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Characterizing Tissue Fate After Transient Cerebral Ischemia of Varying Duration Using Quantitative Diffusion and Perfusion Imaging

Juergen Bardutzky, MD; Qiang Shen, PhD; Nils Henninger, MD; Stefan Schwab, MD; Timothy Q. Duong, PhD; Marc Fisher, MD

Background and Purpose—The purpose of this study was to investigate the effects of reperfusion on ischemic lesion evolution and pixel-by-pixel apparent diffusion coefficient–cerebral blood flow (ADC-CBF) dynamics of core and mismatch tissues after 35, 60, and 95 minutes of transient focal ischemia in rats (n=28).

Methods—Serial diffusion-, perfusion-, and T2-weighted imaging were performed up to 24 hours. The evolution of the magnetic resonance image-derived lesion volume was investigated and ADC-CBF scatterplots were performed to prospectively characterize the ADC and CBF dynamics of core and mismatch tissues with different fates. For comparison, similar analysis was performed on a historical 60-minute transient ischemia and permanent ischemia group.

Results—ADC-derived lesions markedly decreased on reperfusion at 35 minutes to an average of $15 \pm 5\%$ of prereperfusion lesion size ($P < 0.00001$). At 24 hours, lesion volume as determined by T2 imaging increased again to $51 \pm 10\%$ of prereperfusion lesion size. In the 95-minute group, ADC lesions only briefly decreased on reperfusion and then secondarily enlarged at 180 minutes, almost reaching prereperfusion lesion volume. Pixel-based analysis demonstrated that $>85\%$ of mismatch pixels were salvaged by reperfusion independent of ischemia duration. Recanalization at 35, 60, and 95 minutes resulted in recovery of 46%, 28%, and 9% of core pixels, respectively. Core and mismatch pixels that were ultimately salvaged had persistently higher ($P < 0.001$) CBF values during ischemia in all reperfusion groups, associated with higher ($P < 0.05$) ADC values.

Conclusion—This study demonstrated substantial salvage of mismatch tissue after reperfusion independent of ischemia duration and substantial permanent recovery of initial core pixels with early reperfusion. Severity of CBF reduction during ischemia seems to be the main factor determining tissue fate. (*Stroke*. 2007;38:1336-1344.)

Key Words: brain ischemia ■ MRI ■ reperfusion

Diffusion-weighted and perfusion-weighted imaging are powerful imaging modalities to noninvasively investigate the evolution of acute cerebral ischemia. Data from animal stroke models have shown that initially, a central core with severely compromised cerebral blood flow (CBF) is surrounded by a rim of moderately ischemic tissue with diminished CBF but preserved cellular metabolism, commonly referred to as the ischemic penumbra.¹ The region with perfusion abnormality but without diffusion abnormality, termed the diffusion/perfusion mismatch, is thought to represent an approximation of the ischemic penumbra.² The mismatch region may represent potentially salvageable brain tissue with timely restoration of blood flow. However, the effects of reperfusion after varying ischemic periods on the fate of the ischemic core and penumbra have not been well characterized during the acute and subacute phases in human

stroke nor in animal models. There is usually a gradual progression of potentially reversible ischemic injury toward infarction. The transition from reversible to irreversible cerebral injury is complex and highly dependent on the duration and the severity of ischemia.^{1,3} Different areas in the penumbra could have variable outcomes at different time points of reperfusion. Previous studies using region-of-interest analysis demonstrated that some portions of acute diffusion-weighted imaging abnormalities are reversible if reperfusion occurs in a timely fashion, although partial secondary apparent diffusion coefficient (ADC) declines may occur.³⁻⁶ The underlying mechanisms for permanent and transient ADC reversals, including the role of blood flow dynamics, are still poorly understood.⁷ Using a pixel-based analysis approach, recent data from our laboratory indicated that 28% of the core pixels and most of the mismatch pixels were salvaged by reperfusion at 60 minutes and that the severity of

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reduced ADC and CBF were likely critical.⁸ In contrast, van Dorsten et al did not observe a clear relationship between blood flow dynamics and tissue recovery after 60 and 90 minutes of ischemia.⁹

In this study, we used quantitative perfusion and diffusion imaging to investigate the effects of reperfusion after temporary focal cerebral ischemia of varying duration in rats. The main goals were (1) to delineate the temporal evolution of the core and mismatch volume after different reperfusion times, and (2) to characterize the ADC and CBF pixel-by-pixel dynamics in core and mismatch pixels that were subsequently salvaged by reperfusion at distinct time points and those that subsequently became infarcted.

Methods

Animal Preparations

Male Sprague-Dawley rats ($n=22$, 280 to 320 g; Taconic Farms, NY) were anesthetized with chloral hydrate (400 mg/kg intraperitoneally). Rectal temperature was kept at $37\pm 0.5^\circ\text{C}$ throughout the entire experiment using a feedback-controlled heating pad. PE-50-tubing was inserted into the right femoral artery for continuous monitoring of arterial blood pressure and heart rate and for measuring blood gases at baseline and 3.5 hours after induction of ischemia. Transient focal cerebral ischemia was produced by suture occlusion of the right middle cerebral artery (MCAO).¹⁰ Once the animal was in the magnet, anesthesia was switched to 1% isoflurane. Reperfusion was accomplished in the magnet by gently withdrawing the occluding filament. For the last imaging time point at 24 hours after MCAO, animals were reanesthetized with 1% isoflurane.

The study consisted of two experimental groups: (1) transient MCAO for 35 minutes (35-minute group, $n=11$) and (2) transient MCAO for 95 minutes (95-minute group, $n=11$).

