Association between a quantitative CT scan measure of brain edema and outcome after cardiac arrest

Robert B. Mettera, Jon C. Rittenbergera, Francis X. Guyettea, Clifton W. Callawaya,b,*

報告者:PGY 倪旻白
指導者: VS 王瑞芳
100.09.10

1) Introduction

- Cerebral edema:
  - physical change associated with brain injury
  - decreased survival after cardiac arrest.
- Edema on brain CT scan:
  - decreased X-ray attenuation by gray matter.
- This study tested whether the gray matter attenuation to white matter attenuation ratio (GWR) was associated with survival and functional recovery.

- Two previous studies:
  - patients with good outcomes (awake and GOS 3–5, respectively)
  - post-cardiac arrest patients with poor outcomes (comatose and Glasgow Outcome Scale 1–2, respectively)
    - gray matter to white matter differentiation was significantly lower
- A third study:
  - patients with good outcomes (CPC 1–3)
  - patients with poor outcomes (CPC 4–5)
    - attenuation in the putamen and cerebral cortex were decreased

- cerebral edema is a potentially useful early marker for brain injury.
  - Because cranial CT scans are easily obtained in comatose cardiac arrest patients,
- This study tested the hypothesis
  - gray matter to white matter differentiation on the initial cranial CT scan was associated with hospital outcome after cardiac arrest.
- Gray matter to white matter differentiation was quantified ➔the attenuation in gray matter to the attenuation in white matter ratio (GWR).
- Outcomes included survival, Cerebral Performance Category (CPC) and Modified Rankin Score (MRS) at hospital discharge.

2) Methods

2-1) Patient selection

- All patients admitted to UPMC-Presbyterian hospital
  - after in-hospital or out-of-hospital cardiac arrests
  - prospective quality improvement database.
- Inclusion criteria:
  - age >18 years, cardiac arrest and return of spontaneous circulation (ROSC).
- We defined cardiac arrest as:
  - having received a rescue shock and/or
  - chest compressions initiated by a health professional.

- January 1, 2005→ June 30, 2010.
  - identified subjects who received a cranial CT scan <24 h after cardiac arrest
  - Usual clinical care for this cohort, and included increasing use of cardiac catheterization and therapeutic hypothermia after 2006.
- However, this institution recommended no specific treatment for post-cardiac arrest cerebral edema.

2-2) CT measurements

- only non-contrast CT scans of the head
- CT scans with 5 mm slices.
- An investigator blinded to clinical information opened CT scans for each patient with windowing adjusted to "brain,"
- identified comparable brain slices at the level of the basal ganglia, and two levels of the superior cortex as depicted in prior reports.

- Circular regions of measurement (0.1–0.15 cm2) were placed over these regions, and average attenuation in Hounsfield Units (HU) was recorded.
- At the basal ganglia level, values were recorded bilaterally for caudate nucleus (CN), putamen (PU), corpus callosum (CC), thalamus (THL), and posterior limb of internal capsule (PIC).
- Gray matter to white matter ratio (GWR) in the basal ganglia was calculated according to previously reported methods as:
  - **GWRbg = (CN + PU)/(CC + PIC)**

- We recorded values bilaterally for the medial cortex and medial white matter at the level of the centrum semiovale (MC1 and MWM1, respectively) and high convexity area (MC2 and MWM2, respectively).
- Cerebrum GWR was calculated as:
  - **GWRcerebrum = (MC1 + MC2)/(MWM1 + MWM2)**
- We calculated Average GWR as the mean of the Basal Ganglia GWR and Cerebrum GWR.
- Increasing cerebral edema results in lower attenuation by gray matter and a lower GWR.

