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ABSTRACT

BACKGROUND AND PURPOSE: Cerebral infarction evolves at different rates depending on available blood flow suggesting that treatment time windows vary depending on the degree of pial collateral recruitment. This work sought to mathematically model infarct growth and determine whether infarct volume growth can be predicted by angiographic assessment of pial collateral recruitment in an experimental MCA occlusion animal model.

MATERIALS AND METHODS: Pial collateral recruitment was quantified by using DSA, acquired 15 minutes following permanent MCA occlusion in 6 canines based on a scoring system (average pial collateral score) and arterial arrival time. MR imaging–based infarct volumes were measured 60, 90, 120, 180, 240 and 1440 minutes following MCA occlusion and were parameterized in terms of the growth rate index and final infarct volume (V_{Final}) as $V(t) = V_{Final}\,[1 - e^{(-G \times t)}]$ (t = time). Correlations of the growth rate index and final infarct volume to the average pial collateral score and arterial arrival time were assessed by linear bivariate analysis. Correlations were used to generate asymptotic models of infarct growth for average pial collateral score or arterial arrival time values. Average pial collateral score– and arterial arrival time–based models were assessed by *F* tests and residual errors.

RESULTS: Evaluation of pial collateral recruitment at 15 minutes postocclusion was strongly correlated with 24-hour infarct volumes (average pial collateral score: $r^2 = 0.96$, $P < .003$; arterial arrival time: $r^2 = 0.86$, $P < .008$). Infarct growth and the growth rate index had strong and moderate linear relationships to the average pial collateral score ($r^2 = 0.89$; $P < .0033$) and arterial arrival time ($r^2 = 0.69$; $P < .0419$), respectively. Final infarct volume and the growth rate index were algebraically replaced by angiographically based collateral assessments to model infarct growth. The *F* test demonstrated no statistical advantage to using the average pial collateral score– over arterial arrival time–based predictive models, despite lower residual errors in the average pial collateral score–based model ($P < .03$).

CONCLUSIONS: In an experimental permanent MCA occlusion model, assessment of pial collaterals correlates with the infarct growth rate index and has the potential to predict asymptotic infarct volume growth.

ABBREVIATIONS: AAT = arterial arrival time; G = growth rate index; MCAO = MCA occlusion; Pc = average pial collateral score; SSE = sum square of the error; V_{Final} = final infarct volume; V(t) = volume at a given time

Reperfusion treatment in acute ischemic stroke due to major vessel occlusion aims to rescue brain at risk for ischemic injury. Compromise in cellular function during the early phases of cerebral ischemia precedes but does not consistently predict irreversible dysfunction or infarction. On the basis of the premise that discrepancies exist between tissue with irreversible damage and tissue with reversible functional compromise, reversible functional compromise could be operationally defined as a component of the diffusion-perfusion mismatch profile derived from MR imaging.[1-3] Tissue infarction is known to depend on both the degree to which blood flow is compromised and the duration of the compromise (time from onset of ischemia).[4] In major vessel occlusion, blood flow via pial collateral vessels sustains tissue at risk, so an effective measure of the collaterals may approximate the tissue state as indicated by the perfusion-diffusion mismatch. Furthermore, given the identical cerebrovascular occlusion site,

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From the Department of Radiology (G.A.C., S.A.A., T.J.C.), University of Chicago, Chicago, Illinois; College of Medicine (P.V.), University of Illinois, Chicago, Illinois; Departments of Radiology, Neurology, and Neurological Surgery (S.A.A.), Northwestern University, Chicago, Illinois; and Department of Economics and Decision Sciences (F.H.D.), Western Illinois University, Macomb, Illinois.

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Please address correspondence to Gregory A. Christoforidis, MD, University of Chicago, Department of Radiology, 5841 South Maryland Ave, MC 2026, Chicago, IL 60637; e-mail: gchristoforidis@radiology.bsd.uchicago.edu

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patients with acute cerebrovascular occlusion with the same degree and time of reperfusion can vary in their final irreversible tissue damage or infarct volume.[5] Final infarct volumes in patients with prolonged occlusion of the middle cerebral artery, for example, vary depending on the degree of sustained pial collateral recruitment and on the degree to which the cerebral tissue type at risk is able to withstand permanent ischemic damage.[5,6] A better understanding of the infarct growth rate has the potential to lead to a more personalized treatment plan based on tissue rather than time selection alone and to improve the effectiveness of reperfusion therapy in the current era of precision medicine.

