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Clinical paper

Agonal breathing upon hospital arrival as a prognostic factor in patients experiencing out-of-hospital cardiac arrest

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Abstract

Background: Agonal breathing is a relatively common symptom that follows cardiac arrest when the brainstem function is preserved. Agonal breathing is associated with favorable survival in patients experiencing out-of-hospital cardiac arrest (OHCA). While previous studies focused on agonal breathing observed in the pre-hospital setting for all study subjects, we focused on agonal breathing observed upon hospital arrival. In this multicenter prospective study, we aimed to assess the prognosis of patients exhibiting agonal breathing upon hospital arrival were compared. We hypothesized that agonal breathing at hospital arrival would be associated with favorable neurological outcomes among patients with OHCA.

Methods: The data on incidence of agonal breathing were prospectively collected for all evaluable participants in a multicenter, observational study in Japan (SOS-KANTO [Survey of Survivors after Out-of-Hospital Cardiac Arrest in Kanto Area] 2017 Study). Groups with and without agonal breathing were compared upon hospital arrival. Propensity-score with inverse probability of treatment weighting (IPTW) analysis was performed to adjust for confounding factors. The primary outcome was a favorable neurological outcome (Cerebral Performance Category 1–2) at 1 month.

Results: A total of 6,457 participants out of the 9,909 registered in SOS-KANTO 2017 (in which 42 facilities participated) were selected for the current study. There were 128 patients (2.0%) in the with-agonal breathing group and 6,329 (98.0%) in the withoutagonal breathing group. The primary outcome was 1.1% in the with-agonal breathing group and 0.6% in the without-agonal breathing group (risk difference, 0.55; 95% confidence interval, 0.23–0.87) after IPTW analysis.

Conclusion: In this multicenter prospective study, agonal breathing at hospital arrival was significantly associated with better neurological outcomes and increased survival at 1 month. Thus, agonal breathing at hospital arrival may be a useful prognostic predictor for patients experiencing OHCA.

Keywords: Cardiac arrest, Agonal, Cardiopulmonary resuscitation

Introduction

Out-of-hospital cardiac arrest (OHCA) is a public health issue impacting more than 400, 000 individuals in North America, 275, 000 in Europe, and approximately 100, 000 in Japan, annually.[1,2] The average survival rate after OHCA is approximately 10%, and the prognosis for favorable neurological outcomes is unknown.[3] A prior study suggested that factors contributing to favorable neurological outcomes include 1) witnessed OHCA, 2) bystander cardiopulmonary resuscitation (CPR), and 3) shockable rhythm.[4]

After achieving return of spontaneous circulation (ROSC) and being admitted to the hospital, several neurological and laboratory tests can be conducted for prognostication. These include brain wave assessments, neurotransmission tests, measurements of biochemical markers, and brain imaging.[5] These tests are considered reliable tools for predicting favorable neurological outcomes and serve as important prognostic factors for patients with OHCA after ROSC.[5] However, these neurological and laboratory tests cannot be performed during CPR.

Agonal breathing indicates the presence of brainstem activity, even during OHCA, and is reportedly correlated with favorable

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neurological outcomes in patients who have experienced OHCA.[6] Previous studies in OHCA have reported that patients with agonal breathing have a 3.5 times higher survival rate than those without agonal breathing.[6,7] Additionally, in a study in which extracorporeal CPR (ECPR) was performed on patients who had agonal breathing during EMS transport, it served as a prognostic factor for improved outcomes.[8] However, this study did not examine patients with agonal breathing while on no ECPR during EMS Transport.[8] We considered that agonal breathing upon arrival at the hospital may be an important factor; however, there is no evidence to support this yet. Agonal breathing often appears in the early stages of OHCA or when brainstem function is preserved. We hypothesized that patient with OHCA presenting with agonal breathing upon hospital arrival have better neurological outcomes compared to those who do not present with agonal breathing. In this multicenter prospective cohort with control study, we aim to examine agonal breathing upon hospital arrival as a prognostic factor for favorable neurological outcomes post OHCA.

