Medicine®

OPEN

The association of early diarrhea after successful resuscitation following out-of-hospital cardiac arrest with neurological outcome
A retrospective observational study

Christoph Schriefl, MD[a],[*] [ID], Philipp Steininger, MD[b], Christian Clodi, MD[a], Matthias Mueller, MD[a], Michael Poppe, MD[a], Florian Ettl, MD[a], Alexander Nuernberger, MD[a], Juergen Grafeneder, MD[a], Heidrun Losert, MD[a], Michael Schwameis, MD[a], Michael Holzer, MD[a], Fritz Sterz, MD[a], Christian Schoergenhofer, MD[c]

Abstract

Gastrointestinal ischemia with reperfusion tissue injury contributes to post-cardiac arrest syndrome. We hypothesized that diarrhea is a symptom of intestinal ischemia/reperfusion injury and investigated whether the occurrence of early diarrhea (≤12 hours) after successful cardiopulmonary resuscitation is associated with an unfavorable neurological outcome.

We analyzed data from the Vienna Clinical Cardiac Arrest Registry. Inclusion criteria comprised ≥18 years of age, a witnessed, non-traumatic out-of-hospital cardiac arrest, return of spontaneous circulation (ROSC), initial shockable rhythm, and ST-segment elevation in electrocardiogram after ROSC with consecutive coronary angiography. Patients with diarrhea caused by other factors (e.g., infections, antibiotic treatment, or chronic diseases) were excluded. The primary endpoint was neurological function between patients with or without "early diarrhea" (≤12 hours after ROSC) according to cerebral performance categories.

We included 156 patients between 2005 and 2012. The rate of unfavorable neurologic outcome was higher in patients with early diarrhea (67% vs 37%). In univariate analysis, the crude odds ratio for unfavorable neurologic outcome was 3.42 (95% confidence interval, 1.11–10.56, $P = .03$) for early diarrhea. After multivariate adjustment for traditional prognostication markers the odds ratio of early diarrhea was 5.90 (95% confidence interval, 1.28–27.06, $P = .02$).

In conclusion, early diarrhea within 12 hours after successful cardiopulmonary resuscitation was associated with an unfavorable neurological outcome.

Abbreviations: CI = confidence intervals, CPC = cerebral performance category, CPR = cardiopulmonary resuscitation, OHCA = out-of-hospital cardiac arrest, OR = odds ratio, PCAS = post-cardiac arrest syndrome, ROSC = return of spontaneous circulation.

Keywords: critical care, diarrhea, intestinal ischemia, out-of-hospital cardiac arrest, prognosis, resuscitation, survival

1. Introduction

Out-of-hospital cardiac arrest (OHCA) is a global health burden and the third leading cause of death in Europe. Survival rates differ between health care systems, but overall only approximately 10% of patients survive to hospital discharge.[1,2]

Alongside established prehospital factors linked to improved outcome, such as early initiation of cardiopulmonary resuscita-

tion (CPR) or use of automated external defibrillators,[2] there are also several mechanisms after successful CPR with return of spontaneous circulation (ROSC) that impact on neurological outcome. These are summarized as post-cardiac arrest syndrome (PCAS) and also include tissue injury due to an ischemia reperfusion phenomenon, a systemic inflammatory response, and organ dysfunction with circulatory failure.[3–6]

Ischemia-reperfusion injury to the gastrointestinal tract, possibly with subsequent bacteremia or endotoxemia, may also contribute to PCAS. Animal models of low-flow shock or cardiac arrest reported intestinal tissue injury and an impaired gastrointestinal perfusion, also in the post-resuscitation period.[7–10] Human data on this topic are scarce. In a multicenter study in critically ill patients gastrointestinal symptoms in general, but also the early occurrence of diarrhea, were common and associated with increased mortality.[11] In a small study in OHCA patients those with bacteremia (n = 12) and diarrhea died within a few hours of admission.[12] More recently, it has been shown that patients with increased biomarkers of enterocyte damage or small bowel mucosal damage after successful CPR were more likely to have an unfavorable neurological outcome.[13]

We hypothesized that diarrhea, similarly to ischemic colitis,[14] was a result of intestinal ischemia during or after cardiac arrest, and investigated whether diarrhea occurring early after CPR was associated with an unfavorable neurological outcome.