With respect to the mathematic modeling of cerebral infarct volume growth within the first 24 hours of ictus, growth rate decreases as infarct volume increases. This characteristic indicates that infarct volume evolves in a nonlinear fashion; thus, nonlinear growth models more accurately reflect true infarct volume growth relative to a linear model. Nonlinear models can be divided into asymptotic (those that level off with time) and nonasymptotic models (those that grow indefinitely). Because infarct volume does not enlarge indefinitely but rather approaches a point in time after which any growth is negligible or cannot be measured, an asymptotic model makes more sense. This work sought to mathematically model the infarct growth rate as a nonlinear asymptotic function of time and hypothesized that the infarct growth rate can be predicted by pial collateral recruitment in a setting of acute and permanent MCA occlusion (MCAO) in a canine model.

MATERIALS AND METHODS

Animal care guidelines of the University of Chicago were followed. Six mongrel dogs (20–30 kg) underwent 4-vessel cerebral angiography and permanent endovascular MCAO from its origin at the carotid terminus, to the M1 segment by using previously described endovascular techniques.[7,8] Briefly, following induction, animals were anesthetized (1.5%–2.0% isoflurane) and ventilated. Cardiac rhythm, end-tidal CO_2, glucose, body temperature, hematocrit, and arterial pressure were maintained within physiologic range. The MCA was accessed from the posterior circulation via the circle of Willis by using a microcatheter (Echelon 10; Covidien, Irvine, California) and was occluded by using embolic coils (Axium; Covidien).[7] DSA images were acquired (OEC 9800; GE Healthcare, Milwaukee, Wisconsin) to confirm occlusion and quantify pial collateral blood supply by selective injection of the contralateral internal carotid artery and the vertebral artery 15 minutes following MCAO.

MR Imaging Protocol

All MR images were acquired on a 3T human magnet (Achieva; Philips Healthcare, Best, the Netherlands). Animals were placed in the head-first, prone position within a 32-channel transmit-receive head coil. Diffusion-weighted MR imaging (FOV = 140 × 140 mm, matrix = 128 × 128, NEX = 1, TR/TE = 192–2131/71 ms, b-values = 0, 1000 s/mm^2, section thickness = 3 mm) was acquired 1, 1.5, 2, 3, and 4 hours post-MCAO; and T2-weighted fluid-attenuated inversion recovery MR imaging (FOV = 160 mm, matrix = 512 × 512, NEX = 1, TR/TE/TI = 11,000/125/2800 ms, section thickness = 3 mm, scan time ~ 8 minutes) was acquired at 24 hours to quantify final infarct volume. Susceptibility-weighted imaging (FOV = 160 mm, matrix = 148 × 148, NEX = 1, TR/TE = 14.89/21.00 ms, flip angle = 10°, section thickness = 0.5 mm) was acquired after the 1-, 2-, and 4-hour DWI scans and at 24 hours.

Quantification of Pial Collateral Arterial Recruitment

Two interventional neuroradiologists (G.A.C., S.A.A.) semiquantitatively assessed pial collateral recruitment (average pial collateral score [Pc]) by using a previously published scoring method.[7] The results of the 2 observers were averaged. Briefly, this 11-point scoring system compares postocclusion with preocclusion arteriographic images to assess the extent of reconstitution of the occluded MCA territory and transit time relative to jugular vein opacification. Extent is evaluated within each of 3 sections of the MCA territory (anterior, middle, and posterior). For each section, 1 point is assigned if only the medial parts of the MCA distal branches were reconstituted; and 2 points, if the lateral parts of the MCA branches were reconstituted within that section. Up to 2 additional points were added if there was reconstitution of the distal and proximal M2 segments within the operculum. Transit time was assigned up to 1 point for each section of the MCA territory (anterior, middle, and posterior) if contrast arrived in the MCA branches along the lateral aspect of each section before contrast arrived to the jugular bulb. The Bland-Altman statistic for this pial collateral scoring system between 2 observers has been reported at 22.6% (95% of scores within 1.3 points of each other) and the mean difference of 0.23 between observers.[7] Pial scores were averaged and treated as continuous variables in all statistical analyses. Agreement of Pc between the 2 observers in this study was assessed by using a Bland-Altman analysis.