An additional group ($n=8$) of rats were subjected to permanent MCAO for establishing the T2 threshold at 24 hours after occlusion. T2 thresholds were systematically lowered (through the Matlab program; math-Works, Natick, Mass) until the T2-defined lesion volume at 24 hours equaled the histologically defined (2,3,5-triphenyltiazolium chloride [TTC]) infarct volume at 24 hours. This method set a fixed value above which the pixels within the T2 map were considered ischemic in groups 1 and 2. The T2 threshold was 77.9 ± 3.6 ms, a $30\pm 4\%$ increase as compared with the mean of the normal hemisphere values.

For comparison, similar volumetric and pixel-based analysis was performed on a permanent ischemia group ($n=11$) and a 60-minute transient ischemia group ($n=6$) previously described in detail.⁸

MRI

MRI was performed on a Bruker 4.7T/40 cm horizontal magnet (Billerica, Mass). The average ADC was obtained by averaging three ADC maps acquired separately with diffusion-sensitive gradients applied along the three directions as previously described.¹¹ Quantitative CBF measurements were carried out using the continuous arterial spin-labeling technique with 60 pairs of arterial spin-labeling scans obtained before and 60 pairs after the ADC measurements.¹¹ T2-weighted images were performed using the fast spin-echo pulse sequence with identical parameters and two different echo times (53 and 106 ms), echo train length 16, and 16 signal averages.

The postocclusion time quoted was at the middle of the MRI acquisition at each time point. A complete ADC and CBF data set was performed at 30, 60, 90, 120, and 180 minutes after occlusion and immediately after reperfusion. At 24 hours after MCAO, a data set of perfusion-, diffusion-, and T2-weighted imaging was acquired.

After the final MRI data set 24 hours after occlusion, the brains were cut into eight 1.5-mm thick coronal slices corresponding to the MRI slices and stained with TTC. To correct for the effects of brain edema, a corrected infarct volume was calculated by the following formula: corrected infarct volume = infarct volume - (ischemic hemi-

sphere volume - nonischemic hemisphere volume) (ImageJ, <http://rsb.info.nih.gov/ij/>).

Data Analysis

MRI measurements were analyzed using the programs Matlab and STIMULATE. Quantitative CBF, ADC_{avg} , and T2 maps were calculated as previously described.¹¹

Calculation of In Vivo Lesion Size

ADC- and CBF-derived lesion volumes were derived using the ADC and CBF viability thresholds previously established and validated in our laboratory in a permanent MCAO model.^{10,11} These thresholds were identified by adjusting the respective threshold values so that the ADC- and CBF-derived lesion volumes at 3 hours were equal to the TTC infarct volume at 24 hours. The 3-hour time point was chosen because diffusion-weighted imaging-defined lesion volume was shown to stop growing by 180 minutes in this permanent occlusion model.¹⁰ These thresholds (0.53×10^{-3} mm²/s for ADC and 0.30 mL/g/min for CBF) were used to identify all pixels with abnormal ADC or CBF characteristics. Because pseudonormalization of the ADC may occur in some infarcted tissue at 24 hours after occlusion,⁴ we used the T2 viability threshold to distinguish between viable and infarcted pixels at 24 hours after MCAO. T2 imaging has been demonstrated to reliably detect irreversible infarction at this time point.⁴

Pixel-by-Pixel Analysis

According to the technique previously described for the 60-minute ischemia group in our laboratory,⁸ pixel-by-pixel scatterplots of the CBF and ADC values (or CBF and T2 values at 24 hours) were analyzed to evaluate the distribution and the ADC and CBF values of different clusters over time. Only the four anterior slices were analyzed to minimize the effect of susceptibility distortion around the ear canals. Coregistration of images obtained during the acute phase and at 24 hours was performed with an in-house software, which involved both manual and automatic alignment without spatial interpolation (<http://www.quickvol.com>).

Definition of Different Clusters

Core and mismatch pixels were defined at the time point immediately before reperfusion: the core cluster, in which both ADC and CBF were below their respective thresholds, and the mismatch cluster, in which ADC was above but CBF was below their respective thresholds.

Thirty-Five-Minute Group

Core pixels were further divided into: (1) "no recovery": ADC < threshold at 3 hours; T2 > threshold at 24 hours after MCAO; (2) "transient recovery": ADC > threshold at 3 hours; T2 > threshold at 24 hours; and (3) "permanent recovery": ADC > threshold at 3 hours; T2 < threshold at 24 hours.

Mismatch pixels were further divided into: (1) "recovery": T2 < threshold at 24 hours; and (2) "no recovery": T2 > threshold at 24 hours.

Ninety-Five-Minute Group

In the 95-minute group, pixel-by-pixel coregistration of acute and 24-hour images was not feasible as a result of substantial edematous swelling and midline shift observed at 24 hours in each rat. Hence, pixel-by-pixel analysis was only performed up to 3 hours after MCAO. Because there was essentially no change in lesion volume between the 3- and 24-hour time points (see "Results"), the ADC value at 3 hours was used to delineate the fate of different core and mismatch pixels (identified at 90 minutes). "Recovery" was defined when ADC was above the threshold at 180 minutes, and "no recovery" was defined when ADC was below the threshold at 180 minutes.