2. Methods

2.1. Study design

We analyzed data from the Vienna Clinical Cardiac Arrest Registry. The registry includes prospectively collected data on all adult cardiac arrest patients, admitted to - and treated at the Department of Emergency Medicine of the Medical University of Vienna.

Data acquisition and documentation was conducted in accordance with the Utstein style recommendations for cardiac arrest related documentation[15] and has recently been described in detail for our registry.[16] The study complies with the declaration of Helsinki and was approved by the local Ethics Committee of the Medical University of Vienna (EK No. 1219/2018).

Early diarrhea was defined as at least 2 liquid stools within the first 12 hours after ROSC, based on nurses' or physicians' documentation.[17] We focussed on early diarrhea to exclude causes other than CPR (e.g., antibiotic treatment).

2.2. Study population

Adults ≥18 years of age who suffered a witnessed, non-traumatic OHCA and had achieved ROSC were eligible. Furthermore, only patients with an initial shockable rhythm and ST-segment elevation in the electrocardiogram, who consecutively underwent coronary angiography, were included. Patients with other possible causes for diarrhea (e.g., infections, antibiotic treatment, or chronic diseases) were excluded. In- and exclusion criteria were chosen to obtain a homogenous population with an obvious reason for cardiac arrest.

2.3. Endpoints

Patients were dichotomized in a "diarrhea" or "no diarrhea" group according to the above-mentioned criteria. The primary endpoint was neurological function, as defined by the cerebral performance category (CPC), at 6 months after CPR.

Favorable neurological outcome was defined as a CPC 1 (good neurologic function) or 2 (moderate disability) and unfavorable neurological outcome was defined as CPC 3–5 (severe disability, vegetative state, or death) in accordance to the Utstein recommendations.

Secondary endpoints included mortality at 6 months and an exploratory analysis of factors linked to the occurrence of diarrhea.

2.4. Statistical analysis

We present categorized data as counts (relative frequency), and continuous data as median (25–75% interquartile range). We compared binary variables using the Fisher-exact test and the log-rank test as applicable, and compared continuous variables using the Mann–Whitney U test.

We used a binary logistic regression analysis (backward stepwise elimination approach according to Wald test-statistics step-by-step) to estimate the effect of diarrhea on the primary endpoint. The effect was quantified as odds ratio (OR) with 95% confidence intervals (95% CI).

We selected covariables for the multivariable model based on both clinical reasoning and previous studies. These variables included age, sex, no-flow, low-flow, number of shocks, cumulative epinephrine dose, pH, and blood lactate concentration. The variables eliminated by the testing procedure were omitted.

Correlations were calculated by applying the nonparametric spearman procedure.

For data management and analyses we used MS Excel (Microsoft Corporation Redmond, WA) and IBM SPSS Statistics (Version 26, Armonk, NY: IBM Corporation). A 2-sided P value < .05 was considered statistically significant.

3. Results

During the 2005 to 2012 observation period, 156 OHCA patients fulfilled the inclusion criteria and were analyzed. Baseline characteristics including resuscitation-related parameters according to neurological outcome and diarrhea category are presented in Table 1. Patients with early diarrhea tended to be older, to have longer low-flow time intervals, and higher blood lactate concentrations. C-reactive protein levels 6 hours after ROSC did not significantly differ between the groups. As expected, patients with unfavorable outcome were significantly older (P = .004) and had longer low-flow intervals (P < .001), lower pH values (P < .001), and higher lactate levels (P < .001).

3.1. Outcome analysis

More patients with early diarrhea had an unfavorable neurological outcome (67% vs 37%, P = .049). In univariate analysis, the crude OR for unfavorable neurologic outcome was 3.42 (95% CI, 1.11–10.56, P = .03) for early diarrhea. After multivariate adjustment for age, sex, no-flow, low-flow, number of shocks, cumulative epinephrine dose, pH, and lactate the adjusted OR of early diarrhea was 5.90 (95% CI, 1.28–27.06, P = .02).