Arterial Arrival Time

Pial collateral recruitment was also quantitatively assessed by arterial arrival time (AAT). Signal-versus-time curves were extracted from time-resolved angiograms by using a combination of Amira software (www.amira.com) and Matlab, Version 2012b (MathWorks, Natick, Massachusetts), which measured contrast density across time within ROIs. The AAT was defined as the time interval between contrast arrival at the normal M1 segment and contrast arrival at the reconstituted M3/4 junction on the hemisphere distal to the permanent MCAO (Fig 1).

Quantification of Infarct Volume

The evolution of the infarct was determined from parametric images of mean diffusivity and T2 FLAIR images independently by 2 trained observers. A previously described semiautomated infarct segmentation algorithm was used to quantify infarct volumes across time.[7] Briefly, infarct volumes by mean diffusivity maps and FLAIR MR imaging were estimated by using a quantitative voxelwise threshold by setting a threshold of 1.5 SDs relative to normal values based on an ROI drawn to cover the entire contralateral normal hemisphere inclusive of gray and white matter but exclusive of the ventricles on a section-by-section basis. "Total infarct volume" was defined as the number of voxels that were 1.5 SDs greater than the mean value of normal tissue multiplied by the voxel volume. Volumes were calculated by using ImageJ software (National Institutes of Health,

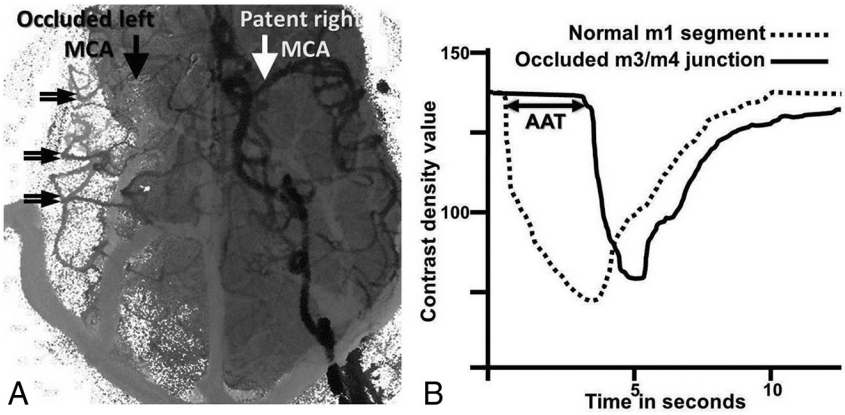

FIG 1. Arterial arrival times measured from angiographic time-density curves. ROIs within the normal MCA proximal M1 segment (*white arrow*, *A*) and from collateralized MCA branches (*double arrows*, *A*) are identified on composite angiographic images. ROIs were used to calculate time-density curves (*B*). "Average arterial time" (in seconds) was defined as the time interval between contrast arrival at the normal M1 segment (*interrupted curve*, *B*) and the average of 3 ROIs at the M3/4 junction of the MCA corresponding to the occluded MCA (*continuous curve*, *B*). AAT is graphically depicted by the *horizontal double arrow line*.

Table 1: Raw data

	Experiment No.					
	1	2	3	4	5	6
Pc	9.00	7.00	10.50	5.50	4.00	3.50
AAT (sec)	1.344	3.469	1.812	4.938	4.656	4.156
V (60 min) (mm^3)	3533	8960	3575	9842	14,947	15,074
V (90 min) (mm^3)	3976	9221	4009	10,310	15,428	16,464
V (120 min) (mm^3)	3922	9174	4430	14,493	16,805	18,134
V (180 min) (mm^3)	5492	13,043	5312	16,811	18,034	20,694
V (240 min) (mm^3)	5058	14,800	6461	17,419	19,257	22,197
V (24 hr) (mm^3)	9612	17,987	9668	20,946	24,479	25,419

Note:—V (time) indicates infarct volume at "time" evaluated with diffusion-weighted MRI; V (24 hour), final infarct volume from FLAIR MRI.

Bethesda, Maryland). Previous results by Bland-Altman statistics indicated that there is good reproducibility of infarct volume estimations by using the mean diffusivity maps (15.9%) acquired between 0 and 240 minutes post-MCAO and FLAIR images (13.3%) acquired at 24 hours.[7] Therefore, a combination of early (ie, 0–240 minutes) mean diffusivity measured infarct volume at a given time [V(t)] and 24-hour T2 FLAIR (V_{Final}) images was used to determine the evolution of the infarcted volume over time.