2-3) outcomes

- From chart review
- within 6 h of return of pulses.
  - performed the baseline neurological examination
- BP was optimized
  - prior to examination
- Cerebral Performance Category (CPC) and Modified Rankin Score (MRS)
  - at hospital discharge

3) Results

3-1) Patient demographics

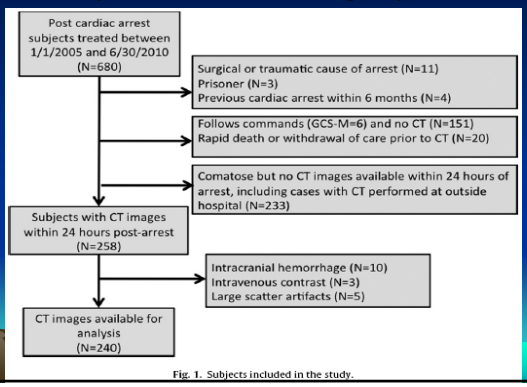


Fig. 1. Subjects included in the study.

Table 1
Patient demographics for study cohort, comatose patients without CT, all excluded patients, and entire database.

	Study cohort (N = 240)	Comatose but no CT available (N = 233)	All excluded patients (N = 440)	All cardiac arrest patients (N = 680)
Mean age (SD)	60 (17)	60 (16)	60 (16)	60 (16)
% Male	128 (53%)	131 (56%)	258 (59%)*	386 (57%)
Initial rhythm*				
VF	75 (31%)	99 (43%)	191 (43%)	266 (39%)
PEA	75 (31%)	66 (28%)	119 (27%)	194 (29%)
Asystole	53 (22%)	39 (17%)	69 (16%)	122 (18%)
Unknown	36 (15%)	28 (12%)*	50 (11%)	86 (13%)
Initial GCS motor*				
1	113 (47%)	99 (43%)	124 (28%)	237 (35%)
2	12 (5%)	8 (3%)	8 (2%)	20 (3%)
3	19 (8%)	19 (8%)	25 (6%)	44 (6%)
4	53 (22%)	61 (26%)	69 (16%)	122 (18%)
5	11 (5%)	37 (16%)	39 (9%)	50 (7%)
6	29 (12%)	0 (0%)	157 (36%)	186 (27%)
In-hospital arrest	64 (27%)	132 (57%)*	260 (59%)*	324 (48%)
Out-of-hospital arrest	176 (73%)	101 (43%)	177 (40%)	353 (52%)
Hypothermia treatment	167 (70%)	115 (49%)*	131 (30%)*	298 (44%)
Hypothermia and GCS-M < 6	166 (80%)	115 (51%)	128 (29%)	294 (62%)
Arrest-to-CT time interval				
0–6 h	161 (67%)			
6–12 h	47 (20%)			
12–18 h	16 (7%)			
18–24 h	12 (5%)			
Survival to hospital discharge	87 (36%)	92 (40%)	221 (50%)*	308 (45%)

Out-of-hospital cardiac arrest and therapeutic hypothermia were more common in the study cohort than in the entire cardiac arrest population.

* $p < 0.05$ versus study cohort.

3-2) Attenuation measurements

Table 2
(A) Median (IQR) attenuation values for survivors and non-survivors. (CN, caudate nucleus, PU, putamen, THL, thalamus, PIC, posterior limb of internal capsule, MC, medial cortex, MWM, medial white matter). (B) Median (IQR) GWR for survivors and non-survivors.

(A)			Survivors	Non-survivors	p-Value
Basal ganglia	Gray matter	CN	33.5 (31.8–34.9)	32.6 (30.8–34)	0.002
		PU	34.3 (32.6–35.9)	33.3 (31.2–34.9)	0.001
		THL	33.1 (32.1–34.6)	32.3 (30.5–33.8)	<0.001
	White matter	CC	26.2 (25.1–27.5)	26.7 (25.4–28.1)	0.213
		PIC	26.6 (24.8–27.5)	26.4 (25.2–27.8)	0.410
Cerebrum	Gray matter	MC1	31.9 (30.6–33.4)	30.9 (29.3–32.3)	0.001
		MC2	31.4 (30.5–33.6)	30.8 (28.8–32.3)	0.004
	White matter	MWM1	25.6 (24.4–26.8)	25.7 (24.3–27)	0.771
		MWM2	25.5 (23.9–26.8)	25.8 (24.5–26.9)	0.516

