Stroke

CLINICAL AND POPULATION SCIENCES

Correlation Between Computed Tomography-Based Tissue Net Water Uptake and Volumetric Measures of Cerebral Edema After Reperfusion Therapy

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BACKGROUND: Cerebral edema after large hemispheric infarction is associated with poor functional outcome and mortality. Net water uptake (NWU) quantifies the degree of hypoattenuation on unenhanced-computed tomography (CT) and is increasingly used to measure cerebral edema in stroke research. Hemorrhagic transformation and parenchymal contrast staining after thrombectomy may confound NWU measurements. We investigated the correlation of NWU measured postthrombectomy with volumetric markers of cerebral edema and association with functional outcomes.

METHODS: In a pooled individual patient level analysis of patients presenting with anterior circulation large hemispheric infarction (core 80–300 mL or Alberta Stroke Program Early CT Score ≤5) in the HERMES (Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke trials) data set, cerebral edema was defined as the volumetric expansion of the ischemic hemisphere expressed as a ratio to the contralateral hemisphere(rHV). NWU and midline-shift were compared with rHV as the reference standard on 24-hour follow-up CT, adjusted for hemorrhagic transformation and the use of thrombectomy. Association between edema markers and day 90 functional outcomes (modified Rankin Scale) was assessed using ordinal logistic regression.

RESULTS: Overall (n=144), there was no correlation between NWU and rHV (r_s=0.055, *P*=0.51). In sub-group analyses, a weak correlation between NWU with rHV was observed after excluding patients with any degree of hemorrhagic transformation (r_s=0.211, *P*=0.015), which further improved after excluding thrombectomy patients (r_s=0.453, *P*=0.001). Midline-shift correlated strongly with rHV in all sub-group analyses (r_s>0.753, *P*=0.001). Functional outcome at 90 days was negatively associated with rHV (adjusted common odds ratio, 0.46 [95% CI, 0.32–0.65]; *P*<0.001) and midline-shift (adjusted common odds ratio, 0.85 [95% CI, 0.78–0.92]; *P*<0.001) but not NWU (adjusted common odds ratio, 1.00 [95% CI, 0.97–1.03]; *P*=0.84), adjusted for age, baseline National Institutes of Health Stroke Scale, and thrombectomy. Prognostic performance of NWU improved after excluding patients with hemorrhagic transformation and thrombectomy (adjusted odds ratio, 0.90 [95% CI, 0.80–1.02]; *P*=0.10).

CONCLUSIONS: NWU correlated poorly with conventional markers of cerebral edema and was not associated with clinical outcome in the presence of hemorrhagic transformation and thrombectomy. Measuring NWU postthrombectomy requires validation before implementation into clinical research. At present, the use of NWU should be limited to baseline CT, or follow-up CT only in patients without hemorrhagic transformation or treatment with thrombectomy.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: hemorrhage ■ iodine ■ infarction ■ reperfusion ■ thrombectomy

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Nonstandard Abbreviations and Acronyms

cOR	common odds ratio
HERMES	Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke
mRS	modified Rankin Scale
NWU	net water uptake
rHV	relative hemispheric volume ratio

Malignant cerebral edema is a life-threatening complication of large hemispheric infarction with limited treatments available.[1,2] In the recent Stroke Treatment Academic Industry Roundtable X recommendations on future cytoprotective therapies research, establishing accurate imaging biomarkers of cerebral edema has been identified as a key priority in the development of novel adjunct antiedema treatments.[3]

Midline-shift is a widely used measure of edema in clinical practice and correlates well with increased intracranial pressure, poor outcome, and early mortality from malignant infarction.[4–8] Alternatively, direct volumetric quantification of tissue swelling by comparing interhemispheric volumes correlates with histological water content in animal stroke models and has been used as a reference standard for cerebral edema in preclinical studies.[9–11] Relative hemispheric volume increase has also been shown to be superior to midline-shift in prognostic performance in 2 independent analyses of recent international multicenter randomized clinical trials.[8,12]

Net water uptake (NWU) is an alternative recently described imaging biomarker of cerebral edema that is increasingly used in stroke research.[13–16] NWU quantifies the reduction in Hounsfield units on unenhanced-computed tomography (CT) of the infarct as a nonvolumetric measure of pathological water uptake and was first validated in vivo on pretreatment admission CT in patients presenting within 12 hours of middle cerebral artery infarcts before thrombectomy became standard practice.[17] The method is based on the inverse relationship between water content and Hounsfield units that was established in vitro with varying dilutions of iodine. The accuracy of this metric is, therefore, highly susceptible to radio-opaque artifacts.

