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## The association between hemoglobin concentration and neurologic outcome after cardiac arrest<sup>\*</sup>

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### Abstract

**Purpose**—The purpose of the study is to determine the association between hemoglobin concentration (Hgb) and neurologic outcome in postarrest patients.

**Methods**—We conducted a retrospective cohort study using the Penn Alliance for Therapeutic Hypothermia (PATH) cardiac arrest registry. Inclusion criteria were resuscitated cardiac arrest (in-hospital or out of hospital) and an Hgb value recorded within 24 hours of return of spontaneous circulation. The primary outcome was favorable neurologic status at hospital discharge. Survival to hospital discharge was a secondary outcome.

**Results**—There were 598 eligible patients from 21 hospitals. Patients with favorable neurologic outcome had significantly higher median Hgb in the first 2 hours (12.7 vs 10.5 g/dL;  $P < .001$ ) and 6 hours (12.6 vs 10.6 g/dL;  $P < .001$ ) postarrest. Controlling for age, pulseless rhythm, etiology, location of arrest, receipt of targeted temperature management, hematologic or metastatic malignancy, or preexisting renal insufficiency, there was a significant relationship between Hgb and neurologic outcome within the first 6 hours after arrest (odds ratio, 1.23; 95% confidence

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interval, 1.09–1.38) and survival to hospital discharge (odds ratio, 1.20; 95% confidence interval, 1.08–1.34).

**Conclusion**—Higher Hgb after cardiac arrest is associated with favorable neurologic outcome, particularly within the first 6 hours. It is unclear if this effect is due to impaired oxygen delivery or if Hgb is a marker for more severe illness.

### Keywords

Cardiac arrest; Postcardiac arrest syndrome; Anemia; Hemoglobin

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## 1. Introduction

An estimated 600 000 patients have cardiac arrest in the United States each year [1]. Many patients who survive the initial event have the postcardiac arrest syndrome (PCAS), a condition characterized by ischemia-reperfusion injury leading to oxidative stress, neurologic injury, myocardial dysfunction, and a systemic inflammatory response [2]. Inhospital mortality for resuscitated patients remains high, with estimates ranging from 63% to 72% [2–4].

Targeted temperature management (TTM) has been shown in randomized, prospective clinical trials to improve outcomes for patients with postarrest anoxic encephalopathy, although the optimal target temperature remains controversial [5–7]. In addition to TTM, researchers have suggested that optimal PCAS care is a comprehensive bundle that includes the following: early percutaneous coronary interventions, hemodynamic optimization (goal-directed resuscitation), low tidal volume mechanical ventilation, electrolyte management including glucose control, comprehensive neuromonitoring, and objective criteria for prognostication and withdrawal of life-sustaining therapy [8–11].

An essential component of PCAS care is optimizing oxygen delivery to the brain and other injured organs. Oxygen delivery is dependent both on cardiac output and arterial oxygen content, which is heavily influenced by the hemoglobin concentration (Hgb). Improving oxygen delivery to tissues by increasing the Hgb has been studied in several populations of critically ill patients, with the most robust trials showing that a liberal transfusion strategy is no better than a conservative one [12–18]. Patients with active myocardial ischemia and recent cardiac arrest were excluded from most of these studies, and data regarding patients undergoing cardiovascular surgery suggest that some subgroups might benefit from higher Hgb [12]. Limited data exist regarding the association between Hgb and outcome in resuscitated postarrest patients or whether increasing the Hgb via blood transfusion is associated with improvement in outcome [19–21].

The aim of this study is to investigate the relationship between Hgb and neurologic outcome after cardiac arrest. We hypothesize that higher Hgb during the first 24 hours postarrest is associated with favorable neurologic outcome and improved survival at hospital discharge.

## 2. Methods

### 2.1. Setting

We performed a retrospective, observational cohort study of PCAS patients from 21 member institutions of the Penn Alliance for Therapeutic Hypothermia (PATH) registry. The study was approved by the University of Pennsylvania Institutional Review Board.

### 2.2. Patients

The cohort included successfully resuscitated adult patients who experienced a nontraumatic cardiac arrest with subsequent cardiopulmonary resuscitation, achieved return of spontaneous circulation (ROSC), and had at least 1 recorded Hgb value within 24 hours postarrest. Patients were excluded if they had an active “do not resuscitate” or “do not intubate” order. Patients with hemorrhage as the suspected etiology for their cardiac arrest were excluded from the analysis.