Methods

Study design and setting

This was a prospective multi-center cohort study conducted in Japan, specifically the Kanto region, which includes Tokyo. Our study is a sub-study of the Survivors after Out-of-Hospital Cardiac Arrest in Kanto Area (SOS-KANTO) 2017, a Survey of Survivors after Out-of-Hospital Cardiac Arrest in Kanto Area, a study which prospectively collected data from patients who experienced OHCA and transported to 42 emergency hospitals. The SOS-KANTO 2012 study group has conducted multi-center prospective studies between 2002 and 2012.[9–12] The SOS-KANTO 2017 was a multicenter study conducted from September 2019 to March 2021. The study was supported by the Kanto branch of the Japanese Association for Acute Medicine. The study protocol was approved by the institutional review board or ethics committee of all participating medical institutions, and the requirement for informed consent was waived to ensure participant anonymity. Data were collected using an opt-out method. Information about data collection is publicly disclosed on the websites of the participating medical facilities and has been approved through an ethical review process.

Participants

The participants were divided into two groups for comparison as follows: those with agonal breathing at the time of hospital arrival and those without. The exclusion criteria were ROSC upon arrival at the hospital, unknown presence or absence of agonal breathing at the scene, unknown agonal breathing upon arrival at the hospital, and unknown survival at 1 month or neurologic outcomes. We have not attempted to define or determine the extent of agonal breathing. However, agonal breathing was clinically defined by the emergency physicians or ER clinical staff.

Data collection

In this study, we prospectively collected data both before and after hospital arrival in a format consistent with the Utstein Registry. Pre-hospital data, collected by the ambulance team, included the patient's age, sex, pre-admission health conditions and co-morbidities, bystander CPR, initial rhythm on scene, time interval to hospital arrival, and return to ROSC prior to hospital arrival. n-hospital data collected by the researchers at each facility included admission status, initial examination data, medication and treatment during/after resuscitation (e.g. ROSC after arrival, pupil diameter, light reflex, presence of agonal breathing, Glasgow Coma Scale score, ECG waveform, use of automatic chest compression devices, 12-lead ECG, rib fractures, pneumothorax, echocardiograms, defibrillation, intubation, extracorporeal treatments, intra-aortic balloon pump. implementation, and coronary angiography), cause of cardiac arrest (cardiac or non-cardiac), hospitalization period, and neurological outcomes at 30 days post hospital admission. Post-resuscitation interventions, including therapeutic hypothermia, renal replacement therapy, mechanical circulatory support, and others, were also evaluated.

Outcomes

The main outcome measure was a favorable neurological outcomes at 30 days post hospital admission., and the secondary outcomes were ROSC post hospital arrival and survival at 30 days post hospital admission. Neurological outcomes were classified using the Cerebral Performance Category (CPC) scale as follows: CPC1, Good cerebral performance; CPC2, moderate disability; CPC3, severe disability; CPC4, coma or vegetative state; and CPC5, brain death or death. CPC1 and 2 were defined as favorable neurological outcomes.[7]

Statistical analyses

Continuous variables are presented as means ± standard deviations (sd), and categorical variables were presented as counts and proportions. We used multiple imputations to manage missing data, and this resulted in five imputed datasets. We developed a propensity score to estimate the probability of enrolment in the agonal breathing group versus non-agonal breathing group based on the clinical opinion and other variables upon hospital admission. These variables included in our propensity score logistic regression were age, sex, witnessed OHCA, bystander CPR, agonal breathing on scene, procedures such as (IV fluids, or adrenaline), shockable initial rhythm, advanced airway management prior to hospital admission, response time interval (call to scene), transport time to hospital, and the cause of cardiac arrest.[10,13] Propensity scores with inverse probability of treatment weighting (IPTW) analysis was performed to compare the outcomes between the agonal and non-agonal groups.[14] We examined balance in baseline variables using standardized differences, where values >0.10 were considered as imbalances.[15] we used risk difference (RD) with 95% confidence interval (CI) to measure our main and secondary outcomes. SPSS version 29.0 (IBM, Armonk, NY, USA) and Stata ver14.2 (StataCorp, College Station, TX, USA) were used for statistical analyses.