Postthrombectomy hyperdensity from hemorrhagic transformations and contrast staining occur in up to 84% of follow-up CT.[18] Even in the absence of obvious hyperdensity, visually inapparent iodine contrast staining after thrombectomy has been shown to substantially alter NWU measurements.[19] Although NWU has not been validated in the postreperfusion setting to account for these phenomena, this metric has been increasingly applied to post-thrombectomy follow-up CT without accounting for patients with postthrombectomy hemorrhage or contrast staining.[14–16]

We aimed to investigate the accuracy of NWU on follow-up CT after treatment with or without hemorrhagic transformation and the use of thrombectomy by examining its correlation with conventional volumetric-orientated measures of cerebral edema. We hypothesized that hemorrhagic transformation and thrombectomy would adversely affect the validity of NWU on follow-up imaging.

METHODS

Patients presenting with large hemispheric infarction who had follow-up CT at 24-hours derived from an individual patient-level meta-analysis of 7 randomized controlled trials comparing thrombectomy versus medical therapy in anterior circulation ischemic stroke published between January 1, 2015, and May 31, 2017 (HERMES [Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke trials] collaboration) were included.[20] Large hemispheric infarction was defined on baseline diffusion weighted imaging or CT-perfusion as core volume 80 to 300 mL, or CT-Alberta Stroke Program Early CT Score ≤5 on unenhanced-CT if CT-perfusion or diffusion weighted imaging were not performed.[20] Patients with core volume <80 mL irrespective of Alberta Stroke Program Early CT Score, and those with neurosurgical procedure performed within 24 hours (n=3) were excluded. The details of the HERMES collaboration initiation, methodology of meta-analysis search strategy, individual participant data gathering and checking, and qualitative assessment of between-trial differences including patient eligibility and assessment of bias have been previously reported.[21] Clinical data were extracted and pooled by the study statistician. A flow diagram for data inclusion is reported in Figure S1. All participants gave written consent. Each study was approved by respective ethics committees.

Anonymized study data are available on request to the VISTA-Endovascular data repository. This study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Imaging and Statistical Analysis

Imaging data were de-identified and pooled for analysis. Cerebral edema was defined as the volumetric expansion of the ischemic hemisphere relative to the contralateral hemisphere (rHV) obtained by manual segmentation of the hemispheres to exclude sulci and cerebrospinal fluid spaces, and expressed as a ratio where >1 represents swelling of the ischemic hemisphere (Figure 1).[8,22]

Midline-shift and NWU were compared with rHV as the reference standard on follow-up unenhanced-CT at 24 hours.[8–11,22] Midline shift in millimeters was measured at the level of maximal lateral displacement of medial structures. NWU was measured in accordance with the methodology previously reported.[14,16,17,23] Briefly, the ischemic lesion was manually segmented with the resultant region-of-interest reflected on to the contralateral hemisphere as a homolog for interside HU