Similar analysis on the migrating pixels was also performed for the 60-minute and the permanent ischemia group.⁸ Core and mismatch pixels were defined at 30 minutes for the permanent occlusion and at 60 minutes for the 60-minute group. Because pixel-based

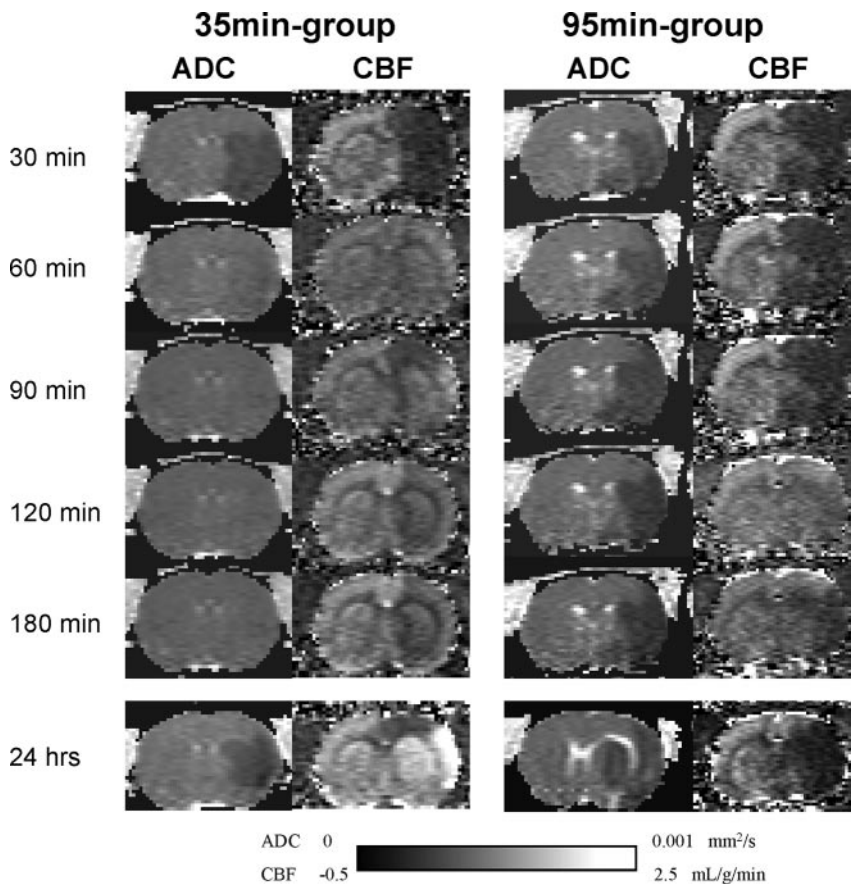


Figure 1. Representative apparent diffusion coefficient and cerebral blood flow maps (slice 4) from an animal subjected to 35 and 95 minutes of transient ischemia, respectively.

coregistration of acute and 24-hour images was not feasible as a result of substantial midline shift in both groups, the 3-hour time point was used to define tissue fate, comparable to the 95-minute group.

Statistics

Data are presented as mean \pm SD. Continuous variables were analyzed using analysis of variance with post hoc Fisher least significant difference method or Dunnett's test to correct for multiple comparisons as appropriate. A two-tailed unpaired *t* test was used to compare the parametric values. Linear regression analysis was used to correlate the MRI-derived lesion volumes with TTC-defined infarct volumes. A probability value <0.05 was considered significant.

Results

In Vivo Lesion Evolution

Physiological parameters were within the normal range and did not vary among the groups. Figure 1 shows representative ADC and CBF maps from an animal subjected to 35 and 95 minutes MCAO, respectively. As illustrated in Figure 2A through 2D, the MRI-derived lesion evolution differed substantially among the groups.

Thirty-Five-Minute Group

After reperfusion, the CBF-derived lesion volume markedly decreased ($P<0.0001$) and remained essentially unchanged up to 180 minutes. The ADC-derived lesion volume also markedly decreased on reperfusion to an average of $15\pm 5\%$ of the prereperfusion lesion ($P<0.0001$). At 24 hours, lesion volume as determined by T2 imaging increased to $51\pm 10\%$ of the prereperfusion ADC-defined lesion size ($P<0.05$ compared with 180 minutes). However, the T2-defined lesion

volume at 24 hours was still substantially smaller than the prereperfusion ADC lesion ($P<0.0005$). The T2-derived lesion volume at 24 hours was well correlated with the TTC-defined infarct volume (correlation coefficient $r=0.95$).

Sixty-Minute Group

After reperfusion, both the ADC- and CBF-derived lesion volume decreased significantly ($P<0.01$ and $P<0.0001$) and remained relatively stable up to 180 minutes. The TTC-defined lesion at 24 hours was slightly larger than the 180-minute ADC lesion (115 ± 47 versus 132 ± 33 mm³; $P=0.4$; $r=0.89$).

Ninety-Five-Minute Group

After reperfusion at 95 minutes, the CBF lesion declined significantly ($P<0.0001$), whereas the ADC lesion volume only briefly decreased ($P>0.05$) and then secondarily enlarged at 120 and 180 minutes, almost reaching the prereperfusion lesion size. The ADC lesion at 180 minutes (173 ± 48 mm³) was almost identical to the T2-defined lesion (179 ± 49 mm³, $r=0.94$) and TTC-defined lesion (170 ± 41 mm³, $r=0.93$) at 24 hours. Interestingly, CBF lesion volume had increased again at 24 hours and was well correlated with the ADC-defined lesion volume at 180 minutes ($r=0.92$).