(B)		Survivors	Non-survivors	p-Value
GWR	Basal ganglia	1.29 (1.26–1.33)	1.24 (1.18–1.29)	<0.001
	Cerebrum	1.24 (1.21–1.29)	1.21 (1.15–1.26)	<0.001
	Average	1.26 (1.24–1.3)	1.22 (1.16–1.27)	<0.001

3-3) GWR measurements

- In the 29 subjects who were awake on presentation (GCS-motor = 6), median GWR
  - cerebrum: 1.24 (IQR 1.20–1.32)
  - basal ganglia: 1.30 (IQR 1.28–1.35)
  - Average: 1.27 (IQR 1.24–1.33).
- GWR measured in cerebrum and basal ganglia were correlated (Pearson's r = 0.448; p < 0.01).
- Cerebrum GWR tended to be lower

3-4) Association of GWR with initial GCS motor score

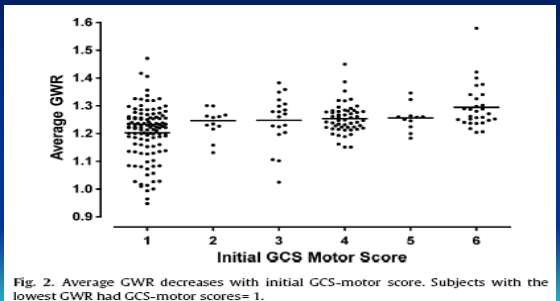


Fig. 2. Average GWR decreases with initial GCS-motor score. Subjects with the lowest GWR had GCS-motor scores = 1.

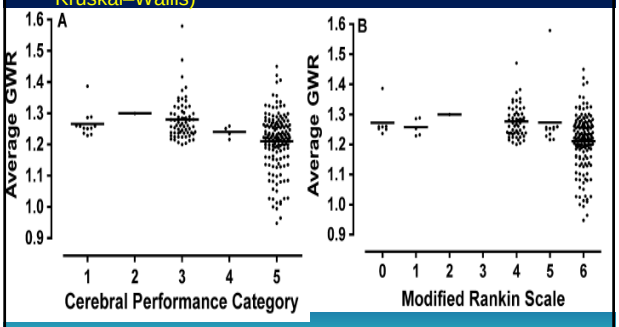
3.5) influence of arrest-to-CT time interval

- The time elapsed between the cardiac arrest and cranial CT (arrest-to-CT interval) varied from 9 min to 23.8 h (median 4.2 h, IQR 2.7–6.9).
  - Arrest-to-CT interval was 6 h or less in the majority of cases (67%).
- There was no association between arrest-to-CT interval and gray matter attenuation in any measured region.
- Likewise, arrest-to-CT interval was not associated with basal ganglia GWR (p = 0.24), cerebrum GWR (p = 0.08), or average GWR (p = 0.09).

3-6) Association of GWR with survival and outcome

- Average, basal ganglia, and cerebral GWR were significantly higher in survivors than in non-survivors ($p < 0.005$), and all were positively associated with survival ($p < 0.005$).
- Average GWR was the strongest predictor of mortality as assessed using ROC curves (basal ganglia AUC = 0.69; cerebrum AUC = 0.67; average AUC = 0.72).
- Average GWR < 1.20 predicted death
  - sensitivity of 36% (CI 29–45%), a specificity of 98% (CI 91–100%), a positive predictive value of 97% (CI 87–99%), and a negative predictive value of 46% (CI 39–54%).
  - false positive rate 3% (CI 1–13%).

Average, basal ganglia, and cerebral GWR were statistically associated with CPC and MRS ($p \leq 0.001$, Kruskal–Wallis)



the low GWR in patients who died (MRS = 6; CPC = 5).