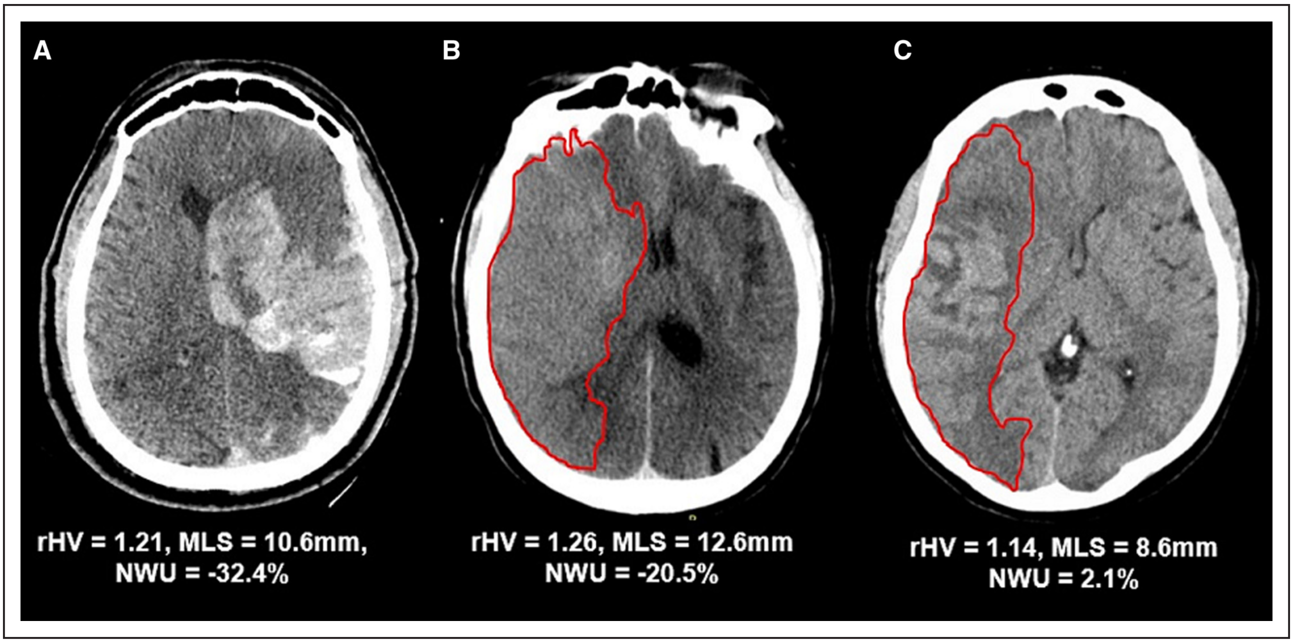

Figure 1. Comparative measures of cerebral edema.

Relative hemispheric volume ratio was derived by manual segmentation of the ipsilateral and contralateral hemisphere volume and expressed as a ratio. Midline shift (MLS) in millimeters was measured at the level of maximal lateral displacement of medial structures. Net water uptake (NWU) was derived by first calculating mean Hounsfield unit (D) of the infarct lesion and a contralateral homolog for the voxels with Hounsfield unit 20–80. NWU is calculated according to the equation: % NWU=$(1-_{D_{ischemic}/D_{normal}})\times100$. rHV indicates relative hemispheric volume.

comparison. Voxels with Hounsfield unit <20 or >80 were excluded from analysis. Mean lesional Hounsfield unit within the paired region-of-interest were calculated ($D_{ischemic}$ and D_{normal}). NWU was calculated according to the equation: % NWU=(1−Dischemic /Dnormal)×100 (Figure 1).

Successful reperfusion was defined as a core-lab adjudicated expanded Thrombolysis in Cerebral Infarction score 2b-3 on completion of thrombectomy. Hemorrhagic transformation was scored according to the European Cooperative Acute Stroke Study II classification.[24]

Prognostic performances of rHV, NWU, and midline-shift were assessed in multivariable ordinal logistic regression analysis with ≥1 point reduction in 90-day modified Rankin Scale (mRS) as the outcome, adjusted for age, National Institutes of Health Stroke Scale and treatment modality, and expressed as an unadjusted and adjusted common odds ratio (cOR) from ordinal logistic regression. Mixed-effects modeling was used for all regression analyses. Spearman rho (σ) was used to assess correlation as rHV, midline-shift, and NUW were nonparametrically distributed. Analyses were stratified for hemorrhagic transformation and thrombectomy sequentially. Differences between groups were analyzed with Kruskal-Wallis test. A 2-tailed *P* value of <0.05 was considered significant. Statistical analysis was performed using SPSS (IBM.v26).

Additional sensitivity analyses were performed to test the correlation between NWU and percentage of volumetric swelling per mL infarct volume,[17] the association between NWU and functional outcome with sex, pretreatment ischemic core lesion volume and study origin as added covariates, and the association between NWU, rHV, and midline shift with outcome with mRS score of 0 to 1 and mRS score of 0 to 2 categories merged (Supplemental Material).

