The density ratio of grey to white matter on computed tomography as an early predictor of vegetative state or death after cardiac arrest

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ABSTRACT

Objectives: To evaluate whether the ratio (in Hounsfield units; HU) of grey matter (GM) to white matter (WM) on computed tomography (CT) scans taken within 24 h of resuscitation can be used as a predictor of outcome.

Methods: 28 patients who resuscitated from cardiac arrest and had head CT performed within 24 h of resuscitation were retrospectively investigated. 27 subjects with normal head CT findings served as controls. Comatose patients were divided into two groups: those with a Glasgow outcome scale (GOS) score of 3–5 (good outcome subgroup) and those with a GOS score of 1–2 (poor outcome subgroup). HU were measured in GM and WM at the level of the basal ganglia on non-contrast CT scans.

Results: The density ratio of GM to WM was significantly lower in comatose patients than in controls (mean 1.21 vs 1.32, $p<0.001$). The GM:WM ratio was significantly lower in the poor subgroup than in the good subgroup (mean 1.19 vs 1.28, $p<0.001$). Receiver operating characteristic curve analysis determined a cutoff value of a GM:WM ratio of less than 1.22 for vegetative state or death. This value predicted vegetative state or death with a sensitivity of 63%, a specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 56%.

Conclusion: The GM/WM ratio correlates with the outcome of hypoxic ischaemic encephalopathy and may be useful as an objective early predictor of vegetative state or death in comatose patients after cardiac arrest.

Only approximately 50% of cardiopulmonary resuscitation attempts are successful in restoring spontaneous circulation,[1] and most survivors of cardiac arrest are comatose after resuscitation. Moreover, family members and doctors who treat comatose patients after cardiac arrest are often faced with difficult decisions as to whether to continue intensive care management. Therefore, accurate methods of predicting patient outcome at the earliest possible time are much needed.

The majority of patients need intensive care with sedative and paralytic agents under ventilatory care and/or therapeutic hypothermia, especially during the first 24 h after the return of spontaneous circulation (ROSC). Predictors such as neurological examinations, electroencephalograms, and short latency somatosensory evoked potentials, which are influenced by these drugs and hypothermia, are thus difficult to apply within 24 h of cardiac arrest.[2–4]

Computed tomography (CT) scans of the brain are, however, not influenced by anaesthetic agents or other treatments, and CT is frequently ordered to evaluate comatose patients after cardiac arrest.[5 6] CT findings of hypoxic ischaemic encephalopathy following cardiac arrest include: a loss of difference between grey matter (GM) and white matter (WM), diffuse brain swelling and a decreased basal ganglia density.[7–9] Moreover, these findings were observed within 24 h and a few days after resuscitation and they were correlated with a poor outcome.[6–8] Recently, Torbey *et al*[5] measured the densities of the caudate nucleus and posterior limb of the internal capsule on non-contrast CT performed within 48 h of cardiac arrest and quantified the loss of GM–WM differentiation using GM to WM ratios, and they found that a ratio of less than 1.18 was 100% predictive of death. However, these CT scans were performed primarily between 24 and 48 h of ROSC.[2] We thus analysed the densities of GM and WM in Hounsfield units (HU) and calculated GM/WM ratios using CT images taken within 24 h of ROSC in order to evaluate whether these ratios predict vegetative state or death in comatose patients after cardiac arrest.

METHODS

Subjects

Between January 2003 and December 2006, 180 adult patients (⩾18 years) who had out-of-hospital cardiac arrest unrelated to trauma were brought to our emergency department. Of them, 98 patients achieved ROSC by resuscitation. We retrospectively evaluated 58 patients who survived for more than 24 h after ROSC and finally included 28 patients who satisfied the following criteria: a comatose state at least 6 h after ROSC; head CT performed within 24 h of ROSC; exclusion of intracranial haemorrhage as a cause of arrest and no previous history of neurological disease. The reasons for exclusion were as follows: lack of CT data (n = 13); cardiac arrest due to intracranial haemorrhage (n = 11); CT data beyond 24 h of ROSC (n = 3); previous history of Parkinson's disease (n = 1), brain operation (n = 1) and cerebral infarction (n = 1). The study group included 21 men and seven women ranging in age from 27 to 86 years (mean age 54.0) (table 1). The study was approved by the local ethics committee of our university hospital.

