Hemodynamics and vasopressor support during targeted temperature management after cardiac arrest with non-shockable rhythm: A post hoc analysis of a randomized controlled trial

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Abstract

Background: Patients admitted after cardiac arrest with non-shockable rhythm frequently experience hemodynamic instability. This study assessed the hemodynamic consequences of TTM in this sub population.

Methods: This is a post hoc analysis of the HYPERION trial (NCT01994772), that randomized patients to either hypothermia or normothermia after non-shockable rhythm related cardiac arrest. Patients with no, moderate or severe circulatory failure were identified with cardiovascular Sequential Organ Failure Assessment at randomization. Primary outcome was the number of patients at day 7 with resolution of shock, accounting for the risk of death (competing risk analysis). Secondary endpoint included neurological outcome and death at day-90.

Results: 584 patients were included in the analysis: 195 (34%), 46 (8%) and 340 (59%) had no, moderate and severe circulatory failure, respectively. Resolution of circulatory failure at day 7 was more frequently observed in the normothermia group than in the TTM group (60% [95 %CI 54–66] versus 53% [95 %CI 46–60], Gray-test: p = 0.016). The severity of circulatory failure at randomization was associated with its less frequent resolution at day 7 accounting for the risk of death (76 % [62–86] versus 54% [49–59] for patients with moderate versus severe circulatory failure, Gray test, p < 0.001, respectively). At day 90, the proportion of patients with Cerebral Performance Category score of 1 or 2 was lower in patients presenting severe circulatory failure (p = 0.038).

Conclusion: Circulatory failure is frequent after CA with non-shockable rhythm. Its severity at admission and TTM were associated with delayed resolution of circulatory failure.

Keywords: Cardiac arrest, Targeted temperature management, Post resuscitation shock, Circulatory failure

Introduction

In consequence of whole body ischemia–reperfusion syndrome subsequent to cardiac arrest (CA), successfully resuscitated patients often develop severe post-resuscitation circulatory failure, associating vasoplegia, myocardial dysfunction and systemic ischemic injury. This circulatory failure, included in the well-known “post-resuscitation disease”, may be associated with different other organ failure and drastically impacts outcome. Targeted temperature management (TTM) is so far recommended by international guidelines to prevent or limit hypoxic-ischemic brain damage in CA patients remaining comatose after restoration of spontaneous circulation resuscitation (ROSC). Circulatory failure may be potentially worsened by induced hypothermia, which is potentially a stress to the cardiovascular system with significant hemodynamic impact involving decreased cardiac index, lower heart rate and increased systemic vascular resistance. While there is a lot of experimental and animal data on the impact of temperature management and hemodynamics, very few data have been published so far to describe the potential longitudinal impact of TTM on early hemo-
In this post hoc analysis, all the patients included in the Hyperion trial recently provided data in favor of hypothermia in CA patients with initial non-shockable rhythm. Impact of such a strategy on hemodynamic parameters in patients presenting post-resuscitation circulatory failure has not been fully studied in this situation.

In the present study, using the Hyperion trial data, we aimed to investigate cardiovascular consequences of hypothermia in CA patients with non-shockable rhythm and its association with outcome.

**Methods**

**Design**

This was a post-hoc analysis of the Hyperion trial (NCT01994772), a multicentric French randomized controlled trial investigating TTM at 33°C versus normothermia during the first 24 hours in comatose (score ≤ 8 on the Glasgow Coma Scale) CA patients with non-shockable rhythm survivors. Among patients presenting circulatory failure at admission, resolution of shock at day-7 was more frequently observed in the normothermia group (60% [95 %CI 54–66] versus 53% [95 %CI 49–59]; Gray-test: p = 0.016) (Fig. 2). Mortality at day 7 was similar in TTM group and normothermia group (36% [95 %CI 30–42] versus 43% [95 %CI 36–50]; Gray-test: p = 0.18). Among survivors at day 7, median duration of circulatory failure was 2 [1;3] days in normothermia group versus 3 [2;4] days in TTM group (p < 0.001). The severity of circulatory failure at randomization was associated with a lower概率 of resuscitated CA patients. The HYPERION trial recently provided data in favor of hypothermia in CA patients with initial non-shockable rhythm. Impact of such a strategy on hemodynamic parameters in patients presenting post-resuscitation circulatory failure has not been fully studied in this situation.

In the present study, using the Hyperion trial data, we aimed to investigate cardiovascular consequences of hypothermia in CA patients with non-shockable rhythm and its association with outcome.

**Statistical analysis**

Continuous variables were expressed as median (1st–3rd quartiles) while categorical variables were expressed as frequencies (percentage). Baseline characteristics were compared across cSOFA categories using ordered Cochran-Armitage test and Jonckheere’s test for categorical and continuous variables, respectively.