RESULTS

Among 144 patients analyzed, thrombectomy was performed in 67 (46.5%) patients, of whom 44 (65.7%) had successful reperfusion. Hemorrhagic transformation of any subtype was identified in 70 (48.6%) patients with 12 having parenchymal hematoma (Table 1). Thrombectomy was associated with reduced NWU (16.6% versus 19.3%, *P*=0.005) but not with rHV (1.2 versus 1.1, *P*=0.15) or midline-shift (5.1 versus 5.6 mL, *P*=0.60) on 24-hour CT.

Correlation Between Measures of Cerebral Edema

There was no correlation between NWU and rHV in the overall cohort (n=144, rho=0.055, *P*=0.509). Negative NWU values were observed in 14 patients (median NWU, −14.5%; rHV, 1.28; midline shift, 12.3 mm), 10 of whom had parenchymal hematoma, 3 had petechial hemorrhagic infarction, and 1 had pure contrast staining without hemorrhagic transformation (Figure 2A through 2C). Excluding PH (n=132, rho=0.211; *P*=0.015) and hemorrhagic transformation of any kind (n=74, rho=0.400; *P*=0.001) improved the correlation between NWU and rHV.

Among patients who underwent thrombectomy, NWU did not correlate with rHV, even when patients with hemorrhagic transformation were excluded (n=25, rho=0.358; *P*=0.078). Correlation between NWU and rHV were

Table 1. Clinical and Radiological Characteristics of Patient Presenting With Large Hemispheric Infarction

Characteristic	Medical treatment cohort (n=71)	Thrombectomy cohort (n=73)	*P* value
Age, y, median, IQR	66.3 (55.9–75.0)	63.1 (51.0–73.0)	0.16
Gender, male, % (n)	60.6% (43/71)	75.3% (55/73)	0.074
NIHSS at baseline, median, IQR	20.0 (17.0–22.0)	19.0 (17.0–22.0)	0.37
ASPECTS at baseline, median, IQR	4.0 (3.0–5.0)	5.0 (4.0–5.0)	0.095
Onset to baseline imaging, min, median, IQR	123.0 (90.8–182.1)	131.5 (82.5–188.8)	0.97
Onset to follow-up imaging, h, median, IQR	25.7 (21.9–112.8)	28.3 (22.1–164.3)	0.18
Midline shift, mm, median, IQR	5.6 (2.8–8.2)	5.1 (3.1–9.3)	0.60
Net water uptake, %, median, IQR	19.3 (14.8–22.4)	16.6 (9.7–20.6)	0.005
Relative hemispheric volume, median, IQR	1.1 (1.1–1.2)	1.2 (1.1–1.3)	0.15
Final infarct volume, mL, median, IQR	224.9 (150.5–349.1)	214.0 (95.2–294.5)	0.28
Parenchymal hematoma, % (n)	5.6% (4/71)	11.0% (8/73)	0.37
modified Rankin Scale at 90 days			0.009
0	1.4% (1/70)	1.4% (1/73)	
1	1.4% (1/70)	5.5% (4/73)	
2	5.7% (4/70)	8.2% (6/73)	
3	11.4% (8/70)	20.5% (15/73)	
4	20.0% (14/70)	26.0% (19/73)	
5	14.3% (10/70)	8.2% (6/73)	
6	45.7% (32/70)	30.1% (22/73)	

ASPECTS indicates Alberta Stroke Program Early CT Score; IQR, interquartile range; and NIHSS, National Institutes of Health Stroke Scale.

consistently stronger in patients receiving medical treatment compared with thrombectomy, regardless of the presence of hemorrhagic transformation. Excluding both hemorrhagic transformation and thrombectomy had an additive effect in improving the correlation between NWU and rHV (n=49, rho=0.455; *P*=0.001). A similar pattern was observed for the correlations between NWU and midline shift (Table 2).

Midline-shift correlated strongly with rHV in all subgroup analyses, regardless of the presence of hemorrhagic transformation or treatment modality (rho>0.753; *P*=0.001; Table 3).