All data were collected through review of CT images and medical records pertaining to clinical presentation, patient age, gender, cause of death, witnessed collapse, bystander cardiopulmonary resuscitation, initial electrocardiogram on admission, resuscitation time, time between CT and ROSC, discharge status and Glasgow outcome

Table 1 Clinical characteristics of 28 comatose patients resuscitated from cardiac arrest

	Good subgroup	Poor subgroup	p Value
Patients, n	9	19	
Age, years (SE)	51.0 (3.5)	55.4 (3.4)	0.440
Gender, male/female	6/3	15/4	0.646
Witnessed arrest, n	6	15	0.417
Bystander CPR, n	6	10	0.687
Initial ECG on admission, n			0.379
PEA	0	1	
VF/pulseless VT	4	4	
Asystole	5	14	
Resuscitation duration, minutes (SE)	15.8 (3.6)	18.9 (3.0)	0.539
Time to CT after ROSC, hours (SE)	4.4 (1.5)	3.6 (1.2)	0.729
Cause of arrest, n			0.689
Cardiac	5	8	
Respiratory	4	11	
GOS, n			
1. Death	0	8	
2. Vegetative state	0	11	
3. Severe neurological impairment	0	0	
4. Mild to moderate neurological impairment	1	0	
5. Complete recovery	8	0	

CPR, cardiopulmonary resuscitation; CT, computed tomography; ECG, electrocardiogram; GOS, Glasgow outcome scale; PEA, pulseless electrical activity; ROSC, return of spontaneous circulation; VF, ventricular fibrillation; VT, ventricular tachycardia.

scale (GOS) score.[10] The neurological outcomes of the patients were assessed using the GOS score at the time of discharge. In addition, brain CT scans obtained during routine health examinations at our hospital were selected as controls. Patients were excluded if the head CT was read as abnormal by a radiologist. A total of 27 subjects with a normal CT reading (15 men, 12 women; mean age 47.4 years; range 24–69) were assigned to the control group. The comatose patients were divided into two groups: patients who regained consciousness (GOS 3–5; good outcome subgroup) and patients who remained unconscious or died (GOS 1–2; poor outcome subgroup).

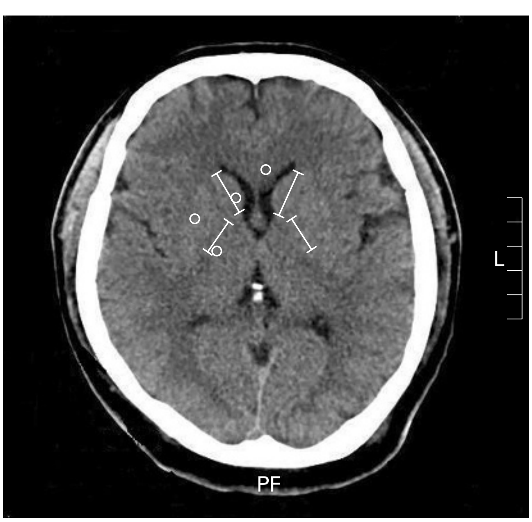

Figure 1 Head computed tomography imaging showing measurements in Hounsfield units at the basal ganglia level, in which the caudate nucleus, internal capsule, genu of the corpus callosum and sylvian fissures are all well visualised. ○, circular regions of interest (10 mm²) positioned in the caudate nucleus, putamen, posterior limb of internal capsule and genu of the corpus callosum.

