete cessation of perfusion that is likely to progress to infarction. The correlation of CBF and CBV with cluster maps of $k > 2$ or with identified sub-clusters c1–c7 using DBSCAN and its impact on decision making for recanalization therapy remains to be investigated in larger patient samples.

Appropriate models to quantify CBF, CBV and TTP (or MTT) are needed to differentiate various stages of cerebral ischemia. For our investigations we used Siemens Syngo perfusion software which creates perfusion maps based on the maximal slope model.[5,9] To be valid, this model requires a very short injection time accompanied by a high injection rate of the intravenous contrast medium. Wintermark et al.[5] described injection rates between 5 and 20 ml/s, all showing an underestimation of the absolute CBF. Models based on the *central volume principle* have been validated and seem to be more appropriate for estimating absolute CBF, CBV and MTT values in CT.[10–12,17] However, cluster analysis, which runs on the normalized data space ($\mu = 0$, $\sigma^2 = 1$) of CBF, CBV and TTP maps, is thus unaffected by the underlying perfusion model. Absolute cluster values, of course, reflect the accuracy of the model to measure cerebral perfusion, which may limit the clinical interpretation of functional values.

CONCLUSION

Our preliminary results show that functional cluster analysis of CT perfusion maps is a promising means for the identification of acute cerebral ischemia. It facilitates the segmentation of tissue at risk as well as the estimation of areas with different severity of ischemia and collateralization within the endangered brain parenchyma. Further studies are now warranted to investigate the correlation between functional clusters and pathophysiology and histological characteristics

of the identified tissues, as well as to correlate different clusters with clinical outcome.

ACKNOWLEDGMENTS

We thank Mr. Mattias Bair for the software implementation. This study was supported by the Austrian Industrial Research Promotion Fund FFF (Grant no. HITT-10 UMIT).

REFERENCES

1. Miles KA: Acute cerebral stroke imaging and brain perfusion with the use of high-concentration contrast media. Eur Radiol 13(Suppl 5):117–120, 2003

2. Bohner G, Forschler A, Hamm B, Lehmann R, Klingebiel R: Quantitative perfusion imaging by multi-slice CT in stroke patients. Rofo, Fortschr Geb Rontgenstrahlen Neuen Bildgeb Verfahr 175:806–813, 2003

3. Wintermark M, Reichhart M, Thiran JP, Maeder P, Chalaron M, Schnyder P, Bogousslavsky J, Meuli R: Prognostic accuracy of cerebral blood flow measurement by perfusion computed tomography, at the time of emergency room admission, in acute stroke patients. Ann Neurol 51:417–432, 2002

4. Keith CJ, Griffiths M, Petersen B, Anderson RJ, Miles KA: Computed tomography perfusion imaging in acute stroke. Australas Radiol 46:221–230, 2002

5. Wintermark M, Maeder P, Thiran JP, Schnyder P, Meuli R: Quantitative assessment of regional cerebral blood flows by perfusion CT studies at low injection rates: a critical review of the underlying theoretical models. Eur Radiol 11:1220–1230, 2001

6. Konig M, Banach-Planchamp R, Kraus M, Klotz E, Falk A, Gehlen W, Heuser L: CT perfusion imaging in acute ischemic cerebral infarct: comparison of cerebral perfusion maps and conventional CT findings. Rofo, Fortschr Geb Rontgenstrahlen Neuen Bildgeb Verfahr 172:219–226, 2000

7. Kaufman L, Rousseeuw PJ: Finding Groups in Data: An Introduction to Cluster Analysis. New York: John Wiley & Sons, 1990

8. Everitt BS, Landau S, Leese M: Cluster Analysis, 4th edition. New York: Oxford University Press, 2001

9. Konig M, Klotz E, Heuser L: Cerebral perfusion CT: theoretical aspects, methodical implementation and clinical experience in the diagnosis of ischemic cerebral infarction. Rofo, Fortschr Geb Rontgenstrahlen Neuen Bildgeb Verfahr 172:210–218, 2000

10. Cenic A, Nabavi DG, Craen RA, Gelb AW, Lee TY: Dynamic CT measurement of cerebral blood flow: a validation study. Am J Neuroradiol 20:63–73, 1999

11. Nabavi DG, Cenic A, Craen RA, Gelb AW, Bennett JD, Kozak R, Lee TY: CT assessment of cerebral perfusion: experimental validation and initial clinical experience. Radiology 213:141–149, 1999

12. Nabavi DG, Cenic A, Dool J, Smith RM, Espinosa F, Craen RA, Gelb AW, Lee TY: Quantitative assessment of cerebral hemodynamics using CT: stability, accuracy, and precision studies in dogs. J Comput Assist Tomogr 23:506–515, 1999

13. Meier P, Zierler KL: On the theory of the indicator-dilution method for measurement of blood flow and volume. J Appl Physiol 12:731–744, 1954

14. Zierler KL: Equations for measuring blood flow by external monitoring of radioisotopes. Circulation 16:309–321, 1965

15. Theiler J, Gisler G: A contiguity-enhanced *k*-means clustering algorithm for unsupervised multispectral image segmentation. Proc SPIE 3159:108–118, 1997

16. Ester M, Kriegel HP, Sander J, Xu X: A density based algorithm for discovering clusters in large spatial databases with noise. Proceedings of the 2nd International Conference on Knowledge Discovery and Data Mining (KDD'96). Menlo Park, CA: AAAI Press, 1996, pp 226–231

17. Wintermark M, Thiran JP, Maeder P, Schnyder P, Meuli R: Simultaneous measurement of regional cerebral blood flow by perfusion CT and stable xenon CT: a validation study. Am J Neuroradiol 22:905–914, 2001