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Short communication

Automated assessment of early hypoxic brain edema in non-enhanced CT predicts outcome in patients after cardiac arrest☆

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ABSTRACT

Introduction: Early prediction of potential neurological recovery in patients after cardiac arrest is challenging. Recent studies suggest that the densitrometic gray-white matter ratio (GWR) determined from cranial computed tomography (CT) scans may be a reliable predictor of poor outcome. We evaluated an automated, rater independent method to determine GWR in CT as an early objective imaging predictor of clinical outcome.
Methods: We analyzed imaging data of 84 patients after cardiac arrest that underwent noncontrast CT within 24 h after arrest. To determine GWR in CT we applied two methods using a recently published automated probabilistic gray-white matter segmentation algorithm (GWR_aut) and conventional manual measurements within gray-white regions of interest (GWR_man). Neurological outcome was graded by the cerebral performance category (CPC). As part of standard routine CPC was assessed by the treating physician in the intensive care unit at admission and at discharge to normal ward. The performance of GWR measures (automated and manual) to predict the binary clinical endpoints of poor (CPC3–5) and good outcome (CPC1–2) was assessed by ROC analysis with increasing discrimination thresholds. Results of GWR_aut were compared to GWR_man of two raters.
Results: Of 84 patients, 55 (65%) showed a poor outcome. ROC curve analysis revealed reliable outcome prediction of GWR_aut (AUC 0.860) and GWR_man (AUC 0.707 and 0.699, respectively). Predictive power of GWR_aut was higher than GWR_man by each rater ($p = 0.019$ and $p = 0.021$, respectively) at an optimal cut-off of 1.084 to predict poor outcome (optimal criterion with 92.7% sensitivity, 72.4% specificity). Interrater reliability of GWR_man by intra-class correlation coefficient (ICC) was moderate (0.551).
Conclusion: Automated quantification of GWR in CT may be used as an objective observer-independent imaging marker for outcome in patients after cardiac arrest.

Introduction

Recent advances in emergency medicine and resuscitation management such as mild therapeutic hypothermia have increased the number of survivors of cardiac arrest.[1,2] However cognitive and neurologic outcomes are still poor in patients following resuscitation, especially in initially comatose patients.[3] Early assessment of the potential of neurological recovery in comatose cardiac arrest survivors remains challenging.[4,5] As the number of survivors of cardiac arrest increase and more effective therapies become available the need to identify those patients who remain comatose with likely good neurologic outcome becomes essential.[4,6] Recent studies suggest that a reduced GWR in cranial computed tomography (CT) scans indicating hypoxic brain edema may be an early predictor of poor outcome in cardiac arrest patients.[4,7–9] However, in these studies GWR measurements were not objective and only

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assessed visually or by manual placement of regions of interest (ROI) in gray and white matter.

We hypothesise that an observer independent method to determine in CT may be superior to the manual ratings limited by rater variability. We therefore present an automated method to determine GWR in CT as an early objective imaging predictor of clinical outcome and compared the results to conventional manual measurements.

Methods

Study population

Between 1-2011 and 12-2014 we consecutively included 87 data sets acquired from comatose cardiac arrest patients who underwent non-contrast spiral CT of sufficient quality within 24 h after arrest. Electronic patient records were anonymized prior to analysis and our study design was entirely retrospective. In this setting, the need for patient consent was waived by our institutional review board. In our department, routine neurological evaluation of patients after cardiac arrest consists of laboratory, electrophysiological and clinical examinations including the Cerebral Performance Category score (CPC).[10] The CPC was assessed by the treating physician in the intensive care unit (ICU) at admission and at the time of discharge to normal ward. Neurological evaluation included pupillary light reflex (PLR), corneal reflex (CR) (day 3) and Glasgow coma scale (GCS) (days 1 and 3). Exclusion criteria were haemorrhage or ischemic infarction in CT.