Results

During the study period, 9,909 patients who experienced OHCA were identified in the database. Of these, 6,457 patients were included. These patients were categorized into two groups, as follows: a group with agonal breathing upon arrival at the hospital (n = 128) and a control group (n = 6,329) (Fig. 1). Table 1 shows the characteristics of the patients in both groups after weighting by overlapping using propensity scores (Table 1). When comparing data before weighting between the control group and the group with agonal breathing upon arrival at the hospital, the variables with a standardized difference of less than 10% were: age (71 vs. 70 years), bystander CPR (42.6% vs. 43.8%), advanced airway management

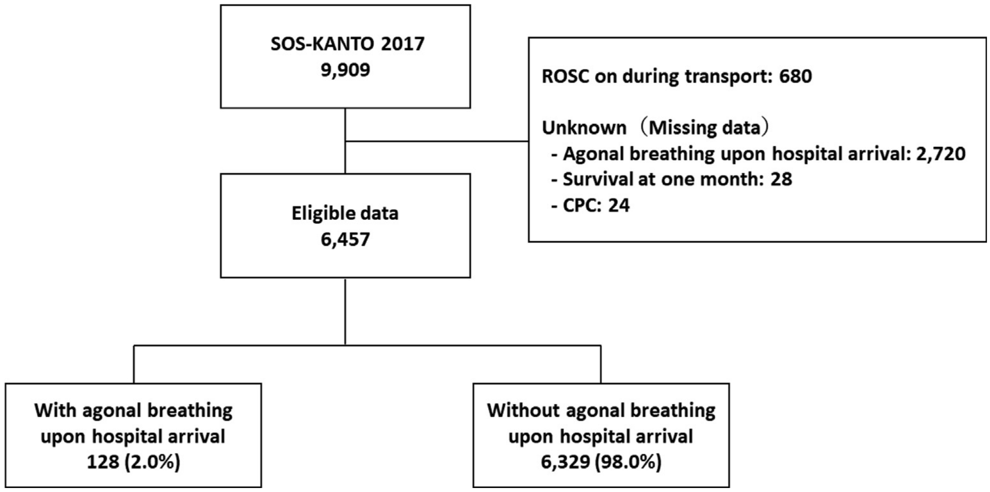

Fig. 1 – Patient selection flowchart. CPC, cerebral-performance category; ROSC, return of spontaneous circulation; SOS-KANTO, Survey of Survivors after Out-of-Hospital Cardiac Arrest in Kanto Area.

Table 1 – Baseline patient characteristics in the unweighted and weighed groups.

	Unweighted group					Weighted group				
Variable	Without agonal (n = 6,329)		With agonal (n = 128)		Standardized differences, %	Without agonal (n = 6,454)		With agonal (n = 6,389)		Standardized differences, %
Age, years (SD)	71	(18.3)	70	(17.7)	5.6	71	(18.3)	74	(14.7)	−18.1
Male	3,881	(61.3%)	87	(68.0%)	−13.9	3,968	(61.5%)	3,926	(61.4%)	0.0
Witness	2,642	(41.7%)	82	(64.1%)	−45.9	2,724	(42.2%)	2,870	(44.9%)	−5.5
Bystander CPR	2,699	(42.6%)	56	(43.8%)	−2.2	2,755	(42.7%)	2,343	(36.7%)	12.3
Agonal breathing on scene	909	(14.4%)	65	(50.8%)	−84.3	974	(15.1%)	1,003	(15.7%)	−1.7
Prehospital procedure by EMS										
Shockable rhythm	398	(6.3%)	21	(16.4%)	−32.3	419	(6.5%)	379	(5.9%)	2.3
Intravenous fluid	2,397	(37.9%)	56	(43.8%)	−12.0	2,454	(38.0%)	2,786	(43.6%)	−11.4
Adrenaline	1,883	(29.8%)	46	(35.9%)	−13.2	1,929	(29.9%)	2,236	(35.0%)	−11.0
Advanced airway management	3,907	(61.7%)	77	(60.2%)	3.2	3,985	(61.7%)	4,486	(70.2%)	−18.0
Time										
Response (SD)	8.2	(3.9)	7.9	(3.1)	8.5	8.2	(3.9)	7.9	(3.1)	8.5
Scene time (SD)	15.5	(7.7)	16.1	(6.0)	−8.7	15.5	(7.7)	16.1	(6.0)	−8.7
Transport time (SD)	11.6	(8.6)	12.3	(9.9)	−7.5	11.6	(8.6)	12.3	(9.9)	−7.5
Cause of cardiac arrest										
Presumed cardiogenic	3,876	(61.2%)	79	(61.7%)	−1.0	3,955	(61.3%)	4,384	(68.6%)	−15.5