Association Between Edema Markers and 3 Months Outcome

In the overall cohort (n=144), rHV (cOR, 0.46 [95% CI, 0.32–0.65]; *P*<0.0001) and midline-shift (cOR, 0.85 mm [95% CI, 0.78–0.92]; *P*=0.0002) but not NWU (cOR, 1.00 [95% CI, 0.97–1.03]; *P*=0.829) were associated with day 90 mRS adjusted for age, baseline National Institutes of Health Stroke Scale, and thrombectomy. Prognostic performance of NWU tended to improve after excluding patients with hemorrhagic transformation or who treated with thrombectomy (n=49; cOR, 0.90 [95% CI, 0.80–1.02]; *P*=0.095).

Sensitivity analyses testing the correlation between NWU and volumetric swelling per mL infract volume, and the association between NWU with 3-months outcome in an expanded model including sex, infarct lesion volume, and trial yielded the same findings (Supplemental Material).

DISCUSSION

In patients with large hemispheric infarction undergoing reperfusion treatment, NWU poorly correlated with validated volumetric markers of cerebral edema (rHV and midline shift) on follow-up CT and was not associated with clinical outcome, especially in the presence of hemorrhagic transformation and thrombectomy. In comparison, midline-shift was independently associated with 3-month outcome and strongly correlated with swelling volumes, regardless of hemorrhagic transformation and treatment modality. Our data suggest NWU may have limited accuracy on follow-up imaging after endovascular reperfusion, possibly due to hemorrhagic transformation and occult contrast staining.

In comparison with rHV and midline-shift, 2 standard biomarkers of edema used in experimental studies and clinical practice, respectively, the accuracy of NWU was suboptimal in the presence of hemorrhagic transformation and thrombectomy. Hemorrhagic transformation likely artifactually elevated mean Hounsfield unit of the measured region-of-interest. This has been previously recognized as an intrinsic limitation of the NWU method. However, exclusion of hemorrhagic transformation on follow-up imaging at a patient or voxel-level has not been consistently

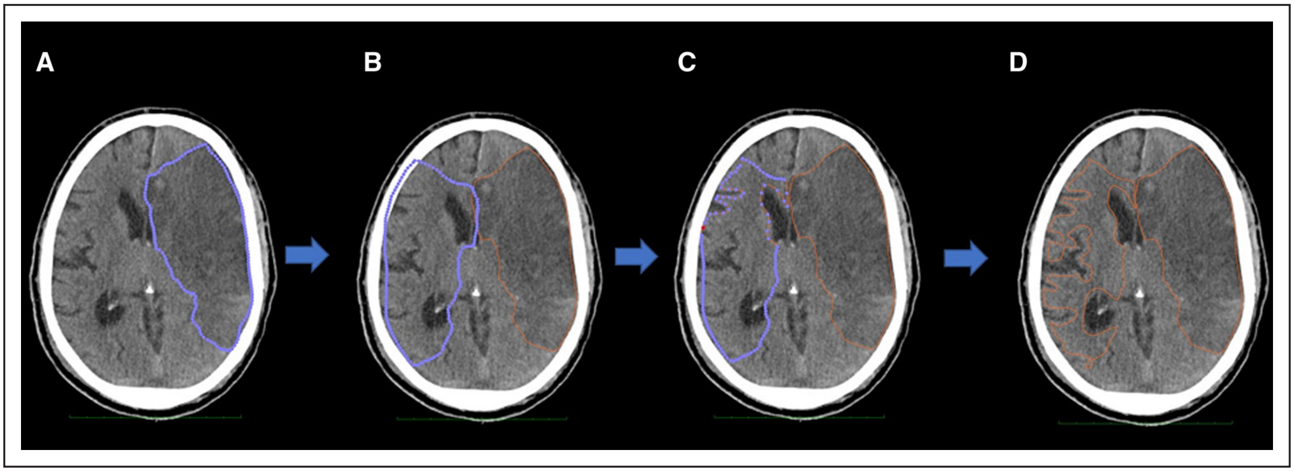

Figure 2. Representative cases of disproportional net water uptake (NWU).
A, Hemorrhagic transformation elevates CT attenuation resulting in negative NWU, implying less edema despite 21% increase tissue volume and mass effect. **B**, Diffuse contrast staining similarly resulted in negative NWU. **C**, Normal NWU despite significant swelling on relative hemispheric volume (rHV) and midline shift (MLS) was also seen in cases with less overt hemorrhage or contrast staining.