3-7) Hypothermia-treated cohort

- Average and basal ganglia GWR were associated with survival in both groups ($p < 0.05$, binary logistic regression)
- cerebral GWR was only associated with survival in the hypothermia group (hypothermia $p < 0.001$; no-hypothermia $p = 0.12$).

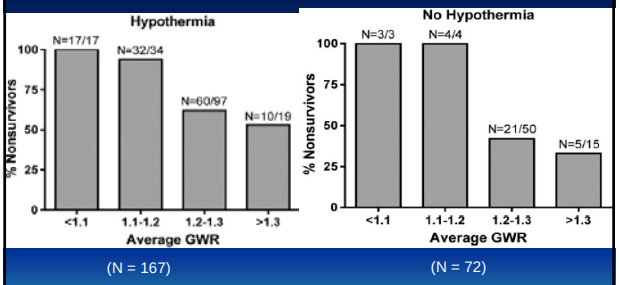


Fig. 4. Mortality increases in subjects with lower average GWR receiving hypothermia (top) and patients not receiving hypothermia (bottom).

4)Discussion

- This study confirms prior studies
  - the ratio of gray matter to white matter attenuation on cranial CT images obtained within 24 h after cardiac arrest is associated with survival.
- More precise description of the performance characteristics of this test.
- An average GWR less than 1.20 had specificity of 98% for predicting mortality, similar to previous study cutoffs of 1.18 and 1.22, which yielded specificities of 100%.

- Even in patients treated with therapeutic hypothermia there was a reliable association between GWR and survival.
- These data suggest
  - the average GWR can estimate risk of mortality for patients after cardiac arrest prior to treatment with or without hypothermia in a modern intensive care unit.

- Changes in GWR
  - edema and decreased x-ray attenuation in gray matter.
- selective vulnerability of gray matter to ischemia
  - higher metabolic rate, greater blood flow, and susceptibility to excitotoxicity
  - vasogenic edema, cytotoxic edema
- The tissue attenuation of white matter was not significantly different between survivors and nonsurvivors.
- GWR was more closely associated with survival than gray matter attenuation alone.

- Cerebral GWR tended to be lower on average than basal ganglia GWR
  - the cerebrum may be more prone to edema than the basal ganglia.
- These regional differences may explain why average GWR is a better predictor of survival than basal ganglia or cerebrum GWR alone.
- Edema throughout the brain has a higher likelihood for mortality than edema in a single region.

- the time from arrest to CT was not related to the GWR or attenuation values for any brain region.
- The only way to determine whether cerebral edema after cardiac arrest evolves over time similar to edema after other cerebral pathologies such as stroke would be to obtain serial images from the same patients.
  - these data were not available in this cohort.
- The fact that significant edema is apparent in some CT scans at very short times after cardiac arrest
  - vasogenic contribution to the edema.

- why the time course of edema appearance after global ischemia may be faster than after stroke? →several potential reasons
  - complete circulatory arrest → venous thrombosis→ compromise venous drainage after reperfusion.
- Cardiac arrest vs. stroke
  - complete tissue ischemia
  - Reperfusion ↓ : high levels of exogenous catecholamines, hypoxia and hypoventilation

  Vs.
  - trickle or low-flow from collaterals.
- Future studies could explore these potential mechanisms.

- Limitations of this study
  - large number of subjects who did not receive a CT scan
  - Some subjects might have had prognosis already deemed to be poor→ bias
- practice variation among providers

- the results can only be applied to patients who are comatose after cardiac arrest.
- Confirmation of these results in larger cohorts in which all post-cardiac arrest patients receive cranial CT scan

5)Conclusion

- Subjects with severe cerebral edema, defined by GWR < 1.20, have very low survival with conventional care, including hypothermia.
- GWR estimates pre-treatment likelihood of survival after cardiac arrest.