Density measurements of GM and WM

CT images were obtained on a GE LightSpeed Volume Computed Tomography and a Siemens Volume Zoom. All brain CT scans were performed according to standardised protocols with non-contrast enhanced 5-mm contiguous slices parallel to the orbital floor from the base of the skull to the vertex. Images were viewed on a standard picture archiving and communication system workstation.

HU of the GM and WM were determined using the method described by Torbey *et al*,[5] with some modification. Circular regions of interest (10 mm²) were used to measure brain densities in HU for GM (caudate nucleus and putamen) and WM (posterior limb of internal capsule and genu of corpus callosum) at the basal ganglia level on non-contrast CT scans (fig 1). Adachi *et al*[11] reported that focal low-attenuating lesions were ill defined, bilaterally symmetrical, and approximately 5 mm in diameter in the posterior half of the posterior internal capsule in 59% of 141 axial brain CT studies of normal patients. Therefore, for the posterior internal capsules, we measured HU in the anterior half of the posterior internal capsule. The caudate nucleus, putamen, genu of the corpus callosum and posterior internal capsule were divided into three sectors in each

Table 2 Assessment of HU of GM and WM and GM/WM ratios at the basal ganglia level in controls and comatose patients

	Control (n = 27)	Comatose (n = 28)	p Value
GM			
CN (SE)	35.7 (0.4)	33.8 (0.5)	0.006
Putamen (SE)	35.9 (0.4)	34.4 (0.5)	0.025
WM			
PIC (SE)	27.0 (0.4)	27.8 (0.4)	0.161
CC (SE)	27.2 (0.4)	27.5 (0.4)	0.662
GM/WM ratio			
CN/PIC (SE)	1.32 (0.01)	1.21 (0.01)	<0.001

CC, corpus callosum; CN, caudate nucleus; GM, grey matter; HU, Hounsfield unit; PIC, posterior limb of internal capsule; WM, white matter.

Table 3 Assessment of HU of GM and WM and GM/WM ratios at the basal ganglia level in the good and poor subgroups of comatose patients

	Good subgroup (n = 9)	Poor subgroup (n = 19)	p Value
GM			
CN (SE)	35.5 (0.7)	33.1 (0.6)	0.023
Putamen (SE)	35.7 (0.9)	33.7 (0.6)	0.063
WM			
PIC (SE)	27.8 (0.6)	27.8 (0.5)	0.998
CC (SE)	28.1 (0.5)	27.1 (0.5)	0.206
GM/WM ratio			
CN/PIC (SE)	1.28 (0.01)	1.19 (0.01)	<0.001

CC, corpus callosum; CN, caudate nucleus; GM, grey matter; HU, Hounsfield unit; PIC, posterior limb of internal capsule; WM, white matter.

hemisphere. We measured HU once per sector and calculated the means, which are referred to as HU. Right and left HU were averaged for each patient. Each CT scan was evaluated independently by an emergency room physician and a neurosurgeon who were blinded to clinical findings, and the results found by the two readers were averaged.

Statistical analysis

Data were expressed as means ± standard errors. Pearson's χ^2 test or the Student's t-test were used for the analysis. Box and whisker plots were constructed to summarise the distributions of HU values among the normal controls as well as in the good and poor subgroups. A receiver operating characteristic (ROC) curve was constructed to determine the cutoff value of the GM/WM ratio that best predicted vegetative state or death. Sensitivity, specificity, positive predictive value and negative predictive value were calculated at this cutoff level. A p value of less than 0.05 was considered significant.

RESULTS

The mean time to CT after ROSC in comatose patients was 3.9 h. GM densities were significantly higher in the controls than in the comatose patients, but there were no differences in WM between the two groups. The density ratios of GM to WM were significantly lower in the comatose patients than in the controls (less than $p<0.001$) (table 2). The lower ratios in the comatose patients were dependent upon lower densities in the caudate nucleus. Regarding HU in the caudate nucleus, putamen, posterior limb of the internal capsule and corpus callosum, strong correlations were observed between the two readers in both the controls and comatose patients (r = 0.933, less than $p<0.001$; r = 0.975, less than $p<0.001$).