applied across studies using NWU. For example, patients with hemorrhagic transformation were excluded from analysis in the initial papers describing the methodology of NWU[17,25] and some subsequent studies[16,26,27] but were included in other analyses.[14,15] However, we demonstrated for the first time that thrombectomy also diminished the accuracy of NWU even when visible hemorrhagic transformation was excluded, possibly due to retained iodine contrast that was visually inconspicuous. Overt contrast staining postthrombectomy can be detected in up to 55% to 85% of patients but is presumed to be exclusive to early postthrombectomy imaging.[28] However, a recent study using serial dual-energy CT postthrombectomy showed only half of contrast staining seen on early postthrombectomy resolved by 24 hours.[29] Moreover, 10% to 27% of patients overall have evidence of residual contrast on routine 24-hour CT brain.[28–30] Although excluding patients with visible hyperdensity artefacts may improve accuracy of NWU, the accuracy and interrater agreement of subjective visual assessment of blood or contrast and manual segmentation to exclude voxels contaminated by hyperdense material is not established. Restricting its application to patients without hemorrhagic transformation would also substantially reduce the method's generalizability on follow-up imaging by excluding up to 50% of patients.[18] As blood-brain barrier disruption is central to the pathogenesis of both hemorrhagic transformation and cerebral edema,[31] restricting edema analysis to patients without hemorrhagic transformation may exclude the very population most at risk of progressive edema. Furthermore, the presence of recognizable contrast staining at 24 hours suggests incomplete iodine washout is likely even in tissue

Table 2. Correlation Between Net Water Uptake Versus Relative Hemispheric Volume and Versus Midline Shift in Different Subgroups

Versus relative hemispheric volume			
	No exclusions for hemorrhagic transformations	Excluding parenchymal hematoma	Excluding hemorrhagic transformations of any kind
Overall cohort	0.055 (*P*=0.509) n=144	0.211 (*P*=0.015)* n=132	0.400 (*P*<0.001)* n=74
Thrombectomy cohort	−0.043 (*P*=0.728) n=67	0.098 (*P*=0.456) n=60	0.358 (*P*=0.078) n=25
Medical treatment cohort	0.156 (*P*=0.175) n=77	0.311 (*P*=0.008)* n=72	0.455 (*P*=0.001)* n=49
Versus midline shift			
Overall cohort	0.065 (*P*=0.438) n=144	0.243 (*P*=0.005)* n=132	0.454 (*P*<0.001)* n=74
Thrombectomy cohort	−0.053 (*P*=0.521) n=67	0.109 (*P*=0.726) n=60	0.368 (*P*=0.110) n=25
Medical treatment cohort	0.168 (*P*=0.102) n=77	0.357 (*P*<0.001)* n=72	0.502 (*P*<0.001)* n=49

*P<0.05.

Table 3. Correlation Between Midline Shift and Relative Hemispheric Volume in Different Subgroups

	No exclusion for hemorrhagic transformations	Excluding parenchymal hematoma	Excluding hemorrhagic transformations of any kind
Overall cohort	0.805 (*P*<0.001)* n=144	0.792 (*P*<0.001)* n=132	0.784 (*P*<0.001)* n=74
Thrombectomy	0.803 (*P*<0.001)* n=67	0.789 (*P*<0.001)* n=60	0.836 (*P*<0.001)* n=25
Medical treatment	0.808 (*P*<0.001)* n=77	0.792 (*P*<0.001)* n=72	0.770 (*P*<0.001)* n=49

*$P<0.05$.

that appears unaffected, confounding quantitative Hounsfield unit assessment. In a case series of 10 patients undergoing conventional unenhanced CT and dual energy CT at 24-hours postthrombectomy, 2 patients (20%) showed substantial disparity in NWU measurements (36% and 24%) between the CT modalities.[19] Further studies in a larger patient cohort using dual energy CT to evaluate for the presence of occult iodine contrast staining on postthrombectomy CT will help clarify the reliability of NWU on postthrombectomy imaging.

