The Capillary Index Score as a Marker of Viable Cerebral Tissue

Proof of Concept—The Capillary Index Score in the MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) Trial

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Background and Purpose—The capillary index score (CIS) is based on the hypothesis that areas lacking capillary blush on pretreatment cerebral digital subtraction angiograms correspond to nonviable cerebral tissue.

Methods—Pretreatment digital subtraction angiograms and post-treatment noncontrast enhanced computed tomographic scans from the MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) trial were evaluated for areas lacking capillary blush and with tissue hypodensity, respectively. Because the superior and middle zones of the CIS correspond to the 7 cerebral cortex regions of the Alberta Stroke Program Early CT (ASPECT) score, capillary blush was scored in these 2 zones (0–2), called sub-CIS, and compared with the ASPECT score in these 7 regions (0–7), called hypodensity score. The presence and extent of hypodensity were compared between sub-CIS zones with contingency tables and nonparametric comparisons between groups, respectively.

Results—On the basis of a sample size of 50 subjects, 100% with sub-CIS <2 had the presence of hypodensity (hypodensity score ≥1) versus 57% for sub-CIS=2 (P=0.004). The extent of hypodensity (numeric hypodensity score) was significantly lower for sub-CIS=2 than 0 or 1 (P=0.02). For 42 subjects with revascularization data, the presence and extent of hypodensity were significantly lower for sub-CIS=2 plus good revascularization than for other combinations of sub-CIS and revascularization (P=0.02 and 0.01, respectively).

Conclusions—The absence of capillary blush on pretreatment digital subtraction angiogram seems to correspond to nonviable cerebral tissue. Successful revascularization reduces the chance of tissue hypodensity (infarction), when capillary blush is present.


Key Words: cerebral cortex ▪ infarction ▪ stroke ▪ tissue

Recent advances in revascularization techniques and devices have improved outcomes for patients with acute ischemic stroke after endovascular treatment (EVT). Further advancements could be achieved by refining selection criteria. The use of the capillary index score (CIS) in patient selection for EVT has been demonstrated previously.1–3

The CIS is based on the hypothesis that the absence of capillary blush on pretreatment cerebral digital subtraction angiograms (DSA) indicates nonviable cerebral tissue, which is destined for infarction regardless of successful revascularization or time to treatment. Conversely, the presence of capillary blush on a DSA indicates viable ischemic tissue,
which may benefit from successful and timely revascularization. The CIS can be used to characterize the capillary blush from a DSA when all potential collaterals to the ischemic territory are opacified, and the images include the venous phase. This study was designed to test the hypothesis by comparing areas with and without capillary blush on the pretreatment DSA with their corresponding locations on post-treatment noncontrast enhanced computed tomographic (NCCT) scans. Hypodensity on a post-treatment NCCT scan was considered evidence of ensuing cerebral infarction. The use of the CIS as a predictor of outcome was also assessed.1–3

Materials and Methods
The study was performed using the database of patient demographics, imaging, and outcomes from the MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) trial. The MR CLEAN trial was a 2 arm multicenter randomized clinical trial evaluating the effect of EVT on overall functional outcome in patients presenting with an acute anterior circulation ischemic stroke due to a proximal intracranial arterial occlusion, treatable within 6 hours after symptom onset.4 The trial included 233 patients in the EVT arm. The study was approved by a central medical ethics committee and the research board of each participating center, and patients or their legal representatives provided written informed consent. The publication committee of the MR CLEAN trial provided only previously collected deidentified data for the current analysis.

Blinded to all other data and with access to only the pretreatment DSAs, a single operator (F.A.-A.) reviewed all available DSAs of subjects who received EVT to ascribe the CIS with prespecified inclusion criteria: (1) all potential collaterals to the ischemic territory were opacified, (2) images including the venous phase were available, and (3) no significant motion artifacts were present. These criteria were necessary to allow clear visualization of the capillary blush, but they were not a part of the protocol of the MR CLEAN trial. The ischemic territory was identified on the DSA as the area normally fed by the occluded vessel, either the middle cerebral artery or the internal carotid artery, which received blood supply mainly in retrograde fashion through pial collaterals after the occlusion. The ischemic territory was divided into 3 zones: zone 1 is the superior third of the ischemic territory; zone 2 is the middle zone; and zone 3 is the inferior zone, which includes the temporal lobe. One point was added to the CIS for each zone with a visible capillary blush, giving a maximum possible CIS of 3 points (Figure 1).