Permanent Ischemia Group

The CBF-derived lesion volume remained relatively constant, whereas the ADC-derived lesion volume gradually increased over time. By 3 hours, the ADC lesion was almost identical

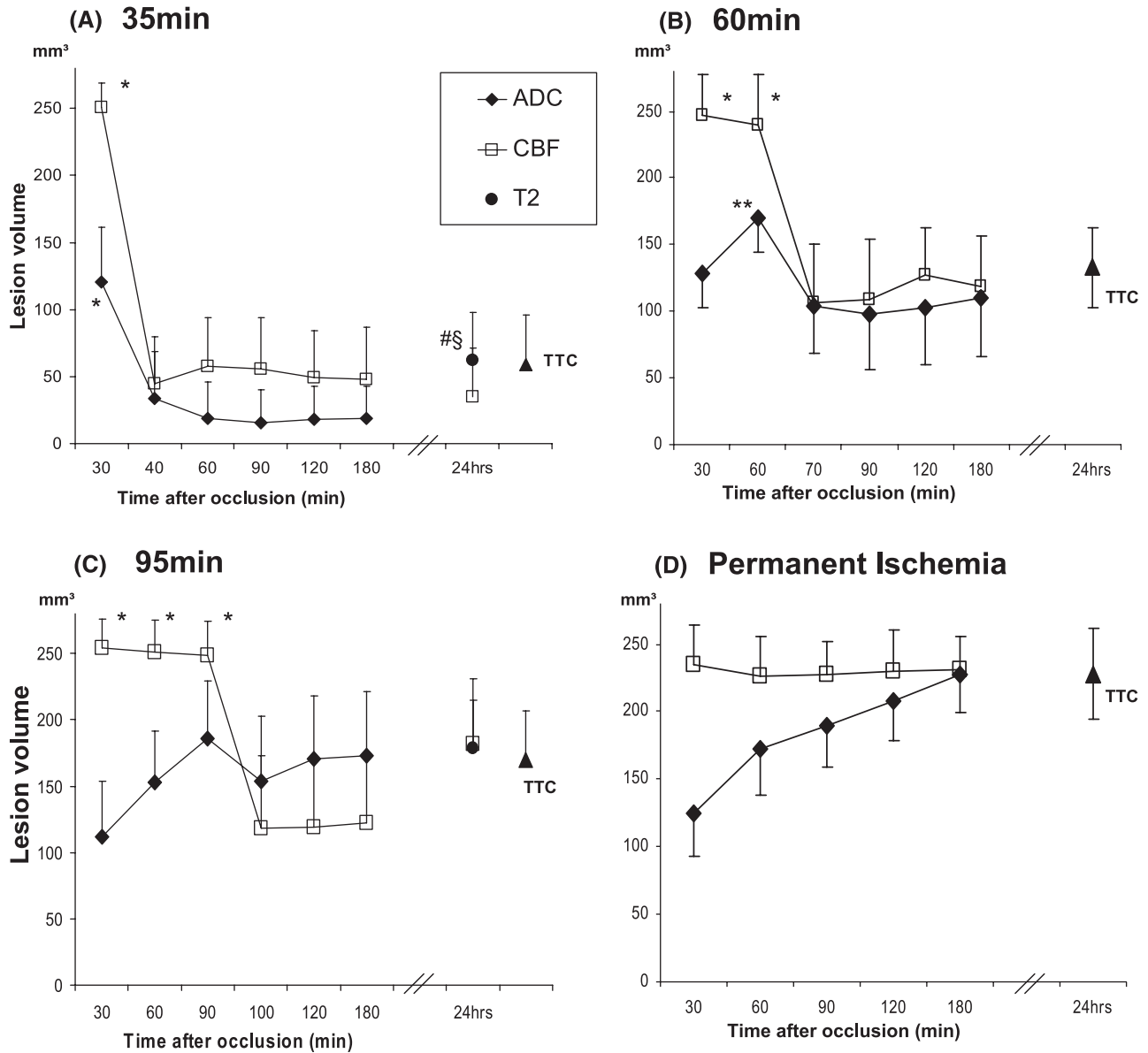


Figure 2. Temporal evolution of magnetic resonance image-derived lesion volumes after (A) 35 minutes, (B) 60 minutes, (C) 95 minutes, and (D) permanent middle cerebral artery occlusion. Cerebral blood flow lesion=open squares; apparent diffusion coefficient lesion=closed diamonds; T2 lesion at 24 hours=closed circle; 2,3,5-triphenyltiazolium chloride lesion at 24 hours=closed triangle. * $P<0.0001$; ** $P<0.01$ compared with postreperfusion values; # $P<0.05$, T2 lesion at 24 hours versus apparent diffusion coefficient lesion at 180 minutes (35-minute group); § $P<0.0005$, T2 lesion at 24 hours versus apparent diffusion coefficient lesion at 30 minutes (35-minute group).

to the CBF lesion volume and was well correlated with the 24-hour TTC infarct volume ($r=0.92$).

Pixel-by-Pixel Apparent Diffusion Coefficient and Cerebral Blood Flow Dynamics of Different Core and Mismatch Pixels

Thirty-Five-Minute Group

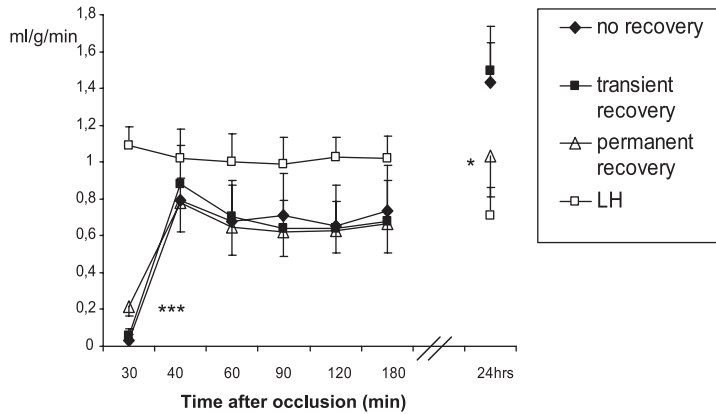
Core pixels that were ultimately salvaged had significantly higher CBF values before reperfusion compared with pixels with no or only transient recovery ($P<0.001$; Figure 3A). After reperfusion, no significant differences in CBF were observed among the different core clusters up to 180 minutes. At 24 hours, each core cluster showed significant hyperperfusion when compared with the mean left hemisphere values

($P<0.05$). However, this hyperperfusion was more pronounced in pixels with no or transient recovery compared with those with permanent recovery ($P<0.05$). The ADC of core pixels with permanent recovery was significantly higher during ischemia compared with those of pixels without or only transient recovery ($P<0.05$) and rapidly increased to normal values following reperfusion (Figure 3B).