A previous study found NWU reduction postthrombectomy to be associated with recanalization and improved mRS, and interpreted this as evidence that edema reduction mediated the benefit of thrombectomy.[14] In this study, we also found that thrombectomy was associated with less NWU. However, we showed NWU was not associated with functional outcome when thrombectomy was included as a covariate, suggesting the reduction in NWU after thrombectomy may be a radiological epiphenomenon of limited clinical relevance, reflecting exposure to angiographic contrast rather than indicating a biological treatment effect (Figure 2B and 2C). As such, the previously reported relationship between improved mRS and reduced NWU may reflect the benefit of having undergone thrombectomy instead of a reduction in tissue edema. In another study, postthrombectomy NWU has been compared with baseline NWU measurements on admission CT and a reduction in NWU interpreted as an improvement or reversal of edema.[14,26,27] Our data on the influence of iodine and hemorrhagic transformation also challenges such interpretation.

NWU correlated poorly with volumetric measures of cerebral edema which were superior to NWU as prognostic markers in this group of patients with large hemispheric infarction, even when patients with hemorrhagic transformation and thrombectomy were excluded. Our findings suggest the clinical impact of edema is primarily related to tissue swelling and mass effect. Volumetric measures reflect parenchymal swelling which is the fundamental mechanism of raised intracranial pressure, tissue compression, and herniation in malignant edema, as described by the Munro-Kellie doctrine. Novel volumetric measures that have shown promise include cerebrospinal fluid-based assessments, but hemispheric volumes and midline-shift remain the most widely used in research and clinical practice.[22,32,33] Our data support the use of volumetric measures of edema over NWU on follow-up imaging, especially in patients most susceptible to malignant cerebral edema with mass effect. Methodologically, we also encountered difficulties in calculating NWU when there is gross distortion of normal brain symmetry which compromised the ability to derive an accurate mirror region with comparable gray versus white matter composition (Figure 3). Conversely, a limitation of volumetric measures of edema is that they may be less sensitive when infarct volumes are small. Therefore, NWU measured on follow-up may still be useful as an intermediate end point to assess a biological effect of anti-edema agents in early phase clinical trials where there is more heterogeneity in stroke volumes of recruited patients.[13] Importantly, such results would only be valid in patients who did not have thrombectomy and had hemorrhagic transformation excluded from analysis. The limitations of NWU reported in this study are specific to posttreatment follow-up imaging. In comparison, NWU measured on admission has been shown to predict malignant edema development and may assist clinical decision making for early decompressive surgery.[23]

In addition to the technical limitations of NWU, another explanation for the observed discrepancy between volumetric and nonvolumetric edema is that tissue water excess and swelling may peak at different times, and that cross-sectional assessments as in this study may fail to capture the trajectories of these 2 distinct pathological processes. Additional factors such as cell density (reduced in leukoaraiosis) and tissue compliance may also be implicated in the biology of how histological tissue water influx evolves into macroscopic tissue expansion.[34,35]

Limitations

We restricted our analysis to patients presenting with large hemispheric infarction which limits overall generalizability. Although this is a small population, this is the specific patient population is which malignant cerebral edema is most clinically relevant. Second, we did not measure pretreatment and posttreatment change in NWU as edema development is likely to have already started at the time of presentation in this cohort. Pretreatment imaging hence would not be a true representation of premorbid baseline status before ischemia. Third, follow-up imaging performed at 24 hours is earlier than the peak of vasogenic edema at 48 to 72