Besides the significant differences in neurological outcome for early diarrhea, there was no significant difference in 6-month

Table 1

Baseline characteristics by outcome group and diarrhea category.

	All n = 156	Favorable neurological outcome n = 94	Unfavorable neurological outcome n = 62	No diarrhea n = 141	Early diarrhea n = 15
Age, median (IQR)	55 (49–64)	55 (47–60)	60 (50–68)	55 (49–64)	56 (50–69)
Female, n (%)	29 (19)	19 (20)	10 (16)	26 (18)	3 (20)
No-flow (min), median (IQR)	1 (0–4)	1 (0–3)	2 (1–6)	1 (0–4)	1 (0–3)
Low-flow (min), median (IQR)	27 (18–43)	17 (10–27)	27 (21–36)	20 (13–34)	25 (18–28)
Total dose of epinephrine in mg, median (IQR)	3 (2–5)	2 (1–4)	4 (2–6)	3 (2–5)	4 (1–4)
Number of shocks applied, median (IQR)	3 (2–6)	3 (1–5)	4 (2–6)	3 (2–6)	4 (2–6)
Admission pH, median (IQR)	7.20 (7.09–7.27)	7.22 (7.12–7.30)	7.14 (7.02–7.23)	7.21 (7.09–7.28)	7.14 (7.09–7.21)
Admission lactate (mmol/L), median (IQR)	7.7 (5.2–9.8)	7.1 (4.7–9.1)	9.3 (7.0–12.3)	7.6 (5.1–9.7)	8.1 (6.2–10.2)
WBC count 6 h after ROSC (G/L), median (IQR)	16.6 (12.0–21.2)	15.3 (11.9–21.1)	17.6 (12.7–21.6)	16.7 (12.3–21.1)	14.3 (10.2–21.8)
CRP level 6 h after ROSC (mg/dL), median (IQR)	0.4 (0.2–0.8)	0.4 (0.2–0.8)	0.4 (0.2–0.7)	0.4 (0.2–0.8)	0.2 (0.1–0.5)
Early stool*, n (%)	21 (13)	11 (12)	10 (16)	6 (4)	15 (100)
Early diarrhea, n (%)	15 (10)	5 (5)	10 (16)	0 (0)	15 (100)
CPC 1/2 at 6 months, n (%)	94 (60)	94 (100)	0 (0)	89 (63)	5 (33)
Mortality at 6 months, n (%)	48 (31)	0 (0)	48 (77)	41 (29)	7 (47)

Favorable neurological outcome was defined as cerebral performance category 1 to 2, unfavorable neurological outcome as cerebral performance category 3 to 5.

CPC = cerebral performance category, CRP = C-reactive protein, IQR = interquartile range, ROSC = return of spontaneous circulation, SD = standard deviation, WBC = white blood cell.

* Defined as stool regardless of consistency within 12 hours after ROSC.

mortality (29% no diarrhea vs 47% early diarrhea group, $P = .24$).

3.2. Exploratory analysis

We analyzed various parameters between patients with or without diarrhea in an exploratory manner, but found no differences regarding age, no- and low-flow intervals, inflammatory biomarkers, pH values, or lactate levels.

4. Discussion

The main finding of this analysis is that patients who developed diarrhea within 12 hours after ROSC were more likely to have an unfavorable neurological outcome.