### 2.3. Outcomes

The primary outcome was neurologic status at hospital discharge, measured as a Cerebral Performance Category (CPC) score dichotomized into “favorable” (CPC 1–2) and “unfavorable” (CPC 3–5). The independent variables were Hgb (main exposure), sex, race, age, location of cardiac arrest (in-hospital or out of hospital), whether the cardiac arrest event was witnessed, the first detected pulseless rhythm, whether the event was of cardiac etiology, and whether the patient received TTM, preexisting hematologic or metastatic malignancy, or preexisting renal insufficiency.

### 2.4. Data collection

The PATH is a multicenter, Web-based national cardiac arrest registry hosted by the University of Pennsylvania [22]. In addition to demographic data, cardiac arrest characteristics, and outcomes, Hgb was abstracted for the following periods: the first 2 hours, the first 6 hours, between 6 and 12 hours, and between 12 and 24 hours postarrest. If multiple Hgb values were available for a given period, the first value recorded was analyzed.

### 2.5. Statistical analysis

Baseline characteristics were compared using 2-tailed  $\chi^2$  tests for categorical variables and  $t$  tests for continuous variables. The Wilcoxon rank sum test was used to compare the median Hgb during each of the 4 periods: the first 2 hours, the first 6 hours, between 6 and 12 hours, and between 12 and 24 hours postarrest. Hemoglobin concentration was investigated as a continuous predictor of neurologic outcome and then as a dichotomized predictor, first with a cutoff of 7 g/dL and again with a cutoff of 10 g/dL. These cutoffs were determined a priori and loosely based on prior transfusion trials in critically ill populations [12,13,15].

Multivariate logistic regression was used to test for the association between Hgb neurologic outcome and hospital mortality at each of the 4 time points. The analyses were adjusted for the following covariates: age, initial cardiac rhythm, cardiac etiology of arrest, location of arrest (in-hospital or out of hospital), receipt of TTM, hematologic or metastatic malignancy,

or preexisting renal insufficiency. All analyses were conducted using STATA 12.0 (College Station, TX).

### 3. Results

#### 3.1. Patient and cardiac arrest characteristics

There were 598 eligible patients. Mean age was  $61 \pm 17$  years, 55% were white, 63% had an out-of-hospital arrest, 34% had a shockable rhythm, and 54% received TTM (Table 1). Patients who had a favorable neurologic outcome were more likely to be younger and male. They were also more likely to have the following: a witnessed cardiac arrest event, a cardiac etiology for their arrest, and an initial shockable rhythm.

A total of 476 patients had preexisting medical comorbidities entered into the PATH database (Table 2). Of these, coronary artery disease, congestive heart failure, and diabetes mellitus were most common. Only 6 patients had hemorrhage as a possible arrest etiology (3 gastrointestinal bleeding, 1 postoperative hemorrhage, 1 tracheal bleeding, and 1 not specified). These patients were excluded from the analyses below.

#### 3.2. Neurologic outcome

Patients with favorable neurologic outcome had significantly higher median Hgb in the first 2 hours (12.7 vs 10.5 g/dL;  $P < .001$ ) and 6 hours (12.6 vs 10.6 g/dL;  $P < .001$ ) postarrest (Table 3). After adjusting for age, shockable rhythm, cardiac etiology, arrest location (in-hospital vs out of hospital), receipt of TTM, malignancy, and preexisting renal insufficiency, there was a significant relationship between higher Hgb within the first 6 hours after arrest and favorable neurologic outcome (odds ratio [OR], 1.23; 95% confidence interval [CI], 1.09–1.38) (Table 4). Each 1 g/dL increase in Hgb within the first 6 hours after arrest was associated with a 25% increase in the odds of having a favorable neurologic outcome at hospital discharge. There was no significant association between median Hgb 6 to 12 hours or 12 to 24 hours postarrest and neurologic outcome at hospital discharge.

More patients with Hgb greater than or equal to 7 g/dL had favorable neurologic outcomes compared with those who had Hgb less than 7 g/dL (36.3% vs 8.8%;  $P < .001$ ). These patients were also more likely to have an initial shockable rhythm and to be treated with TTM. Similarly, more patients with Hgb greater than or equal to 10 g/dL had favorable neurologic outcomes compared to those with Hgb less than 10 g/dL (41% vs 26%;  $P < .001$ ), although again, there were baseline differences. Patients with Hgb greater than or equal to 10 g/dL were more likely to be male, have an initial shockable rhythm, and not receive blood transfusion within the first 72 hours after cardiac arrest.