Two months later, the same operator, blinded to all other data (by means of newly randomly assigned patient ID numbers), reviewed the post-treatment NCCT scans from the same admission of the patients with available CIS. Areas of hypodensity were assessed within the 10 defined Alberta Stroke Program Early CT (ASPECT) score regions.6 To test the CIS hypothesis, the analysis focused on only the 7 cerebral cortex regions of the ASPECT score, M1 to M6 and insula. These regions can be consistently identified on the frontal view of the DSA used to ascribe the CIS because of minimal overlap with other areas of the brain. An NCCT hypodensity score ranging from 0 to 7 was obtained by adding 1 point for hypodensity (consistent with recent infarction) observed in each of these 7 regions on the post-treatment NCCT scan from the same admission. For each subject, the presence of hypodensity was indicated by any region of hypodensity (hypodensity score ≥1). The extent of hypodensity was based on the total hypodensity score, indicating the number of regions evaluated with hypodensity.

The evaluated ASPECT regions (M1–M6 and insula) are located within superior and middle CIS zones of the ischemic territory (zones 1 and 2).7 A modification of the CIS system based on only these 2 zones, referred to as the sub-CIS, was devised for comparison with the presence and extent of NCCT hypodensity. The sum of capillary blush score for only the superior and middle zones was ascribed to each subject, for a sub-CIS ranging from 0 to 2.

Revascularization status and outcomes were obtained from the MR CLEAN database for each subject in the study population, along with additional data related to demographics and pretreatment health. Revascularization was classified using the modified treatment in cerebral ischemia (mTICI) score as poor (mTICI=0–2A) or good (mTICI=2B, 3). Outcomes were characterized based on modified Rankin Scale at 3 months, with modified Rankin Scale score of ≤2 considered a good functional outcome. Incidence of post-treatment intraparenchymal hemorrhage (IPH) was also recorded as the primary complication. Other data collected included age, sex, systolic blood pressure, presence of comorbidity diabetes mellitus, baseline National Institutes of Health Stroke Scale score, and time from ictus to initiation of EVT.

Statistical Analysis
Three primary analyses were performed:

Figure 1. Calculating capillary index score (CIS). A frontal view of a normal cerebral digital subtraction angiogram (A). The territory of the middle cerebral artery (MCA) is used as an example of the ischemic territory. The territory of the anterior cerebral artery (ACA) is also shown. The ischemic territory is divided into 3 equal zones; a zone is given a score of 1 if it exhibits capillary blush or a score of 0 if no capillary blush is present. CIS is the sum of these 3 numbers. The maximum value for CIS=3. An angiogram with CIS=0 is also shown (B). Adapted from Al-Ali et al8 with permission of the publisher. Copyright ©2015, the Authors (see: http://creativecommons.org/licenses/by/4.0/). Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.
Capillary blush on pretreatment DSA, based on the sub-CIS, was evaluated as an indicator of the presence and extent of hypodensity on the post-treatment NCCT. The interaction of capillary blush on pretreatment DSA with revascularization status was evaluated as an indicator of the presence and extent of hypodensity on the post-treatment NCCT. The interaction of CIS and revascularization status was evaluated as an indicator of clinical outcomes.

The presence of hypodensity (hypodensity score of ≥1) was compared between the sub-CIS categories (0, 1, and 2) using a contingency table. Because of small expected cell frequencies, Fisher exact tests were used for the analysis. A post hoc subgroup analysis was performed by combining similar groups and using a Bonferroni correction for multiple comparisons. Sensitivity and specificity of the sub-CIS as a predictor of the presence of hypodensity was quantified, with the accuracy and statistical significance evaluated using receiver-operating characteristic curve analysis.

Variation in the extent of the NCCT hypodensity (total hypodensity score) related to the sub-CIS was evaluated with nonparametric comparisons of the hypodensity score between the sub-CIS groups. Nonparametric analyses were performed because of the ordinal nature of the hypodensity score. The hypodensity score was compared between the 3 sub-CIS groups with a Jonckheere–Terpstra test for ordered groups, including post hoc pairwise comparisons.