Gastrointestinal dysfunction caused by transient hypoperfusion or ischemia may contribute to PCAS and thus impact on neurological outcome. Diarrhea is an unspecific symptom of gastrointestinal dysfunction, but is easy to assess, and by applying strict in- and exclusion criteria we tried to exclude causes other than resuscitation itself. Our results support data from a small study (n = 33) in which all patients with diarrhea and bacteremia (n = 12) after CPR died within hours after admission.[12] Notably, our analysis only focussed on diarrhea and not on bacteremia. Nonetheless, two thirds of patients with early diarrhea had an unfavorable neurologic outcome and 47% died. Although the observed difference in mortality was remarkable, statistical significance was not met, most likely due to the limited sample size in the diarrhea group (n = 15). Plasma citrulline and intestinal fatty acid–binding protein, both biomarkers of enterocyte mass and damage, were associated with poor neurological outcome after CPR.[13] Moreover, cardiac arrest patients with high levels of endotoxins, which are most likely of intestinal origin, were more likely to have an unfavorable outcome.[18] These results indicate an important role for the gastrointestinal system in the post-resuscitation period and may also offer opportunities for therapeutic interventions.

Our hypothesis was based on the assumption that diarrhea after resuscitation, in the absence of other causes, serves as a surrogate of intestinal injury due to transient ischemia. Interestingly, low-flow intervals were only slightly longer (25 minutes vs 20 minutes) in patients with diarrhea. However, the individual constitution of OHCA patients differs substantially, and in addition to quality and duration of CPR other factors, such as stenosed mesenteric arteries or resistance to ischemic events, need to be considered. In that context, it may not be surprising that we missed the association between resuscitation intervals and the occurrence of diarrhea. Somewhat surprisingly, we did not observe an association between diarrhea and systemic inflammation, as assessed by C-reactive protein levels and leukocyte counts during the first 24 hours. Although similar results were reported in animal studies,[8] one could assume that tissue injury and consecutive endotoxemia induce an inflammatory response.

Based on our data, the occurrence of diarrhea soon after CPR may be regarded as a negative prognostic sign. However, further studies are warranted to better understand underlying pathophysiological mechanisms.

5. Limitations

The limitations of this study consist of its observational nature, limited sample size, and single center design. Strict eligibility criteria were chosen to exclude other possible causes of diarrhea. Due to the highly selected patient cohort, however, the generalizability of our study findings is limited. We included only adult cardiac arrest survivors with ST-segment elevation myocardial infarction who underwent coronary angiography. Although the hypothesized mechanism of our observation should theoretically apply to other causes of cardiac arrest as well, because it is based on the duration of intestinal ischemia, our data do not allow such a generalization. Finally, the study hypothesis was based on the assumption that diarrhea is a sign of tissue damage as a consequence of transient ischemia. Further data to

support this hypothesis (biomarkers, radiologic, or histologic analyses) were beyond the scope of this work.

6. Conclusions

Early diarrhea within 12 hours of successful CPR is associated with unfavorable neurological outcome in the included population.

Author contributions

Conceptualization: Christoph Schriefl, Philipp Steininger, Juergen Grafeneder, Michael Schwameis, Christian Schoergenhofer.
Data curation: Christoph Schriefl, Philipp Steininger, Christian Clodi, Matthias Mueller, Michael Poppe, Florian Ettl, Alexander Nuernberger, Heidrun Losert, Michael Holzer, Fritz Sterz.
Formal analysis: Juergen Grafeneder, Christian Schoergenhofer.
Investigation: Christoph Schriefl, Christian Clodi, Matthias Mueller, Michael Poppe, Florian Ettl, Alexander Nuernberger, Heidrun Losert, Michael Holzer, Fritz Sterz.
Methodology: Christoph Schriefl, Philipp Steininger, Juergen Grafeneder, Michael Schwameis, Christian Schoergenhofer.
Project administration: Philipp Steininger.
Supervision: Michael Schwameis, Fritz Sterz, Christian Schoergenhofer.
Validation: Christian Schoergenhofer.
Visualization: Christian Schoergenhofer.
Writing – original draft: Christoph Schriefl.
Writing – review & editing: Philipp Steininger, Christian Clodi, Matthias Mueller, Michael Poppe, Florian Ettl, Alexander Nuernberger, Juergen Grafeneder, Heidrun Losert, Michael Schwameis, Michael Holzer, Fritz Sterz, Christian Schoergenhofer.