Predicting 24-Hour Infarct Volume from Angiography

Least-squares regression analysis was performed to test the hypothesis that angiographic assessment of pial collateral arterial reconstitution (ie, Pc and AAT) can predict final infarct volumes. Both Pc and AAT were compared by using a correlation analysis to determine the level of agreement between both Pc and AAT and V_{Final}. Cytotoxic, ionic, and vasogenic edema were not differentially accounted for when deriving this representative asymptotic function.

Modeling Infarct Growth

Asymptotic infarct growth was mathematically modeled by an asymptotic function. Infarct growth was parameterized as

$$1) \qquad V(t) = V_{Fit} \times [1 - e^{(-G \times \text{time})}],$$

where $V(t)$ was infarct volume at time t, with G and V_{Fit} being free parameters in the fit. For this analysis, infarct-across-time data collected during the acute phase of the stroke (t = 0, 240 minutes) were combined with 24-hour (t = 1440 minutes) infarct volume, V_{Final}. Levenberg-Marquardt fits were performed to extract G and V_{Fit} for each experiment separately. The goodness of fit was then reported as the coefficient of determination, r^2. Growth rates and V_{Fit} values resulting from the fits were then subject to a linear regression analysis to derive an expression that would allow the modeling of infarct growth rate as a function of pial collateral recruitment (Pc and AAT). The modeling of infarct growth by using Pc and AAT was compared. The slope intercept of the correlation plots and correlation coefficients of Pc and AAT were compared to determine which more closely followed a linear model.

Parameterizing Infarct Growth from Collateralization

Expressions for infarct volume and infarct growth rate were back-substituted into Equation 1 to yield infarct-versus-time curves as a function of Pc and AAT, (ie, angiographic measures acquired 15 minutes postocclusion). A 2-sided Wilcoxon signed rank test determined the difference (if any) between the measured and model-predicted volume of the lesion size at all time points. Because Pc- and AAT-derived models used a similar number of parameters, we applied an F test with the following formula for measuring the F statistic: $F = SSE_{AAT}/SSE_{Pc}$, where SSE_{AAT} and SSE_{Pc} are the sum square of the errors (SSE) between the AAT- and Pc-modeled lesion volumes and the 24-hour postocclusion FLAIR-measured volumes. Subsequently, comparison of the F statistic with an F distribution was used to assess the Pc- and AAT-derived models for goodness of fit to the measured data. In addition, mean absolute errors of both models were compared at each time point by using a Wilcoxon signed rank test to determine whether the errors from each model were significantly different. Statistical significance was defined at the 5% level.

RESULTS

All experiments were successful, and all 6 dogs survived to the 24-hour time point. None of the animals showed evidence of hemorrhagic conversion or herniation on the 24-hour MR imaging examinations. The Bland-Altman statistic for Pc determination between the 2 observers in this investigation was 22.4% (95% of scores within 1.5 points of each other), and the mean difference was 0.17 between observers. This result is similar to previously described reproducibility.[7] Raw data for each experiment (infarct volumes by time, Pc, and AAT) are shown in Table 1.

Predicting 24-Hour Infarct Volume from Angiography

Strong linear relations were observed between baseline pial collateral score and final infarct volume ($V_{Final} = -1483.6 \times Pc + 20{,}578$; $r^2 = 0.96$, $P < .003$) as well as AAT and final infarct volume ($V_{Final} = 2596.3 \times AAT + 1994.4$; $r^2 = 0.86$; $P < .008$) (Fig 2*A*, -*B*, respectively). A secondary analysis showed that a strong correlation exists between the pial collateral score and average arterial time ($ATT = -0.4754 \times Pc + 6.52$; $r^2 = 0.78$, $P < .02$) as might be expected from simple physiologic arguments (ie, robust collaterals provide earlier contrast agent arrival distal to an occlusion). The pial collateral score is a semiquantitative assessment, whereas AAT is a continuous quantitative measure of pial collateral recruitment.