GWR determination

For automated GWR determination we employed a recently published brain segmentation algorithm to decompose the CT density of brain into tissue-specific components.[11] In brief, the algorithm uses normalized probabilistic maps of white matter (WM) and gray matter (GM) in standard space derived from partial tissue segmentations of 600 unsuspicious brain MRIs (3.0 T, T1-3D-Turbo-Field-Echo). The voxel-specific partial tissue component (tissue probability) in CT space was obtained by precise non-linear deformation of tissue probability maps in standard space to the individual CT space using a custom CT reference image.[11] The tissue-specific density within GM- and WM-space was then determined by the mean of all voxel densities weighted by probabilistic GM- and WM-content, respectively (Eq. (1)).[11] All CT image operations were performed using the FMRIB Software Library v5.0, Oxford, UK.

$$\frac{\sum(\mathrm{HUxyz} \times \mathrm{Pxyz[tissue]})}{\sum(\mathrm{Pxyz[tissue]})} \qquad (1)$$

(HUxyz = density of voxel xyz in Hounsfield units; Pxyz = partial tissue component at voxel xyz for GM or WM, respectively).

GWR_aut was then calculated as the ratio between the mean CT density within GM- and WM-space (Fig. 1). Manual ratings by ROI placement were performed independently by two readers who were blinded to outcome. ROI measurements were performed under a standardized protocol and included bilateral manual placement of circular ROIs (area = 0.1 cm^2) in the putamen and the posterior limb of internal capsule.[8]

Statistical analysis

Univariable distribution of metric variables is described by median and interquartile range. For categorical data, absolute and relative frequencies are given.

Patients with good (CPC of 1–2) versus poor (CPC of 3–5) outcome were compared by Mann–Whitney *U* test for metric outcome variables and by chi-square test for categorical outcome variables. The performance of GWR measures (automated and manual) to predict poor and good outcome was assessed by ROC analysis with increasing discrimination thresholds. Pairwise ROC comparisons between GWR_aut and both GWR_man were performed by assessing differences in the areas under the empirical ROC curves.[12] Interrater reliability of GWR_man was quantified using intra-class correlation coefficient (ICC).

No adjustment for multiple testing was performed and “significance” refers to local statistical significance defined as a local,

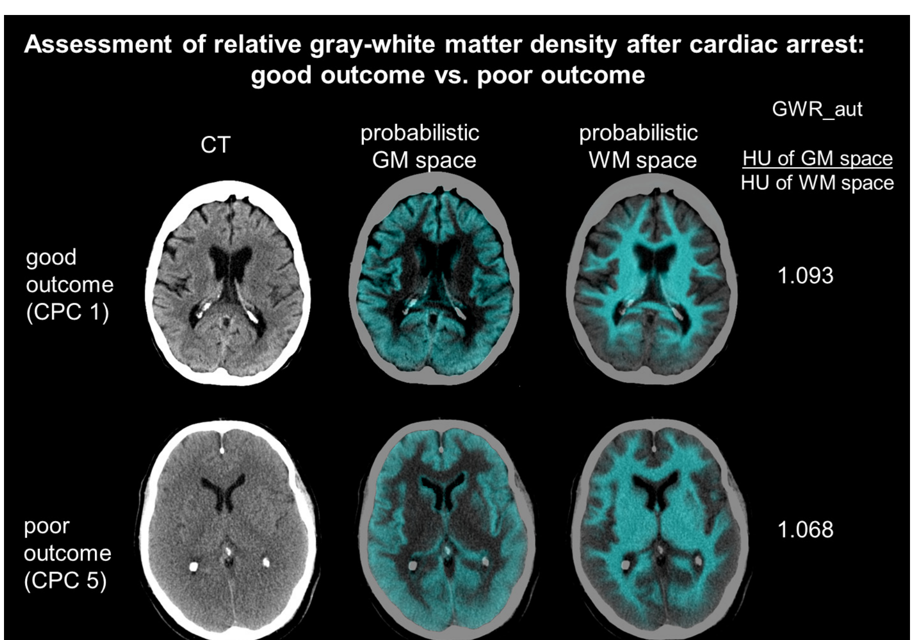
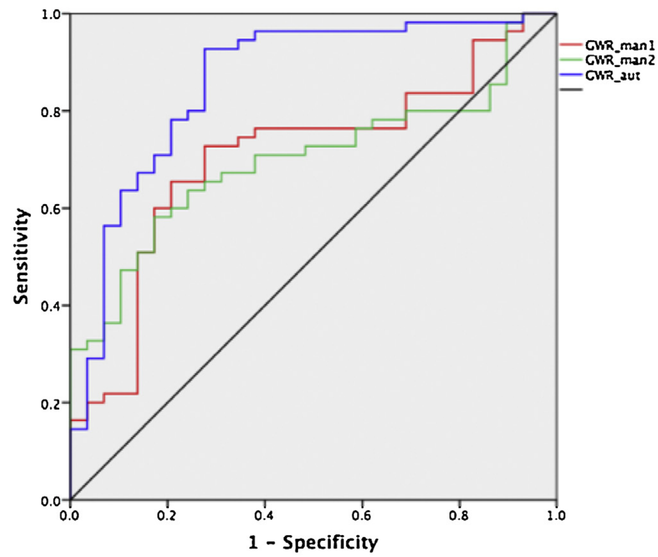