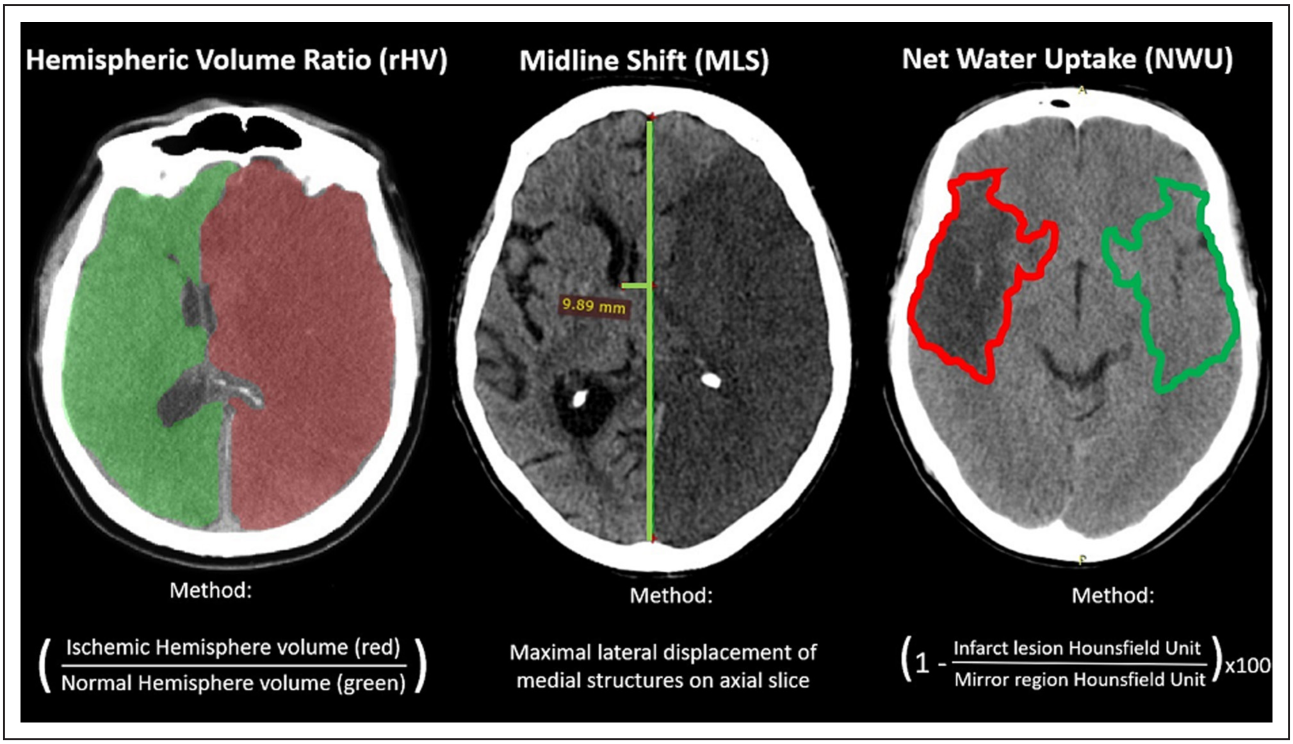

Figure 3. Anatomic distortion and net water uptake calculation.
A patient with left middle cerebral artery (MCA) large hemispheric infarction with mass effect and hemorrhagic infarction type 1 is shown. **A**, The left MCA territory ischemic lesion was manual segmented. **B**, The resultant region-of-interest was then reflected onto the normal right hemisphere. **C** and **D**, Manual adjustment of the mirror region-of-interest contour to account for midline shift distortion (**C**) and pathological sulcal effacement (**D**) before lesional Hounsfield unit was calculated.

hours.[1] However, the timing of follow-up scan in our population is comparable to recent studies using NWU for the purpose of comparing edema imaging markers. Fourth, as a secondary analysis of the pooled individual patient level meta-analysis from 7 multicenter randomized controlled trials, this study comprises imaging data acquired from a number of stroke centers in which interscanner variations may influence Hounsfield unit measurements. However, NWU represents a ratio of lesional density versus the control mirror region in the normal hemisphere which mitigates against interscanner variation. NWU has also been previously applied to multicenter clinical trial data sets.[13] Finally, contrast and blood may also enter the subarachnoid space and potentially obscure sulci, leading to underestimation of NWU and overestimation of rHV. However, the results using midline shift (which is unaffected by subarachnoid blood and iodine) were consistent with rHV. Given the post hoc design of the study, further studies to validate our results will be needed.

Conclusions

In patients receiving reperfusion treatment for large hemispheric infarction with large vessel occlusion, NWU on 24-hour CT brain did not correlate with standard volumetric measures of cerebral edema and was not associated with functional outcome. Our study suggests that rHV or midline shift increase are better markers of cerebral edema in postthrombectomy patients, and that NWU measurements postthrombectomy may be affected by hemorrhagic transformation and exposure to iodinated contrast following endovascular thrombectomy. Our findings suggest that investigators should be cautious about the interpretation of NWU after thrombectomy as an imaging end point. Until NWU measurements can be confidently validated on post-intervention imaging, the use of NWU should be limited to baseline CT, or follow-up CT only in patients without hemorrhagic transformation or treatment with thrombectomy.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S4
Figure S1

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