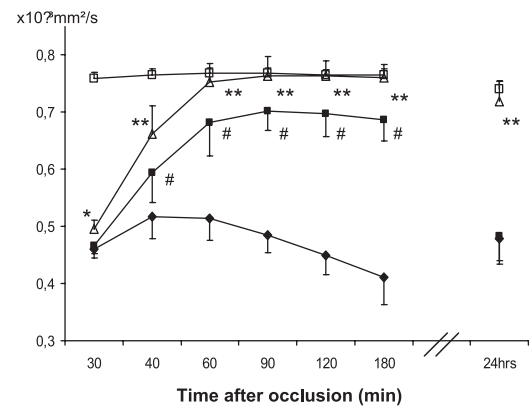
Mismatch pixels that ultimately recovered at 24 hours exhibited significantly higher CBF values during ischemia ($P<0.0001$) and on reperfusion at 120 and 180 minutes ($P<0.01$) compared with pixels that eventually infarcted (Figure 3C). Similar to the core pixels, the CBF of each mismatch cluster at 24 hours exceeded that of the normal left hemisphere. However, the extent of hyperperfusion was

35min-group

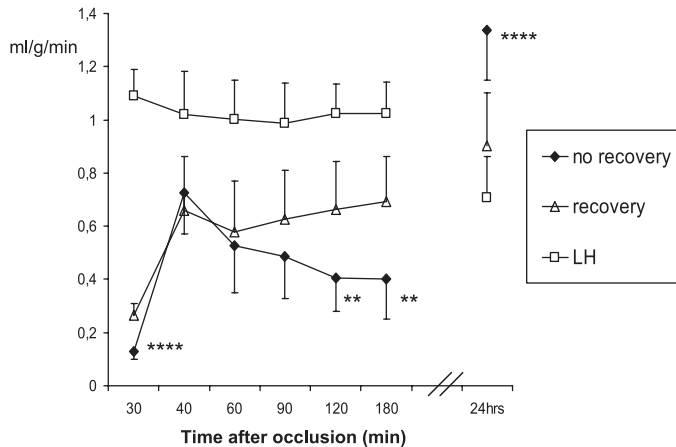
(A) Core-CBF



(B) Core-ADC



(C) Mismatch-CBF



(D) Mismatch-ADC

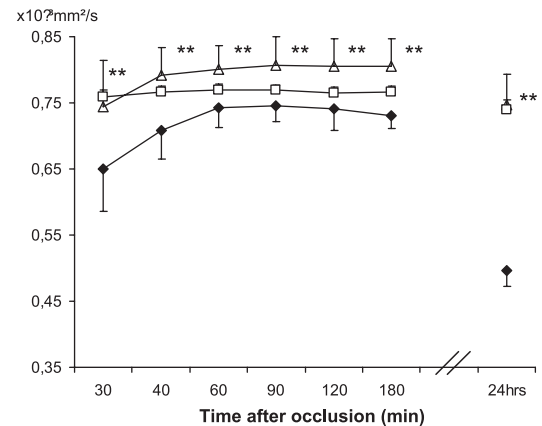


Figure 3. Evolution of cerebral blood flow and apparent diffusion coefficient characteristics of (A, B) core and (C, D) mismatch pixels with different outcomes after 35 minutes middle cerebral artery occlusion. Core pixels with no recovery=closed diamonds; transient recovery=closed squares; permanent recovery=open triangles; nonischemic left hemisphere (LH)=open squares. Mismatch pixels with recovery=open triangle; no recovery=closed diamonds. * $P<0.05$; ** $P<0.01$; *** $P<0.001$; **** $P<0.0001$, recovery versus transient and no recovery; # $P<0.005$, transient recovery versus no recovery.

significantly larger in mismatch pixels that became infarcted compared with those that were salvaged ($P<0.0001$). The ADC of mismatch pixels that did not recover on reperfusion was persistently lower at all time points compared with that of mismatch pixels that did not infarct ($P<0.01$; Figure 3D).

Sixty-Minute Group

The CBF of core pixels with recovery was significantly higher at all time points during ischemia and on recanalization at the 180-minute time point compared with those of core pixels without recovery (>0.2 mL/g/min, $P<0.005$) and reached stable values at subnormal levels during the entire reperfusion period. The ADC of salvaged core pixels was significantly higher ($P<0.001$) at all time points during ischemia and recirculation, although pixels without recovery exhibited a slight, insignificant increase immediately after reperfusion, but then the ADC continued to gradually decrease again.

Mismatch pixels that were salvaged exhibited higher CBF values throughout when compared with mismatch pixels

without recovery ($P<0.001$), similar to the 35-minute group mismatch pixels.

Ninety-Five-Minute Group

Core Pixels

During ischemia, the CBF of the core pixels that recovered after reperfusion was persistently higher compared with that of core pixels without recovery ($P<0.001$; Figure 4A), comparable to the 35-minute and 60-minute groups. In contrast to the 35-minute group, the CBF of distinct core clusters differed significantly during the early phase of reperfusion ($P<0.001$) with CBF dynamics similar to the 60-minute group. The ADC of pixels that were salvaged was significantly higher at all time points, showing a marked and gradual increase on reperfusion to slightly subnormal values (Figure 4B).