Fig. 1. Tissue specific decomposition of a native CT to determine GWR in global cerebral hypoxia. Automated probabilistic assessment of gray matter (middle column) and white matter (right column) in computed tomography (left column): GWR's in two patients resuscitated after cardiac arrest with good outcome versus poor outcome (lower row).



	AUC	95%CI	Optimal cut-off	Sensitivity	Specificity	PPV	NPV
GWR_man1	0.707	0.590-0.824	1.251	72.7	72.4	83.3	58.3
GWR_man2	0.699	0.588-0.810	1.226	58.2	82.8	86.5	51.1
GWR_aut	0.860	0.770-0.950	1.084	92.7	72.4	86.4	84.0

Fig. 2. ROC-analysis for prediction of poor outcome using different GWR-methods. GWR_man1/2 = manual ROI-based GWR (Rater 1/2); GWR_aut = automated Ratio of gray matter and white matter; area under the curve (AUC); 95% confidence interval (CI); PPV = positive predictive value and NPV = negative predictive value.

unadjusted *p*-value below 0.05. Statistical analyses were performed in SPSS version 22 (IBM Corporation, Armonk NY) and in SAS 9.4 (SAS Institute, Cary NC).

Results

Of 87 screened patients after cardiac arrest, one was excluded with hemorrhage and two with territorial infarct in CT. Of the remaining 84 patients, 55 (65%) revealed a poor and 29 (34.5%) a good outcome. The median time interval between cardiac arrest and CT-image was 8.4 h and did not differ significantly between the two outcome groups. Clinical findings (PLR, CR and GCS) on day 3 after cardiac arrest differed significantly between the two outcome groups ($p \leq 0.0001$). In contrast, the GCS on day 1 was not significantly different between the groups ($p = 0.122$) (Table 1).

Automated tissue-specific segmentation of CT was reliable in 84 cases. Fig. 1 exemplary illustrates the automated assessment of GWR in CT in two patients with poor and good outcome, respectively. Tissue density ratio (GWR_aut) and mean density of GM but not WM were different between the outcome groups (Table 1).

Table 1
Demographic characteristics.