The presence of hypodensity was compared between combinations of sub-CIS and revascularization status using a contingency table. Sub-CIS scores of 0, 1, and 2 were combined with good or poor revascularization for a total of 6 groups to compare with the presence of hypodensity. The contingency table was analyzed using a Fisher exact test, with post hoc comparisons performed by combining similar groups and including Bonferroni correction.

Variation in the extent of the NCCT hypodensity (total hypodensity score) related to the sub-CIS was also evaluated for subjects with good and poor revascularization separately. Subjects with a sub-CIS of 0 or 1 were combined because of similar hypodensity scores and small numbers. The hypodensity score was compared between the sub-CIS groups with the Mann–Whitney U tests.

Baseline National Institutes of Health Stroke Scale score, age, systolic blood pressure, and time from ictus to start of EVT were compared between sub-CIS values 0 to 2 using ANOVA. Student–Newman–Keuls tests were used for post hoc comparisons. Sex, presence of comorbid diabetes mellitus, and rate of IPH were compared between the sub-CIS groups using the Fisher exact tests (3×2) with subgroup analyses.

On the basis of previous studies showing that good clinical outcomes are primarily determined by the combination of CIS and revascularization,2,3 Fisher exact tests were used to compare the proportion of subjects with good outcomes between categories determined by the combination of CIS (0–3) and revascularization status (good or poor), for a total of 8 groups. Subgroup analyses were performed to identify differences between specific groups, with a Bonferroni correction applied for multiple comparisons. All analyses were performed with statistical analysis software (SPSS Statistics 22, IBM), and the level of significance was set to P<0.05 for all comparisons.

Results
Of the 233 patients randomized to EVT for the MR CLEAN trial, 215 DSAs were available for review of this study (Figure 2). The DSAs from 53 of the 215 (24%) met the inclusion criteria established to ascribe the CIS. The vast majority of DSAs were excluded because of the lack of opacification of all collaterals or lack of the venous phase on the DSA images. Follow-up NCCT images were not available for 2 patients. Another patient was excluded because of subarachnoid hemorrhage identified on the post-treatment NCCT scan believed to be iatrogenic in nature, and hence changed the natural course of the events, leaving 50 patients for the analyses relating sub-CIS to hypodensity, regardless of revascularization. Revascularization based on the mTICI scale was not available for 8 subjects, leaving 42 patients for the analyses that included revascularization status as a factor.

Relationship Between Sub-CIS and NCCT Hypodensity Score
The presence and extent of hypodensity varied with the sub-CIS. The presence of NCCT hypodensity (hypodensity score ≥1) was found for all subjects (100%) with sub-CIS 0 or 1. The rate of hypodensity was significantly lower (57%, P=0.004) for sub-CIS=2 (Table 1) than for the combination of sub-CIS=0 or 1. With the sub-CIS cutoff to predict post-treatment hypodensity set at <2, the sensitivity of sub-CIS was 54% and the specificity was 100%. The area under the receiver-operating characteristic curve was 0.77 (95% confidence interval, 0.64–0.90, P=0.04). The extent of NCCT hypodensity was
Table 1. Proportion of Subjects With the Presence of Hypodensity Related to Sub-CIS (0, 1, or 2) With and Without Revascularization Status (Poor or Good)

<table>
<thead>
<tr>
<th>Sub-CIS (n=50)</th>
<th>Hypodense/Total (%)</th>
<th>P Value vs Other Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>8/8 (100)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>12/12 (100)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>17/30 (57)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sub-CIS+revascularization (n=42)</th>
<th>Hypodense/Total (%)</th>
<th>P Value vs Other Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>0+Poor</td>
<td>4/4 (100)</td>
<td></td>
</tr>
<tr>
<td>0+Good</td>
<td>3/3 (100)</td>
<td></td>
</tr>
<tr>
<td>1+Poor</td>
<td>6/6 (100)</td>
<td></td>
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<tr>
<td>1+Good</td>
<td>6/6 (100)</td>
<td></td>
</tr>
<tr>
<td>2+Poor</td>
<td>7/8 (88)</td>
<td></td>
</tr>
<tr>
<td>2+Good</td>
<td>7/15 (47)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

CIS indicates capillary index score; and n, number of subjects included in analysis.

also significantly smaller for subjects with sub-CIS=2 than for subjects with sub-CIS=0 or 1 (P=0.02; Table 2).