Mismatch Pixels

The CBF time courses of the different mismatch clusters in the 95-minute group were comparable to those of the 35-

95min-group

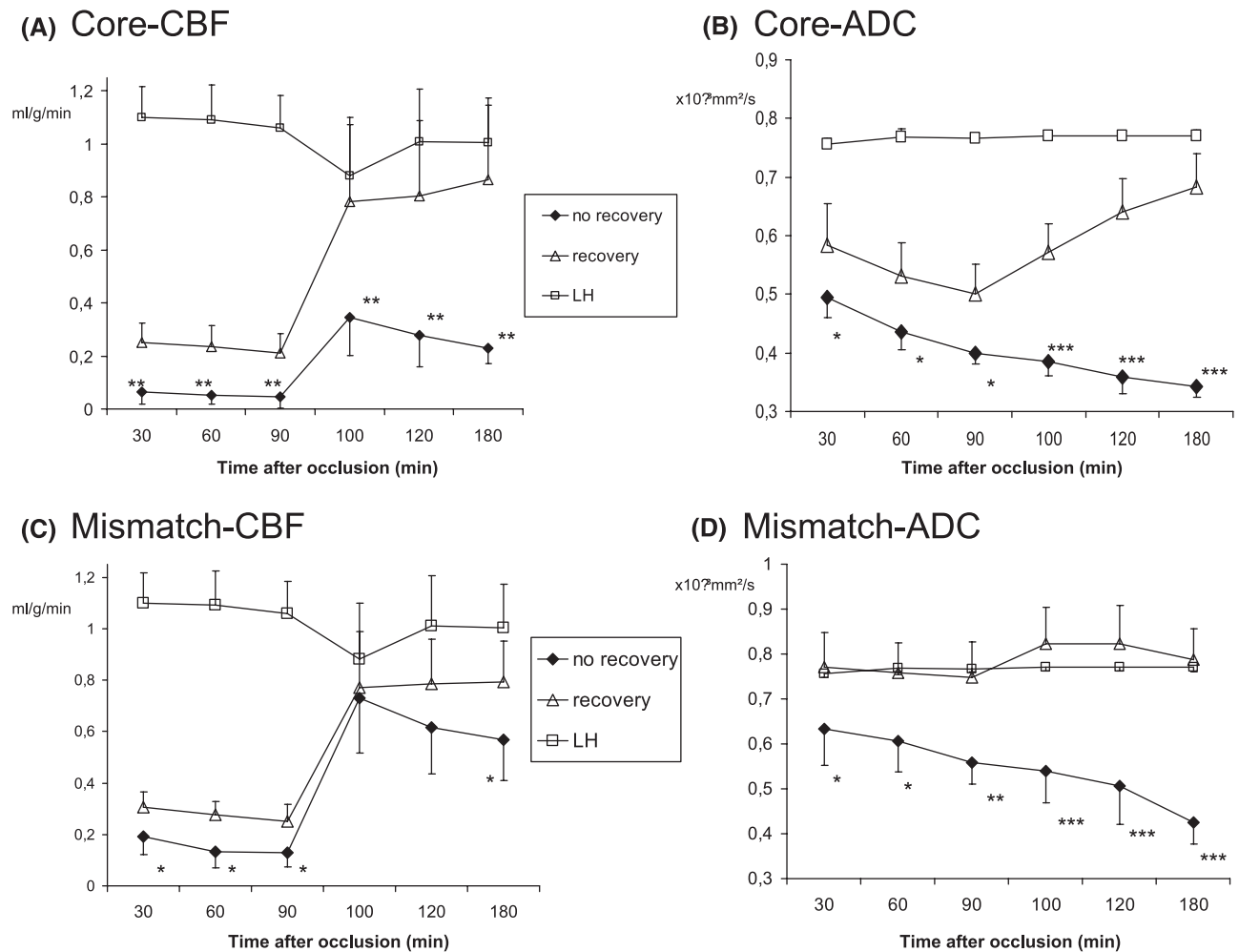


Figure 4. Evolution of cerebral blood flow and apparent diffusion coefficient characteristics of (A, B) core and (C, D) mismatch pixels with different outcomes after 95 minutes middle cerebral artery occlusion. Pixels with recovery=open triangles; pixels without recovery=closed diamonds; nonischemic left hemisphere (LH)=open squares. * $P<0.01$; ** $P<0.001$; *** $P<0.0001$, recovery versus no recovery.

minute and 60-minute group with the CBF of the salvaged pixels being constantly higher than the CBF of the pixels without recovery (Figure 4C). The ADC of mismatch pixels with recovery was within the normal range throughout the observational period, whereas the ADC of mismatch pixels without recovery exhibited significantly lower ADC values at all time points that declined over time (Figure 4D).

Permanent Ischemia Group

All core pixels proceeded to infarction with CBF values being persistently below 0.1 mL/g/min and ADC values gradually decreasing over time. Mismatch pixels that did not progressed to infarction (8% of the mismatch pixels) showed stable CBF values (ranging between 0.26 and 0.31 mL/g/min) and normal ADC values throughout the observational period. Both CBF and ADC values were significantly higher at all time points compared with those of mismatch pixels that eventually infarcted ($P<0.001$).

Fate of Core and Mismatch Pixels

The distribution of core and mismatch pixels with different fates are shown in Figure 5A and 5B. Most mismatch pixels were saved by reperfusion independent of time to recanalization (Figure 5B). In contrast, recovery of the core pixels was strongly dependent on ischemia duration; reperfusion at 35 minutes resulted in ultimate recovery of 46% of the core pixels, whereas 28% and 9% of core pixels were salvaged when blood flow was restored at 60 and 95 minutes, respectively (Figure 5A). Without reperfusion, all of the core pixels and most of the mismatch pixels eventually became infarcted.