Modeling Infarct Growth

Representative images for early (Fig 3*A*, upper part) and final (24-hour, Fig 3*A*, lower part) infarcts are shown along with the results of the semiautomated infarct volume algorithm. In all cases, infarct volumes were observed to increase asymptotically with time until reaching a final infarct volume (Fig 3*B*). Levenberg-Marquardt fits to Equation 1 converged with r^2 values exceeding 0.92 in all cases (Table 2). The growth rate index (G) extracted from the fits of the full time course (combined mean diffusivity for 0–240 minutes and 24-hour FLAIR) exhibited a strong linear relation to Pc ($G = -0.0013 \times Pc + 0.0179$; $r^2 = 0.89$; $P < .003$) and a moderate linear relation with AAT ($G = 0.0022 \times AAT + 0.0017$; $r^2 = 0.69$; $P < .04$) (Fig 2*C*, -*D*, respectively).

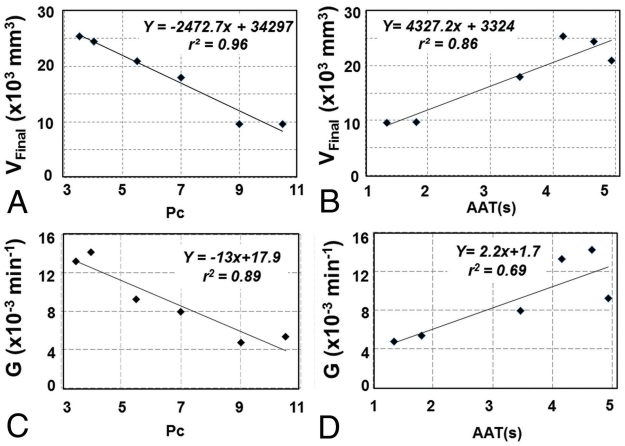

FIG 2. Final infarct volumes by T2 FLAIR images acquired 24 hours post-MCA occlusion are compared with baseline (ie, 15 minutes postocclusion) angiographic measures of pial collateral recruitment. *A*, Angiographic scoring of pial collateral score and arterial arrival time (*B*) strongly correlates with final infarct volume. Both pial collateral score (*C*) and AAT (*D*) are predictive the infarct growth rate index (derived from the fits shown in Fig 3*B*) on the basis of a linear function.

Parameterizing Infarct Growth from Collateralization

Because the experimental data indicated that both V_{Final} and G could be linearly approximated by each of Pc and AAT, a parameterization of infarct volume based solely on angiographic observables determined 15 minutes postocclusion was derived through simple algebraic back-substitution of V_{Fit} and G to obtain

$$2) \qquad V(t) = (A1 \times Pc + B1) \times [1 - e^{(C1 \times Pc + D1) \times t}],$$

with $A1 = -1483$, $B1 = 20{,}578$, $C1 = -0.0013$, and $D1 = 0.0179$). The equivalent expression for AAT was

$$3) \qquad V(t) = (A2 \times AAT + B2) \times [1 - e^{(C2 \times AAT + D2) \times t}],$$

with $A2 = 2596$, $B2 = 1994$, $C2 = 0.0022$, and $D2 = 0.0017$. The resulting curves are displayed on Fig 4 for a range of Pc and AAT values. The sum squares of the error of the AAT-based models were 3.99, 4.06, 1.93, 1.57, 1.31, and 3.98 times greater than the corresponding Pc-based model SSEs at the 60-, 90-, 120-, 180-, 240-minute and 24-hour time points. Congruently, the *F* test did not demonstrate a significant difference between the Pc- or AAT-based model of infarct volume growth at any time point with respective *P* values = .10, .10, .30, .30, .40, and .10. However, a comparison of the mean absolute error showed significantly better agreement between the Pc-based infarct growth modeling ($\varepsilon = -0.66 \pm 0.22$) compared with the AAT-based ($\varepsilon = 1.49 \pm 2.08$) modeling on a 2-sided Wilcoxon signed rank test ($P < .03$).

DISCUSSION

Our experimental results indicate that infarct growth in a permanent MCAO canine model can be mathematically modeled on the basis of an angiographic assessment of pial collateral recruitment. Reperfusion during the evolution of acute ischemia to cerebral infarction has the potential to either salvage brain at risk leading to improved clinical outcomes or cause reperfusion injury/hemorrhage leading to poorer clinical outcomes. Thus, the ability to assess salvageable ischemic tissue during the early phases of an acute ischemic stroke may impact treatment decisions.[1-3] Patients with acute ischemic stroke with large-vessel occlusion are potential candidates for embolectomy and undergo angiography before embolectomy. This circumstance lends itself to angiographic evaluation of pial collateral recruitment and may help in the assessment for embolectomy. Additionally, a clear understanding of the in-