On univariate analysis, continuous as well as dichotomized Hgb with cutoffs of both greater than or equal to 7 g/dL and greater than or equal to 10 g/dL within the first 6 hours postarrest was associated with favorable neurologic outcome (Table 4). Upon adjusting for age, initial rhythm, cardiac etiology, arrest location, treatment with TTM, malignancy, and renal insufficiency, the relationship between Hgb with a cutoff of greater than or equal to 7 g/dL was no longer significant ( $P = .09$ ). The association between Hgb as a continuous

variable and a cutoff of greater than or equal to 10 g/dL continued to be associated with neurologic outcome.

### 3.3. Survival to hospital discharge

In unadjusted analysis, there was a significant association between continuous as well as dichotomized Hgb with cutoffs of both 7 and 10 g/dL and survival to hospital discharge (Table 5). This relationship remained significant at both 6 and 24 hours after cardiac arrest. Upon adjusting for age, initial rhythm, cardiac etiology, arrest location, treatment with TTM, malignancy, and renal insufficiency, the relationship between Hgb with a cutoff of greater than or equal to 7 g/dL was no longer significant at 6 hours after cardiac arrest but remained significant at 24 hours. The relationship between Hgb with a cutoff of greater than or equal to 10 g/dL remained significant at both 6 and 24 hours after cardiac arrest.

## 4. Discussion

This analysis of almost 600 postarrest patients from 21 hospitals in the United States suggests that Hgb may be associated with neurologic outcome after cardiac arrest, especially within the first 6 hours. The mechanism remains unclear; it is possible that Hgb affects neurologic outcome by augmenting oxygen delivery to ischemic tissues, or it may simply be a marker for severity of illness.

Although 2 recent studies have examined the association of Hgb and neurologic outcome, ours is unique in the following ways: it involves a large cohort of diverse patients who had both in-hospital and out-of-hospital cardiac arrests from multiple centers, it includes patients treated with TTM, it analyzes Hgb at multiple time points after ROSC, and it examines how blood transfusion impacted this relationship [19–21]. A study published in early 2016 examined the relationship between Hgb and neurologic outcome after out-of-hospital cardiac arrest among 931 patients at a single institution [21]. Although only 30 patients survived with good neurologic outcome, the authors found an association between a single post-ROSC Hgb greater than or equal to 10 g/dL and favorable neurologic outcome. It is unclear whether these results can be generalized given a single measured Hgb and the small number of patients achieving the primary outcome.

A recent study of 82 patients undergoing therapeutic hypothermia after resuscitated cardiac arrest similarly found an association between Hgb and outcome [19]. Further analysis by these authors points to 1 possible mechanism. They demonstrated that Hgb less than 10 g/dL was associated with lower cerebral tissue oxygenation measured by near-infrared spectroscopy. Furthermore, these authors demonstrated that Hgb less than 12.3 g/dL was associated with worse neurologic outcome and that this effect was entirely driven by patients with low mixed venous or cerebral tissue oxygenation. Because Hgb is a central determinant of oxygen delivery, patients who have had cardiac arrest may be sensitive to lower Hgb and decreased delivery of oxygen to brain and other ischemic tissues. Furthermore, myocardial dysfunction is common after cardiac arrest, which may result in increased tissue oxygen extraction and consequent low mixed venous oxygen content [23]. This may further depress arterial oxygen content, an effect that may be exacerbated by anemia.

The relationship between arterial oxygen content and outcome after cardiac arrest is complex. Cardiac arrest itself is a supply-dependent state, where the core tenet is to maximize oxygen delivery by providing chest compressions (which can provide up to 50% of the native cardiac output) and maximizing arterial oxygen content [24,25]. Return of spontaneous circulation results in a marked increase in pulmonary blood flow, rapid reoxygenation of ischemic tissue, and a burst in production of reactive oxygen species. This is the so-called oxygen paradox associated with ischemia and reperfusion. A number of observational studies have demonstrated an association between supranormal arterial oxygen tension and outcome after cardiac arrest, whereas other studies found no effect [26–31]. None of these previously cited studies examined the impact of Hgb or oxygen saturation, which accounts for greater than 95% of the arterial oxygen content under normal conditions. The ideal balance between optimal oxygen delivery and avoidance of oxidative damage after cardiac arrest remains elusive, with current guidelines recommending targeting a low-normal oxygen saturation of greater than or equal to 94% based on the best available data [11].