CPR, cardiopulmonary resuscitation; EMS, emergency medical system; SD, standard deviation

The number of variables in the weighted analysis is a statistically calculated number, not an actual number.

(61.7% vs. 60.2%), response time (8.2 min vs 7.9 min), scene time (15.5 min vs 16.1 min), transport time (11.6 min vs 12.3 min), and presumed cardiogenic cause of cardiac arrest (61.2% vs. 61.7%). The variables with a standardized difference over 10 were as follows: male (61.3% vs. 68.0%), witnesses (41.7% vs. 64,1%), agonal breathing at the scene (14.4% vs. 50.8%), shockable waveform (6.3% vs 16.4%), intravenous route (37.9% vs 43.8%), adrenaline administration (29.8% vs 35.9%). After propensity score IPTW, the baseline patient characteristics were most likely balanced between the two groups.

Before weighting, the primary outcome (a favorable neurological outcome at 1 month) was 0.6% in the control group and 4.7% in the agonal breathing group upon arrival at the hospital (RD, 4.12; 95% CI, 2.71–5.53). After weighting, the rate was 0.6% in the control group and 1.1% in the agonal breathing group upon arrival at the hospital (RD, 0.55; 95% CI, 0.23–0.87) (Table 2). Before weighting, the secondary outcome (survival at 1 month) was 1.7% in the control group and 8.6% in the agonal breathing group upon arrival at the hospital (RD, 13.60; 95% CI, 10.49–16.71). After weighting, the rate was 1.7% in the control group and 2.8% in the agonal breathing group upon arrival at the hospital (RD, 1.11; 95% CI, 0.60–1.63). before weighting, ROSC upon arrival at the hospital occurred in 19.4% in the control group and 47.7% in the agonal breathing group (RD, 28.30; 95% CI, 21.31–35.29). After weighting, the proportion

Table 2 – Primary and secondary outcomes by unweighted and weighted analysis.

Variable	Unweighted analysis					Weighted analysis				
	Without agonal (n = 6,329)		With agonal (n = 128)		RD (95% CI)	Without agonal (n = 6,454)		With agonal (n = 6,389)		RD (95% CI)
Favorable neurological outcome	36	(0.6%)	6	(4.7%)	4.12% (2.71–5.53)	38	(0.6%)	73	(1.1%)	0.55% (0.23–0.87)
Survival at 1 month	106	(1.7%)	11	(8.6%)	13.60% (10.49–16.71)	111	(1.7%)	181	(2.8%)	1.11% (0.60–1.63)
ROSC after hospital arrival	1,225	(19.4%)	61	(47.7%)	28.30% (21.31–35.29)	1,255	(19.4%)	2,520	(39.4%)	20.01% (10.49–16.71)

CI; confidence Interval, IPTW; inverse probability of treatment weighting, RD; risk difference; ROSC, return of spontaneous circulation.
The number of variables in the weighted analysis is a statistically calculated number, not an actual number.

was 19.4% in the control group and 39.4% in the agonal breathing group upon arrival at the hospital (RD, 20.01; 95% CI, 10.49–16.71).

Discussion

We examined the favorable neurological outcome at 30 days post hospital admission for OHCA patients admitted with agonal breathing prior to ROSC using a prospective dataset. We found that agonal breathing upon arrival to hospital (at one time-point only) prior to ROSC was a significant prognostic factor for favorable neurological outcome at 30 days post hospital admission.