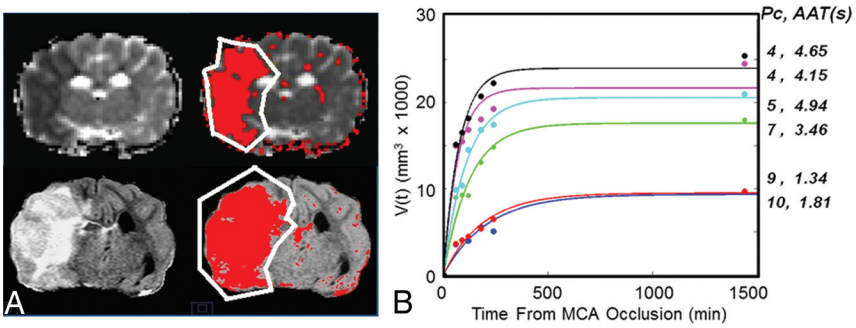

FIG 3. Single-section 120-minute mean diffusivity (upper part) and 24-hour FLAIR (lower part) images (*A*) were used to estimate and plot the growth of the infarct volume with time (*B*). A semiautomated algorithm was used to estimate the volume of the infarct on the basis of signal intensity within the affected hemisphere (red area), varying 1.5 times the SD from the mean of the signal in the contralateral normal-appearing hemisphere exclusive of spinal fluid. *B*, Infarct volume growth with time follows a predicable trend. Each curve corresponds to 1 experiment. The pial collateral scores and AAT measured immediately after occlusion (ie, at $t = 15$ minutes) for each curve are listed on the right.

farct volume growth rate as it relates to specific parameters can assist in estimating residual brain at risk and time available for intervention.

This work demonstrates that infarct growth after permanent occlusion of the MCA follows a predictable trend that can be mathematically modeled with respect to the degree of collateral blood supply distal to the occluded artery. During the early phases of cerebral ischemia after MCAO in mongrel canines, infarct volume measured by MR imaging diffusion restriction can be approximated by an asymptotic function of time. On the basis of this function, the infarct growth rate decreases with time and a growth rate index can be derived from this function. If the growth rate index is known, predictors of the final infarct volume can be used to define the evolution of cerebral infarction during MCAO. Final infarct volume and growth rate index can be linearly fitted to the pial collateral score on the basis of results derived in this study. Even if a linear relationship does not truly exist, an assessment of pial collateral recruitment can be used to estimate the final infarct volume as well as the infarct growth rate index. Ultimately in a controlled animal model with a specific occlusion site, such as the proximal middle cerebral artery, a set of estimated infarct growth curves can be generated for each pial collateral score and for various arterial arrival times (Fig 4). Using these curves, one may be able to estimate the salvageable brain tissue at risk. Given that the assessment of pial collaterals is reflective of the cerebral perfusion during acute ischemic infarction, cross-sectional perfusion imaging may also be predictive of the infarct growth index and final infarct volume.

Previous studies have assessed infarct growth with time and have determined that the growth of infarct volume changes in the early hours and reaches a maximum volume after which it decreases.[9-15] There is tremendous intraspecies and interspecies variation in the time course of cerebral infarct volume growth. Indeed, in humans, the mean time for maximal infarct volume for anterior circulation infarction appears to be around 70 hours.[9] If one compares Wistar rats with Sprague Dawley rats, the time it takes to reach maximum infarct volume appears to be 2 and 4 hours, respectively.[10] In Macaque monkeys, MCA infarction appears to reach a maximum at 24 or 48 hours.[11] Furthermore, the growth rate is suddenly altered if and when reperfusion occurs. Vasogenic edema appears to be more profound if reperfusion occurs later in the time course of infarction.[12] Finally, most studies that use MR imaging to assess infarct volume appear to suggest that a maximal infarct volume is reached on the basis of a logarithmic growth function.[11,13,14] After the maximal volume is reached, infarct volume decreases in size. On the basis of observations from this study as well as prior studies, given similar occlusion sites, the growth rate and the maximum infarct volume within each species vary to a large degree depending on the degree of pial collateral recruitment.[5,16] This feature assumes that less variability in the susceptibility of the cerebral tissues to ischemia exists within each species. The current study did not account for change in the MR imaging–based infarct growth rate as a result of reperfusion, which would represent an additive function likely depending on the degree of blood-brain barrier breakdown—that is, $V(t) = Vf[1 - e^{(-Gt)}] + B(t)$, where $B(t)$ represents this additive function.