Alternatively, anemia may simply be a marker for more severe illness or a less favorable cardiac arrest etiology. Patients with low Hgb may have more severe preexisting chronic disease, less favorable cardiac arrest etiologies such as hemorrhage, or more profound postarrest critical illness. Preexisting anemia has been shown to be a marker of poor outcome among patients with other medical conditions, including those undergoing elective surgery and those with acute myocardial infarction [32–34]. Ample data indicate that patients with serious preexisting medical conditions are less likely to have a favorable outcome after cardiac arrest [35–41]. Furthermore, limited data suggest that patients who have cardiac arrest due to hemorrhage might have less favorable outcomes [42].

Limited data exist regarding transfusion after cardiac arrest. Several studies have included Hgb thresholds of 9 to 10 mg/dL as components of postarrest care bundles that included other measures such as TTM, hemodynamic optimization, ventilator management, and glucose control [43,44]. The impact of individual components of these bundles, including blood transfusion, is unclear. It is unclear whether transfusion trials in other critically ill populations apply to cardiac arrest patients. A landmark trial that compared transfusion thresholds of 7 and 9 mg/dL in 838 critically ill patients found no difference in mortality [15]. There was no difference in mortality among patients with cardiac disease, but the authors cautioned that patients with active myocardial ischemia may have been excluded due to preference of the treating physicians. Although this landmark trial has greatly influenced transfusion practices in emergency and intensive care medicine, it is unclear if these findings can be applied to postarrest patients.

#### 4.1. Limitations

The PATH is large, multicenter registry with overall cardiac arrest mortality rates comparable to those reported throughout the United States, making our findings fairly generalizable. Rare missing data items exist in PATH largely because they were unavailable in the medical record. Given our retrospective design, only association, not causation, can be commented upon. It is possible that survivorship bias affected the relationship between Hgb and neurologic outcome, especially at later time points. Because data on blood transfusion



were only available for a limited subset of our population, we were not able to examine how blood transfusion affects this relationship.

## 5. Conclusion and recommendations

Higher Hgb is associated with favorable neurologic outcome in successfully resuscitated patients after cardiac arrest. This association is most robust within the first 6 hours. Whether this is effect is due to enhanced oxygen delivery or whether hemoglobin concentration is a marker for more severe underlying illness remains to be determined.

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**Table 1**

Patient characteristics according to neurologic outcome

| Characteristic, n (%)    | All patients | CPC 1–2    | CPC 3–5    | <i>P</i> |
|--------------------------|--------------|------------|------------|----------|
| Sex                      |              |            |            |          |
| Male                     | 342 (57.7)   | 138 (69.0) | 202 (52.1) | <.001    |
| Female                   | 251 (42.3)   | 62 (31.0)  | 186 (47.9) |          |
| Race                     |              |            |            |          |
| White                    | 314 (55.2)   | 114 (59.4) | 198 (53.2) | .318     |
| Black                    | 221 (38.8)   | 69 (35.9)  | 149 (40.1) |          |
| Other                    | 34 (6.0)     | 9 (4.7)    | 25 (6.7)   |          |
| Age, mean ± SD           | 61 ± 17      | 57 ± 18    | 63 ± 17    | <.001    |
| Location, n (%)          |              |            |            |          |
| Inhospital               | 221 (37.1)   | 78 (38.8)  | 142 (36.5) | .584     |
| Out of hospital          | 374 (62.9)   | 123 (61.2) | 247 (63.5) |          |
| Witnessed                |              |            |            |          |
| Yes                      | 463 (79.7)   | 175 (87.9) | 283 (75.1) | <.001    |
| No                       | 118 (20.3)   | 24 (12.1)  | 94 (24.9)  |          |
| Rhythm                   |              |            |            |          |
| Shockable                | 189 (34.4)   | 101 (55.3) | 88 (24.0)  | <.001    |
| Nonshockable             | 361 (65.6)   | 81 (44.7)  | 278 (76.0) |          |
| Cardiac etiology         |              |            |            |          |
| Yes                      | 398 (68.6)   | 150 (76.1) | 245 (64.8) | .006     |
| No                       | 182 (31.4)   | 47 (23.9)  | 133 (35.2) |          |
| TTM                      |              |            |            |          |
| Yes                      | 318 (53.5)   | 105 (52.5) | 211 (54.2) | .688     |
| No                       | 276 (46.5)   | 95 (47.5)  | 178 (45.8) |          |
| Transfusion <sup>a</sup> |              |            |            |          |
| Yes                      | 117 (32.7)   | 29 (23.4)  | 86 (37.6)  | .007     |
| No                       | 241 (67.3)   | 95 (76.6)  | 143 (62.4) |          |

<sup>a</sup>Transfusion information was obtained only for a subpopulation of patients (n = 361).