References

[1] Berdowski J, Berg RA, Tijssen JG, Koster RW. Global incidences of out-of-hospital cardiac arrest and survival rates: systematic review of 67 prospective studies. Resuscitation 2010;81:1479–87.
[2] Grasner JT, Wnent J, Herlitz J, et al. Survival after out-of-hospital cardiac arrest in Europe - results of the EuReCa TWO study. Resuscitation 2020;148:218–26.
[3] Adrie C, Adib-Conquy M, Laurent I, et al. Successful cardiopulmonary resuscitation after cardiac arrest as a "sepsis-like" syndrome. Circulation 2002;106:562–8.
[4] Bro-Jeppesen J, Kjaergaard J, Wanscher M, et al. The inflammatory response after out-of-hospital cardiac arrest is not modified by targeted temperature management at 33 degrees C or 36 degrees C. Resuscitation 2014;85:1480–7.
[5] Czerwinska-Jelonkiewicz K, Grand J, Tavazzi G, et al. Acute respiratory failure and inflammatory response after out-of-hospital cardiac arrest: results of the Post-Cardiac Arrest Syndrome (PCAS) pilot study. Eur Heart J Acute Cardiovasc Care 2020;9:S110–21.
[6] Mongardon N, Dumas F, Ricome S, et al. Postcardiac arrest syndrome: from immediate resuscitation to long-term outcome. Ann Intensive Care 2011;1:45.
[7] Deitch EA, Morrison J, Berg R, Specian RD. Effect of hemorrhagic shock on bacterial translocation, intestinal morphology, and intestinal permeability in conventional and antibiotic-decontaminated rats. Crit Care Med 1990;18:529–36.
[8] Schroeder DC, Maul AC, Mahabir E, et al. Evaluation of small intestinal damage in a rat model of 6 minutes cardiac arrest. BMC Anesthesiol 2018;18:61.
[9] Voelckel WG, Lindner KH, Wenzel V, et al. Effects of vasopressin and epinephrine on splanchnic blood flow and renal function during and after cardiopulmonary resuscitation in pigs. Crit Care Med 2000;28:1083–8.
[10] Albrecht M, Gruenewald M, Zitta K, et al. Hypothermia and anesthetic postconditioning influence the expression and activity of small intestinal proteins possibly involved in ischemia/reperfusion-mediated events following cardiopulmonary resuscitation. Resuscitation 2012;83:113–8.
[11] Reintam Blaser A, Poeze M, Malbrain ML, et al. Gastrointestinal symptoms during the first week of intensive care are associated with poor outcome: a prospective multicentre study. Intensive Care Med 2013;39:899–909.
[12] Gaussorgues P, Gueugniaud PY, Vedrinne JM, Salord F, Mercatello A, Robert D. Bacteremia following cardiac arrest and cardiopulmonary resuscitation. Intensive Care Med 1988;14:575–7.
[13] Piton G, Belin N, Barrot L, et al. Enterocyte damage: a piece in the puzzle of post-cardiac arrest syndrome. Shock 2015;44:438–44.
[14] Theodoropoulou A, Koutroubakis IE. Ischemic colitis: clinical practice in diagnosis and treatment. World J Gastroenterol 2008;14:7302–8.
[15] Perkins GD, Jacobs IG, Nadkarni VM, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update of the utstein resuscitation registry templates for out-of-hospital cardiac arrest: a statement for healthcare professionals from a task force of the international liaison committee on resuscitation (American Heart Association, European Resuscitation Council, Australian and New Zealand Council on Resuscitation, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, Resuscitation Council of Asia); and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. Resuscitation 2015;96:328–40.
[16] Weiser C, Schwameis M, Sterz F, et al. Mortality in patients resuscitated from out-of-hospital cardiac arrest based on automated blood cell count and neutrophil lymphocyte ratio at admission. Resuscitation 2017;116:49–55.
[17] Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol 1997;32:920–4.
[18] Grimaldi D, Sauneuf B, Guivarch E, et al. High level of endotoxemia following out-of-hospital cardiac arrest is associated with severity and duration of postcardiac arrest shock. Crit Care Med 2015;43:2597–604.