Characteristics	All (*n* = 84)	Good outcome (CPC 1–2) (*n* = 29)	Poor outcome (CPC 3–5) (*n* = 55)	*p*-value
Age (y), median (IQR)	62 (49; 62)	68 (55; 74)	58 (49; 72)	0.177
Female, *n* (%)	25 (29.8%)	8 (27.6%)	17 (30.9%)	0.751
Primary cause of arrest				0.479
• Cardiac, *n* (%)	33 (39.3%)	10 (34.5%)	23 (41.8%)	
• Respiratory, *n* (%)	12 (14.3%)	3 (10.3%)	9 (16.4%)	
• Other, *n* (%)	39 (46.4%)	16 (55.2%)	23 (41.8%)	
Shockable rhythm	24 (28.6%)	11 (37.9%)	13 (23.9%)	0.168
GCS_Day0, median (IQR)	3 (0)	3 (1)	3 (0)	0.057
Day 3 findings				
• GCS_Day3, median (IQR)	3 (3)	7 (11)	3 (1)	<0.0001
• PLR absent, *n* (%)	32 (38.1%)	0 (0.0%)	32 (58.2%)	<0.0001
• CR absent, *n* (%)	33 (39.3%)	0 (0.0%)	33 (60.0%)	<0.0001
Post cardiac arrest CT (<24 h)				
• Time interval between cardiac arrest and CT-image in h	8.4 (5; 14.5)	8.3 (6.2; 13.4)	7.5 (5.1; 14.3)	0.364
• WM_HU_aut, median (IQR)	33.7 (32.8; 35.6)	33.9 (32.9; 35.8)	33.4 (32.6; 35.3)	0.569
• GM_HU_aut, median (IQR)	36.5 (35.0; 38.1)	37.9 (36.0; 39.2)	35.7 (34.2; 37.0)	0.011
• GWR_aut, median (IQR)	1.07 (1.05; 1.1)	1.10 (1.08; 1.12)	1.06 (1.05; 1.08)	<0.0001

WM_HU_aut = probabilistic global WM-density in Hounsfield Units, GM_HU_aut = probabilistic GM-density; GWR_aut = probabilistic Ratio of gray matter and white matter

According to AUC after ROC curve analysis, both, GWR_aut and GWR_man were significant imaging parameters to predict good or poor outcome (Fig. 2). Pairwise AUC comparison revealed that the predictive power of GWR_aut was higher than GWR_man by each rater ($p = 0.019$ and $p = 0.021$, respectively) at an optimal cut-off of 1.084 (Table I in the online – only data supplement). Interrater reliability of GWR_man by intra-class correlation coefficient (ICC) was moderate (0.551).

Discussion

Different studies suggest GWR measurement in CT as an imaging marker for clinical outcome after cardiac arrest.[7–9,13,14] However, in these studies GWR measurements were not objective and only assessed visually or by manual placement of ROI's in gray and white matter, or by semiautomated atlas based analysis in selected brain areas. In contrast, our method allows a precise and objective measurement of GWR using CT densitometric information of all brain voxel according to decomposed partial tissue components. Our results suggest that the automated algorithm for GWR assessment is superior to manual ROI-based GWR measurement for outcome prediction. This may be explained by the clear advantage that the observer-independent analysis of GWR_aut eliminates interrater variability especially in comparison to inexperienced observers. In addition, the algorithm observes the global GWR and not only isolated anatomical locations which may be the reason for the higher predictive power of GWR_aut compared to GWR_man.

Early assessment of the potential of neurological recovery in comatose cardiac arrest survivors is essential. As more effective therapies become available there is a need to early identify those patients who are comatose with prospect for neurological improvement.[4,6]

Possible limitations of our study are due to the retrospective design. Our clinical endpoint of poor CPC at discharge may be subject to error due to later improvement. Furthermore, our method is limited to the specific image algorithm for tissue segmentation. Variable CT imaging protocols have not been tested.

Conclusion

The presented automated method allows an observer-independent quantification of GWR in CT with objective outcome prediction in patients after clinical cardiac arrest.

Early, rapid and automated GWR determination using CT can be a useful tool for outcome prediction aiding to an optimal clinical decision process.

Conflict of interest statement

Drs. Hanning, Sporns, Lebiedz, Niederstadt, Zoubi, Schmidt, Knecht, Heindel and Kemmling report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.resuscitation.2016.03.018.

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