**Table 2**

Prearrest patient comorbidities (n = 476)

| <b>Comorbidity</b>                     | <b>n (%)</b> |
|--|--------------|
| Chronic respiratory failure            | 1 (0.2%)     |
| Congestive heart failure               | 119 (25%)    |
| Coronary artery disease                | 169 (36%)    |
| Diabetes mellitus                      | 195 (41%)    |
| HIV                                    | 4 (0.8%)     |
| Metastatic or hematologic malignancy   | 39 (8%)      |
| Myocardial ischemia/infarction         | 79 (17%)     |
| Renal insufficiency requiring dialysis | 101 (21%)    |

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**Table 3**

Median hemoglobin concentrations between the neurologically favorable and unfavorable study populations at 4 time points after cardiac arrest: the first 2 hours, the first 6 hours, 6 to 12 hours, and 12 to 24 hours

|       | <b>CPC 1–2, Hgb<sup>a</sup> (IQR)</b> | <b>CPC 3–5, Hgb<sup>a</sup> (IQR)</b> | <b><i>P</i></b> |
|-------|---------------------------------------|---------------------------------------|-----------------|
| 0–2   | 12.7 (10.3–14.6)                      | 10.5 (8.5–12.3)                       | <.001           |
| 0–6   | 12.6 (10.6–14.3)                      | 10.45 (8.55–12.5)                     | <.001           |
| 6–12  | 11.3 (9.6–13.3)                       | 11.3 (8.7–13.4)                       | .97             |
| 12–24 | 11.65 (9.46–13.05)                    | 10.2 (8.8–12.2)                       | .13             |

This table is restricted to subjects for whom complete information on serial hemoglobin concentrations was available within the first 24 hours after cardiac arrest (n = 453).

<sup>a</sup>Median values are expressed as grams per deciliter.

**Table 4**

Odds of favorable neurologic outcome according to dichotomized and continuous hemoglobin concentration in the first 6 hours after cardiac arrest (n = 392)

| Hgb        | Unadjusted OR (95% CI) | Unadjusted <i>P</i> value | Adjusted OR (95% CI) <sup>a</sup> | Adjusted <i>P</i> value <sup>a</sup> |
|------------|------------------------|---------------------------|-----------------------------------|--------------------------------------|
| 7 g/dL     | 4.27 (1.26–14.47)      | .020                      | 3.92 (0.81–18.90)                 | .088                                 |
| 10 g/dL    | 2.77 (1.76–4.37)       | <.001                     | 2.30 (1.26–4.20)                  | .007                                 |
| Continuous | 1.25 (1.15–1.35)       | <.001                     | 1.23 (1.09–1.38)                  | <.001                                |

<sup>a</sup> Adjusted for age, shockable rhythm, cardiac etiology, arrest location (in-hospital vs out of hospital), receipt of TTM, renal insufficiency, and hematologic or metastatic cancer.

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**Table 5**

Odds of survival to hospital discharge according to dichotomized and continuous hemoglobin concentration after cardiac arrest (n = 448)

| Hgb        | Unadjusted OR (95% CI) | Unadjusted <i>P</i> value | Adjusted OR (95% CI) <sup>a</sup> | Adjusted <i>P</i> value <sup>a</sup> |
|------------|------------------------|---------------------------|-----------------------------------|--------------------------------------|
| First 6 h  |                        |                           |                                   |                                      |
| 7 g/dL     | 5.04 (1.49–17.06)      | .009                      | 4.74 (0.97–23.18)                 | .055                                 |
| 10 g/dL    | 2.35 (1.53–3.60)       | <.001                     | 2.05 (1.15–3.66)                  | .015                                 |
| Continuous | 1.23 (1.14–1.32)       | <.001                     | 1.20 (1.08–1.34)                  | .001                                 |
| First 24 h |                        |                           |                                   |                                      |
| 7 g/dL     | 4.17 (1.43–12.16)      | .009                      | 4.80 (1.02–22.53)                 | .047                                 |
| 10 g/dL    | 1.96 (1.35–2.83)       | <.001                     | 1.88 (1.13–3.11)                  | .015                                 |

<sup>a</sup>Adjusted for age, shockable rhythm, cardiac etiology, arrest location (in-hospital vs out of hospital), receipt of TTM, renal insufficiency, and hematologic or metastatic cancer.

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