Relationship Between Sub-CIS, Revascularization, and NCCT Hypodensity Score

The presence and extent of hypodensity were lowest for the combination of good revascularization and sub-CIS=2. The proportion of subjects with any NCCT hypodensity present was significantly smaller for the combination of sub-CIS=2 and good revascularization (47%) than for the combined results from the other groups (P=0.02; Table 1). For subjects with good revascularization, the NCCT hypodensity score (extent of hypodensity) was significantly (P=0.01) smaller for sub-CIS=2 than for sub-CIS=0 or 1 (Table 2). Conversely when considering only subjects with poor revascularization, the NCCT hypodensity score was not significantly different between sub-CIS=2 and sub-CIS=0 or 1 (P=0.3).

Relationship Between Demographic Factors, Pretreatment Condition, Complications, and Sub-CIS

No significant differences in age, sex, presence of comorbid diabetes mellitus, or time to EVT were identified across any of the 3 sub-CIS groups (Table 3). The mean (±SD) systolic blood pressure was significantly higher for sub-CIS=0 (169±52 mm Hg) than sub-CIS=1 (145±20 mm Hg) and sub-CIS=2 (138±22 mm Hg; P=0.03). The baseline National Institutes of Health Stroke Scale score for sub-CIS=2 was significantly lower than for sub-CIS=0 and sub-CIS=1 (P=0.001). The mean baseline National Institutes of Health Stroke Scale score was 20±5, 21±3, and 16±4 for sub-CIS values of 0, 1, and 2, respectively. The rate of IPH varied significantly between the sub-CIS groups, being significantly larger for sub-CIS=0 than for the combination of the other 2 sub-CIS values (P=0.03).

Relationship Between the CIS, Revascularization, and Clinical Outcome

The rate of good outcomes varied significantly with the combination of CIS and revascularization status. The highest rate of good outcomes occurred for the combination of CIS=3 and good revascularization at 86% (Table 4), with this group significantly different from the combination of all other groups (P=0.002). The rate of good outcomes did not exceed 33% for any other combination of CIS and revascularization status, and no other significant differences were noted between the groups.

Discussion

This analysis indicates that the presence and extent of cerebral infarction (area of hypodensity on post-treatment NCCT) vary significantly with the extent of capillary blush on the pretreatment DSA. Subjects with sub-CIS=0 or 1 (partial or total absence of capillary blush) had a 100% presence of hypodensity in at least 1 region. They also had a larger extent of hypodensity based on number of regions than sub-CIS=2 (full capillary blush present). Importantly, the benefit of sub-CIS=2 in significantly decreasing the presence and extent of hypodensity was achieved only for patients with good revascularization. These results indicate that the presence of capillary blush from retrograde pial collaterals reflects viable, but ischemic, cerebral tissue that still needs revascularization. The current data also suggest that revascularization of cerebral tissue that lacks capillary blush has limited impact on decreasing the presence and extent of hypodensity on post-treatment NCCT, raising questions about futility of revascularization for this group that need to be addressed with a prospective trial focused on the CIS. These findings, in our opinion, strongly support the CIS hypothesis.

The relationship between the absence of capillary blush on DSA and hypodensity on post-treatment NCCT scan was shown previously by other investigators, which increases confidence in our results. In their publication, the sensitivity, specificity, and accuracy for prediction of post-treatment hypodensity based on capillary blush were 73%, 90%, and 0.87, respectively. The current results differ slightly (sensitivity=54%, specificity=100%, and accuracy=0.77). The current smaller values for sensitivity and accuracy compared with their results are most likely because of our division of the ischemic territory into only 3 zones, as opposed to the 15 zones used previously. Although dividing the ischemic area into smaller zones should theoretically increase the accuracy.

Table 2. Median (Interquartile Range) Extent of Hypodensity (Total Hypodensity Score) Compared Between Sub-CIS Groups, With and Without Revascularization Status

<table>
<thead>
<tr>
<th></th>
<th>Sub-CIS=0 or 1</th>
<th>Sub-CIS=2</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td>4.5 (3–7)</td>
<td>1.5 (0–3)</td>
<td>0.02</td>
</tr>
<tr>
<td>Good revascularization†</td>
<td>4 (3–5)</td>
<td>0 (0–2.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Poor revascularization‡</td>
<td>5.5 (3.5–7)</td>
<td>3.5 (3–4.8)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

CIS indicates capillary index score.