There are limitations to this study. It is quite possible that a similar asymptotic function predictive of infarct volume may be found in humans, but our results may not be readily translatable across species. Unlike controlled experiments, physiologic parameters, occlusion site, age, and time of onset relative to MR imaging acquisition time are highly variable in the clinical setting. The current study was performed in a homogeneous population of canines with controlled physiologic conditions, permanent MCAO at a known occlusion site, and precisely known times of onset and imaging times. Varying metabolic, physiologic, and vascular events during cerebral infarction may directly and indirectly influence pial collateral recruitment under typical clinical circumstances. Additionally, the relative contributions of vasogenic, cytotoxic, and ionic edema were not differentially incorporated into the derived mathematic function. Cytotoxic and ionic edema are thought to have an immediate influence on infarct volume measured by diffusion-weighted imaging, whereas vasogenic edema would be expected to have a delayed and more prolonged impact.[17] Additionally, vasogenic edema due to reperfusion would be expected to have an additive influence at the time of reperfusion as mentioned earlier. Finally, the confined space of the calvaria may influence the infarct growth rate depending on the baseline difference in cerebral volume relative to calvarial volume, which increases with age. Further refinements of this mathematic function would need to consider the relative contributions of reperfusion and the potential variability of pial collateral recruitment with time.

Table 2: Growth rate index and final infarct volumes

Experiment	G (95% CI) ×(10^{-3})1/min	V_{fit} (95% CI) ×1000 mm^3	r^2
1	4.765 (2.37–7.16)	9.31 (7.08–11.55)	0.92
2	7.951 (4.65–11.25)	17.58 (14.52–20.63)	0.96
3	5.337 (3.629–7.05)	9.467 (8.04–10.89)	0.97
4	9.23 (6.79–11.67)	20.54 (18.41–22.67)	0.98
5	14.20 (5.64–22.75)	21.65 (17.64–25.66)	0.94
6	13.22 (8.79–17.67)	23.95 (21.36–26.54)	0.98

Note:—G indicates growth rate index from fit; V_{fit}, final infarct volume from fit; r^2 = coefficient of determination of fit.

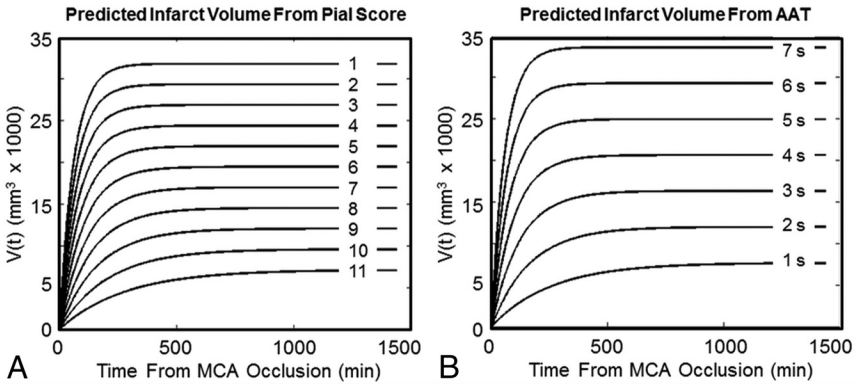

FIG 4. Families of infarct volume growth curves over 24 hours predicted by the pial collateral score and arterial arrival time.

Despite these limitations, the observation that the degree of pial collateral recruitment can estimate infarct volume growth can be incorporated in clinical decision-making. The finding of final infarct volume being dependent on pial collateral recruitment indicates that a variable peripheral zone of benign oligemia also exists in acute ischemic stroke. Finally, the observation that infarct growth rates depend on the time and extent of pial collaterals suggests that the window for potential interventional benefit may be longer in patients with good collaterals versus those with poor collaterals.

CONCLUSIONS

MR imaging–derived cerebral infarct volumes from an experimental MCAO canine model can be mathematically modeled by using an asymptotic function of time governed by final infarct volume and the growth rate index. Because both final infarct volume and the growth rate index can be linearly fitted to pial collateral recruitment, pial collateral assessment may be used to estimate potential infarct growth in the early stages of experimental cerebral ischemia due to MCAO.

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