A previous study suggested that the rates of favorable neurological outcomes (CPC1–2) were 20% for patients with agonal breathing during CPR and 3.7% for those without, representing a significant difference with an odds ratio (OR) of 6.62 and a 95% confidence interval (CI) of 4.10 to 10.55.[6] A systematic review investigated whether agonal breathing predicts short-term and long-term outcomes in OHCA.[7] The review, which included five studies, showed that agonal breathing was associated with a significant increase in the rate of return of spontaneous circulation (risk ratio [RR], 1.87; 95% CI, 1.64–2.13) and with a higher likelihood of favorable neurological outcomes (RR, 3.79; 95% CI, 1.86–7.73) and increased long-term survival (≥6 months) (RR, 3.46; 95% CI, 1.70–7.07)[6,16–18]. Debaty G. 2017 et al, reported that the combination of agonal breathing and appropriate initial shock waveform for electrical shock application had higher for favorable patient outcomes compared to no agonal breathing and no shockable rhythm.[6] While these studies focused on agonal breathing observed in the pre-hospital setting, we focused on agonal breathing observed upon hospital arrival. We included patients without ROSC on scene. A previous study of patients without ROSC on scene reported a survival rate of 1.9% at 1 month. In the same study, the survival rate for patients with ROSC on scene was 24.3%.[19] In the group of patients with agonal breathing on arrival at the hospital, the survival rate was 8.2% (10/122). We found that the survival rate in this study was slightly higher than those in previous studies. This may be because rapid advanced life support can be performed in the emergency department of a hospital, where agonal breathing, known as a favorable prognostic factor, becomes advantageous for the outcome.

Gasping, which is experienced during agonal breathing, results in numerous physiological effects, including respiratory gas exchange, decreased right atrial pressure, enhanced cardiac preload, decreased intracranial pressure, and increased aortic, coronary, and cerebral perfusion pressures. Therefore, gasping enhances respiration and circulation.[20,21] Initiation of gasping after OHCA has been linked to the level of brainstem partial pressure of oxygen, arterial baroreceptor, and chemoreceptor stimulation following a sudden decrease in blood pressure and arterial acid–base balance.[22] Agonal breathing has been previously reported in 30–40% of OHCA during the first few minutes after OHCA. Over time it diminishes to be observed in only 7% of OHCA upon EMS arrival on scene, if EMS time to arrival on scene is more than 9 min.[23–26] In our current study half of patients who presented with agonal breathing upon hospital arrival had also experienced agonal breathing before hospital arrival. Given that the mean transport time was approximately 12 min, it is likely that agonal breathing occurred during CPR at the scene and continued until hospital arrival.

Limitations

There were some limitations to this study. First, despite being a prospective study, the observational nature of this research precludes drawing any cause-and-effect conclusions from its findings. Second, there were 2,720 missing values for agonal breathing upon arrival at the hospital, representing approximately 30% of the missing values in the original data. Missing values occurred in the data set, but it was unavoidable in a time-sensitive clinical setting. We excluded any deficiency regarding agonal breathing both at the scene and upon arrival at the hospital to maintain strict control group entries. We performed imputation for all factors except for the agonal breathing at the hospital. Third, although we performed IPTW weighted propensity score analysis, some of the variables in the weighted groups still exceeded 10% of the standardized differences.

Conclusions

Our multi-center prospective cohort study suggests that although agonal breathing upon hospital arrival was not significantly associated with an increase in survival at 1 month, it was associated with better favorable neurological outcomes at that time. Although further studies are required to validate prognostication models that include agonal breathing, its presence upon hospital arrival may serve as a useful prognostic predictor of favorable neurological outcomes in patients with OHCA.

CRediT authorship contribution statement

Shinnosuke Kitano: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **Kensuke Suzuki:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Chie Tanaka:** Writing – review & editing, Supervision. **Masamune Kuno:** Writing – review & editing, Supervision. **Nobuya Kitamura:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization. **Hideo Yasunaga:** Writing – review & editing, Project administration, Methodology, Conceptualization. **Shotaro Aso:** Writing – review & editing, Project administration, Methodology, Conceptualization. **Takashi Tagami:** Writing – review & editing, Project administration, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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