Nine of the 28 comatose patients were assigned to the good outcome subgroup and 19 were assigned to the poor outcome subgroup. The clinical characteristics of comatose patients are summarised in table 1. Caudate nucleus density was significantly higher in the good subgroup ($p = 0.023$), and the density ratio of GM to WM was significantly higher in this group (less than $p<0.001$) (table 3).

When the relationship between GM/WM ratio and GOS score was investigated in comatose patients, a moderate correlation was observed (r = 0.676, less than $p<0.001$). ROC curve analysis showed that a GM/WM ratio cutoff value of less than 1.22 predicted vegetative state or death (ROC 0.947; 95% CI 0.87 to 1.0; less than $p<0.001$), with a sensitivity of 63%, a specificity of 100%, a positive predictive value of 100% and a negative predictive value of 56% (table 4).

Table 4 Sensitivities, specificities, positive predictive values and negative predictive values of GM/WM cutoffs in terms of predicting vegetative state or death

GM/WM ratio	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
<1.18*	37	100	100	43
<1.22†	63	100	100	56

GM, grey matter; NPV, negative predictive value; PPV, positive predictive value; WM, white matter.
*The best cutoff value for predicting death by Torbey *et al*.[5]
†The best cutoff value for predicting vegetative state or death in the present study.

DISCUSSION

The findings of this study show that the density ratio of GM to WM on head CT images obtained within 24 h of ROSC correlates with outcome in comatose patients after cardiac arrest. A loss of GM–WM differentiation on CT has been reported to predict poor outcome after hypoxic encephalopathy.[7 8] It is, however, often difficult to diagnose early ischaemic and anoxic brain injuries based on CT findings because the loss of GM–WM differentiation can be quite subtle. Therefore, it was suggested that image densities might allow for reliable quantifiable comparisons between GM and WM.[5]

Brain tissue water content is inversely correlated with *x* ray attenuation.[12] The net water increase in ischaemic brain tissue thus results in a subtle decrease in CT density. CT attenuation changes are strongly dependent on the type of brain tissue. GM, with its higher initial water content, is more strongly affected than WM because even small changes in water content have a much more pronounced effect on *x* ray attenuation.[13] Therefore, a diminished difference between GM and WM is explained by a change in net water content.[13]

Yanagawa *et al*[6] recently reported that on CT images obtained within 1 h after resuscitation from cardiac arrest, the average densities of the putamen and cerebral cortex and corticomedullary contrast were correlated with outcome in hypoxic encephalopathy. The authors did not, however, suggest a cutoff value for predicting the outcome of hypoxic encephalopathy using corticomedullary contrast. Torbey *et al*[5] reported that on non-contrast brain CT performed within 48 h of cardiac arrest, a GM/WM ratio of less than 1.18 was 100% predictive of death. However, they failed to find any association between this ratio and functional status as measured by the Rankin index[14] or GOS.

Accordingly, we hypothesised that the GM/WM ratios on head CT scans taken within 24 h of ROSC correlate with outcome in comatose patients after cardiac arrest and that there is an association between this ratio and GOS.

When measuring GM and WM densities on non-contrast CT images in comatose patients after ROSC, we realised that the densities of caudate nuclei and posterior internal capsules were not homogenous. In particular, in control patients with normal scans, the densities of posterior internal capsules varied by an average 2 HU (range 0.2–4.5 HU) between the anterior and posterior halves due to the presence of focal low-attenuation lesions in the posterior half of the posterior internal capsule in 60% of normal brains.[11] Therefore, in the present study, we chose the anterior halves of posterior internal capsules in order to minimise this variation.