*Fifty subjects.
†Twenty-four subjects.
‡Eighteen subjects.
of predicting NCCT hypodensity, using only 3 zones allows
the method to be clinically applicable (the CIS). Nevertheless,
similar to the previous study, the absence of capillary blush
identified tissue destined to infarction, and a lower capillary
blush score portended a greater infarction volume (the extent
of NCCT hypodensity).

Another interesting finding of the current analysis is that
subjects with no capillary blush in the zones of analysis (sub-
CIS=0) had a significantly higher proportion of IPH (63%) than
the subjects with sub-CIS=1 or 2 (17%). We speculate that this
difference is related to the higher volume of infarcted cerebral
tissue before EVT for the sub-CIS=0 group. This higher rate
of IPH may also be a factor contributing to poor outcomes in
this patient cohort. It is not clear, however, from these data
whether the higher rate of IPH is related to the preexisting
loss of capillary blush or revascularization. Verification of
these results in a larger prospective study would further clarify
whether EVT increases the chance of IPH for patients lacking
capillary blush. These unrelated complications may have biased the results toward worse outcomes in this study, especially with a small sample size (8 patients).

The primary limitation of this analysis is the lack of a one-
to-one correlation between CIS zones and ASPECT regions.
Multiple ASPECT regions are within each CIS zone. The
analysis focused on only regions M1 to M6 and the insula of
the ASPECT regions and zones 1 and 2 of the CIS to provide
the best possible correspondence of areas from DSA and post-
treatment NCCT. Although other studies measured the CIS
from 57%1 and 77% 8 of the DSA images, only 24% of sub-
jects analyzed for this study had a sufficient DSA to ascribe
the CIS because the MR CLEAN protocol did not specify the
imaging parameters needed to measure the CIS. Nevertheless,
this study clearly demonstrates a significant difference in the
fate of cerebral tissue without capillary blush compared with
tissue with capillary blush after successful revascularization,
confirming the original hypothesis behind the CIS.

Conclusions
These results indicate that the absence of capillary blush
before treatment indicates infarcted tissue, for which revas-
cularization may be futile. On the contrary, the presence of
capillary blush signifies viable, but ischemic, tissue still in
the need of successful revascularization. A prospective trial is
underway to test the use of the CIS as a selection criteria for
patients with acute ischemic stroke.

Sources of Funding
Funding for the analysis was provided by the Akron General
Development Foundation. The MR CLEAN trial was partly

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<th>Table 3. Demographic Data and Pre-EVT Parameters for Sub-CIS Values (50 Subjects)</th>
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<tr>
<td>Sub-CIS=0</td>
</tr>
<tr>
<td>Age, y</td>
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<tr>
<td>NIHSS score</td>
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<tr>
<td>Systolic BP, mmHg</td>
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<tr>
<td>Time to EVT, min</td>
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<tr>
<td>Male/Total</td>
</tr>
<tr>
<td>DM/Total</td>
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<td>IPH/Total</td>
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BP indicates blood pressure; CIS, capillary index score; DM, diabetes mellitus; EVT, endovascular treatment; IPH, intraparenchymal hemorrhage; and NIHSS, National Institute of Health Stroke Scale.

<table>
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<tr>
<th>Table 4. Proportion of Good Outcomes (mRS≤2) for CIS (0–3) Combined With Good vs Poor Revascularization (42 Subjects)</th>
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<tr>
<td>CIS+Revascularization</td>
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<td>0+Poor</td>
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<td>3+Good</td>
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CIS indicates capillary index score; and mRS, modified Rankin scale.
funded by the Dutch Heart Foundation and by unrestricted grants from AngioCare BV, Medtronic/Covidien/EV3, MEDAC GmbH/ LAMEPRO, Penumbra Inc, Stryker, and Top Medical/Concentric.

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References
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On page 2286, in the author byline, “Willem van Zwam, MD, PhD,” has been changed to read “Wim H. van Zwam, MD, PhD.”

This correction has been made to the online and print version of the article, which is available at http://stroke.ahajournals.org/content/47/9/2286.