Discussion

Previous studies on transient focal ischemia have shown that reperfusion can salvage substantial amount of hypoperfused tissue "at risk of infarction."^{3-6,10} However, the impact of varying reperfusion times on the fate of the core and the mismatch tissues has not been systematically investigated, and the role of blood flow dynamics on tissue outcome of

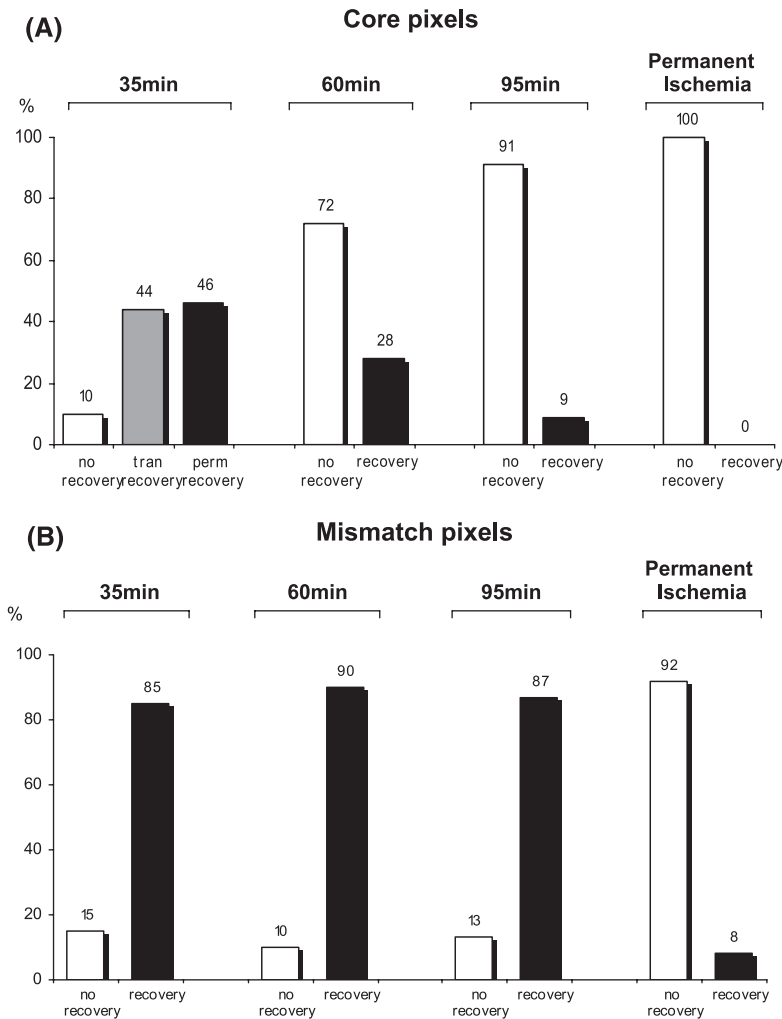


Figure 5. Distribution of core (A) and mismatch (B) pixels with different fates after 35 minutes, 60 minutes, 95 minutes, and permanent middle cerebral artery occlusion. Tran recovery indicates transient recovery; perm recovery, permanent recovery.

distinct pixel clusters is still not clear. In the present study, we analyzed short, moderate, long, and permanent ischemic periods and demonstrated (1) similarly substantial (>85%) salvage of mismatch pixels independent of reperfusion time; (2) recovery of different portions of core pixels that mainly depended on time to reperfusion; and (3) that severity of CBF reduction during ischemia seems to be crucial for further tissue fate in both brief and longer transient ischemia.

Evolution of Ischemic Lesion Volume

Previous studies on transient focal ischemia in rats have shown that recanalization did not reduce the extent of initial diffusion lesion when it was performed after 90 minutes of ischemia³ but could partially reduce initial diffusion lesions during the early phase of recirculation after 45 to 60 minutes of ischemia^{4,10} and could fully revert diffusion lesion within 30 minutes after the onset of ischemia.³ However, secondary ADC declines frequently occurred several hours after reperfusion even after brief periods ischemic periods.^{4,5} In an earlier study on 30-minute transient ischemia, we found a secondary growth in ADC-defined lesion volume to 52% of the prereperfusion ADC lesion with an ADC lesion of 69 mm³ at 12 hours.⁶ In good agreement with this and previous findings, the present study showed substantial dif-

ferences in the evolution of ischemic lesion volume among the different groups; the final infarct volume was small in the 35-minute group (60 mm³), moderate in the 60-minute group (132 mm³), large in the 95-minute group (170 mm³), and largest in the permanent ischemia group (224 mm³). These findings indicate that even small differences in ischemia duration of approximately 30 minutes may lead to substantial differences in tissue survival and strongly support the notice that restoration of blood flow as early as possible is a major goal in acute stroke therapy.

Evolution of Core Tissue

Using the previously described pixel-by-pixel analysis approach,⁸ we demonstrated that a substantial amount of initial core pixels identified by diffusion abnormalities can recover if reperfusion occurred rapidly and that the salvage of core pixels mainly depends on the time to reperfusion, because only a delay of 25 to 35 minutes leads to substantial differences in core tissue recovery; 46% of the core tissue was eventually salvaged by reperfusion at 35 minutes, 28% by recanalization at 60 minutes, and only 9% by reperfusion at 95 minutes, whereas all initial core pixels proceeded to infarction if no reperfusion occurred. Thus, early diffusion lesions include both irreversibly injured tissue and tissue that

is at risk of infarction but is still potentially salvageable, ie, the ischemic penumbra. An important clinical implication of this modified view of diffusion/perfusion mismatch model is that even select patients without mismatch may still derive benefit from recanalization therapy.