Caudate nucleus densities in comatose patients were on average 5.3% lower than in controls, but the WM densities were similar in comatose patients and controls. This reduction in caudate nucleus density is approximately one half of that reported by Torbey *et al*,[5] who reported an 11% decrease

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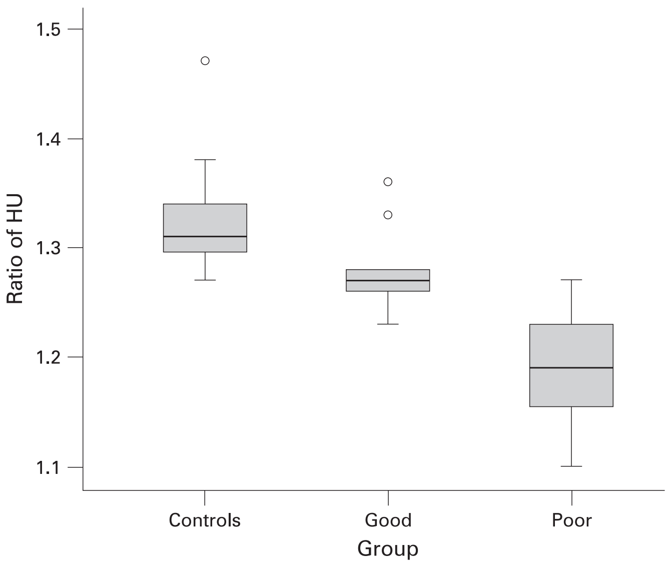

Figure 2 Grey matter/white matter ratios at the basal ganglia level of controls and in the good and poor subgroups. Box and whisker plot with median, lower and upper quartiles and outliers. HU, Hounsfield unit.

compared with controls within 48 h of resuscitation. This may be explained by the correlation between a reduction in density and the delay time to CT imaging in acute ischaemic stroke patients[15] and in an experimental stroke model.[13] In addition, the caudate nucleus densities were higher in the good outcome subgroup than in the poor outcome subgroup, but the WM densities were similar in both subgroups. The results suggested that ischaemic oedema in GM was less severe in the good outcome subgroup than in the poor outcome subgroup, but there was no significant difference in ischaemic oedema in the WM between the two subgroups because the WM is more resistant to ischaemic reperfusion injury and has a lesser effect of change in water content on *x* ray attenuation compared with GM in the early period post-ROSC.[13]

GM/WM ratios discriminated well between the poor subgroup and controls, but not in the good subgroup (fig 2). In the present study, the mean GM/WM ratio in the poor outcome subgroup was 7% lower than that in the good outcome subgroup. A GM/WM ratio cutoff of less than 1.22 predicted vegetative state or death with a sensitivity of 63% and a specificity of 100%. The predictive value of the GM/WM ratio in the present study is comparable to that presented by the bilateral absence of N20 on somatosensory evoked potentials predicting a poor outcome with a sensitivity of 45% (range 29–82%) and a specificity of 100%.[16]

There are several limitations of this study. First, this was a retrospective study and thus two different scanners were used for the patients and controls; however, all brain CT scans were performed according to a standardised protocol. Second, there may be a selection bias because during the study period, 13 patients did not have brain CT scans for several reasons, such as an unstable condition or others, which may have influenced the results. Third, although there were no significant differences in the baseline characteristics of the patients, a type II (β) error resulting from the small sample size of the study group could have obscured the differences in some of these parameters. Fourth, although a head CT was performed within 5 h of ROSC in 23 of the 28 comatose patients, the CT scans were performed at different times, and this could have influenced the CT density changes in hypoxic ischaemic encephalopathy. Therefore, a well-designed prospective study on a larger number of patients is needed to confirm the GM/WM ratio cutoff value for the prediction of vegetative state or death.

In conclusion, our study shows that GM/WM ratios obtained by CT within 24 h of cardiac arrest are correlated with outcome in comatose patients and may be useful as an objective early predictor of vegetative state or death in comatose patients after cardiac arrest.

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Competing interests: None.

Ethics approval: The study was approved by the local ethics committee of the university hospital.

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