Evolution of Mismatch Tissue

Interestingly, reperfusion resulted in recovery of most mismatch pixels (>85%) after brief, moderate, and longer ischemic periods, indicating that restoration of blood flow could prevent substantial amount of mismatch tissue from developing infarction independent of time to reperfusion. In contrast, without reperfusion, the majority of mismatch pixels eventually became infarcted. This finding of time-independent salvage of mismatch tissue may also be of clinical importance, because selective patients with stroke admitted beyond the rigid 3-hour time window for thrombolytic therapy who still demonstrate significant diffusion/perfusion mismatch on MRI imaging may benefit from recanalization therapy, because the diffusion lesion eventually grows into the region of perfusion deficit without therapeutic intervention.¹² Recently, this hypothesis has been strongly supported by the Desmoteplase in Acute Stroke Trial demonstrating that thrombolysis with desmoteplase administered 3 to 9 hours after acute stroke was associated with a better clinical outcome in patients selected according to diffusion/perfusion mismatch.¹³ Moreover, similar observations in patients with stroke have been reported by Markus et al, who found hypoxic tissue survival independent of time up to 48 hours after stroke onset using a hypoxic marker and positron emission tomography.¹⁴ Nevertheless, because our findings that the salvage of mismatch pixels seems to be independent of time to reperfusion resulted from a single focal ischemia model in rats, the general transferability on other animal stroke models or humans remains to be investigated in further studies.

Apparent Diffusion Coefficient and CBF Dynamics in Different Core and Mismatch Clusters

During Ischemia

The mean CBF in pixels that fully recovered was significantly higher compared with that in pixels without ultimate recovery for each core and mismatch cluster in all reperfusion groups with a mean CBF being persistently above 0.2 mL/g/min at all time points of ischemia. As a consequence, in all pixel clusters without recovery, severe CBF reduction during ischemia was accompanied by significantly lower prereperfusion ADC values when compared with pixels with recovery. This association was common, because it was observed in both the core and the mismatch populations and in all reperfusion groups.

During Reperfusion

The current data also demonstrated that the hemodynamics after reperfusion differed significantly between pixels that recovered and pixels that did not recover. The main finding was that all pixel clusters with eventual recovery showed a stable blood flow at subnormal levels at all time points during the acute reperfusion phase, whereas a significant gradual

decline in CBF over time was observed in most pixels that progressed to infarction. It is noteworthy that this post-reperfusion CBF decline was not observed in ultimately infarcted core pixels in the 35-minute group. Nevertheless, this pattern of a stable reflow was a common finding in pixels with ultimate recovery, because it was observed in each salvaged core and mismatch population independent of reperfusion time.

Taken these data together, our results suggest that the degree of CBF reduction during ischemia and stable recirculation in the early phase of reperfusion are crucial for further tissue survival after both 35, 60, and 95 minutes of focal ischemia.

Using a similar pixel-by-pixel technique, van Dorsten et al investigated the evolution of ADC and CBF values in tissue with ADC recovery (>80% at 4.5 hours) in rats with 60 and 90 minutes MCAO⁹; although there was a tendency for lower CBF during the ischemic period in pixels without recovery, and pixels with lowest ADC (<70%) during ischemia exhibited the most pronounced delayed hypoperfusion, the overall CBF dynamics did not significantly differ between pixels with and without recovery in both groups. However, more severe hypoperfusion was associated with lower recovery chance in the 90-minute group comparable to our findings, whereas (unexpectedly) the 60-minute group appeared to show the opposite. The reasons for these discrepancies between this and our study remain unclear. Possibly, the differences in ADC thresholds (80% versus 70% in our study) and time points used to define tissue recovery may contribute to these discrepancies. Another explanation may be the differences in pixel clusters analyzed; whereas van Dorsten defined clusters based on different ADC ranges, we analyzed predefined core and mismatch pixels based on ADC and CBF thresholds.

Transient and Permanent Apparent Diffusion Coefficient Recovery After 30-Minute Middle Cerebral Artery Occlusion

Transient and permanent resolutions of ADC declines were described 12 to 24 hours after 30 minutes of temporary ischemia.³⁻⁶ Using a coregistration of acute and 24-hour images, the present results extend these observations by providing ADC-CBF dynamics of these distinct core populations on a pixel basis up to 24 hours. We observed significantly lower ADC values in pixels with only transient recovery compared with those of pixels with permanent recovery during the 35-minute ischemia period as well as at all time points during recirculation. After reperfusion, the ADC in pixels with permanent recovery rapidly increased to a stable level of normal ADC values but reached only subnormal values (approximately 90% of normal) in pixels with transient resolution and then declined again at the 24-hour time point. The reasons for this bimodal ADC evolution are not fully understood, but initial ADC reversal to subnormal values may indicate only incomplete recovery of energy metabolism, and secondary ADC decline reflects secondary energy failure, because ADC values are closely related to the bioenergetic state.¹⁵ Interestingly, CBF values differed significantly between the 35-minute core pixels with

permanent and transient recovery during ischemia but were comparable during the early reperfusion period, suggesting that the extent of CBF reduction during 30 minutes of ischemia is the major determinant for permanent or transient ADC recovery.

For the 60-minute and 95-minute groups, pixel-based coregistration of acute and 24-hour images was not feasible as a result of substantial edema development. Thus, we cannot exclude that some core pixels in the 60-minute group that showed recovery at 3 hours exhibited secondary ADC decline thereafter, because TTC-derived infarct volume was slightly larger than the ADC-defined lesion at 3 hours. In the 95-minute group, secondary ADC decline after the 3-hour period seems to be unlikely because ADC lesion at 3 hours was essentially identical with T2- and TTC-derived lesion at 24 hours.

In conclusion, this study demonstrates substantial salvage of mismatch tissue after reperfusion independent of ischemia duration. Restoration of blood flow resulted in a time-dependent recovery of portions of the initial core pixels as defined by diffusion/perfusion imaging, suggesting that some tissue with ADC declines likely contains penumbra. Pixel-based analysis demonstrated that the severity of CBF reduction during ischemia is the main factor determining tissue fate after both early and late reperfusion.

Disclosures

None.

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