The primary outcome was assessed using a competing risk model (Gray test, and cumulative incidence curves). All statistical tests were two-sided, with p ≤ 0.05 considered significant. Statistical analysis was computed with R software (Version 3.6.3; R Foundation for Statistical Computing, Vienna, Austria) and the statistical package Crmpsk for the competing risk analysis.

**Results**

** Patients**

All of the 581 patients included in the Hyperion trial were included in this post-hoc analysis: 284 allocated to TTM and 297 to normothermia. At inclusion, 195 (34%), 46 (8%) and 340 (59%) patients had no, moderate and severe circulatory failure, respectively. Baseline characteristics were not different between the 3 groups (Table1), except for a statistically longer no-flow time in patients who did not have circulatory failure (p = 0.045), a lower temperature at enrollment (p = 0.035) and a more frequent use of epinephrine (p = 0.012) in patients with severe circulatory failure. Proportions of patients receiving inotropic or vasopressor support for the first 7 days after CA according to group of randomization are given in Fig. 1. Baseline characteristics and outcome of these patients are described in ESM Table 1. Hemodynamic variables and temperature during the first 68 hours of management are given in ESM Fig. 1. Twenty patients developed circulatory failure after the period of intervention (ESM Table 2).

**Primary outcome**

Among patients presenting circulatory failure at admission, resolution of shock at day-7 was more frequently observed in the normothermia than in the TTM group (60% [95 %CI 54–66] versus 53% [95 %CI 46–60]; Gray-test: p = 0.016) (Fig. 2). Mortality at day 7 was similar in TTM group and normothermia group (36% [95 %CI 30–42] versus 43% [95 %CI 36–50]; Gray-test: p = 0.18). Among survivors at day 7, median duration of circulatory failure was 2 [1;3] days in normothermia group versus 3 [2;4] days in TTM group (p < 0.001). The severity of circulatory failure at randomization was associated with a lower probability of resuscitated CA patients. The HYPERION trial recently provided data in favor of hypothermia in CA patients with initial non-shockable rhythm. Impact of such a strategy on hemodynamic parameters in patients presenting post-resuscitation circulatory failure has not been fully studied in this situation.

In the present study, using the Hyperion trial data, we aimed to investigate cardiovascular consequences of hypothermia in CA patients with non-shockable rhythm and its association with outcome.
resolution of shock at day 7 accounting for the risk of death (76\% [95\%CI 62–86\% for patients with moderate shock, versus 54\% [95\%CI 49–59\% for patients with severe shock, gray test, p < 0.001).

**Secondary outcome**

TTM interruption was not more frequent in patients presenting the most severe circulatory failure and was observed in 22 (13.4\%), 4
(21.1%) and 10 (9.9%) patients with severe, moderate and no circulatory failure at admission, respectively (p = 0.370).

At day-90, survival was similar in the 3 groups (p = 0.49, Table 2). Proportion of patients with a CPC score of 1 or 2 at day 90 was lower in patients presenting severe circulatory failure at randomization (p = 0.038).

Discussion

In this post hoc analysis of the Hyperion trial involving 581 comatose patients after CA with non-shockable rhythm admitted to the ICU, we compared outcomes over severity of post-resuscitation circulatory failure within the first 7 days after ICU admission. To our knowledge, only few small studies have investigated hemodynamic during TTM in this subgroup of patients. We found that 1) while heart rate was significantly lower in patient with TTM, MAP was similar between the two groups of randomization 2) 66 % of patients evidenced post-resuscitation circulatory failure at randomization, and the severity of shock at admission and the intervention were associated with a delay in the timing of hemodynamic improvement 3) severity of shock at admission was associated with a worse functional outcome at day 90 evaluated with CPC score.

Post-CA syndrome is frequent in CA survivors resuscitated from initial non-shockable rhythm. Its pathogenesis is complex, involving at different levels ischemia reperfusion syndrome worsened by the common hypoxic etiology as well as infectious phenomena and myocardial dysfunction. Consequent systemic inflammation induces vasodilatation and lower MAP motivating vasopressor infusion to avoid subsequent cerebral aggression, which may drastically grave the functional outcome of these patients. Precedent studies investigated the hemodynamic implication of TTM and found that several factors were associated with higher need of vasopressor, as time to return to spontaneous circulation, age, or percutaneous coronary intervention. While the circulatory failure after ROSC is now well identified as a factor of poor prognosis, the impact of TTM in these patients, potentially worsening the shock, is still unknown. Moreover, these moribund/instable patients are very frequently excluded from these studies, precluding us to drive conclusions. In non-shockable rhythm CA survivors...
admitted to the ICU, we found that the severity of shock at admission was associated with a worse functional outcome at day-90. Furthermore, TTM delay the timing of shock resolution at day-7 although the rate of TTM interruption was similar in the three subgroups. Grand et al. found similar findings in patient with prolonged TTM in their post-hoc analysis of the TT48 trial. Similar results have been described in a retrospective registry-based study of 412 CA patients.6

In these situation, TTM may worsen the hemodynamic status, and consequently, could alter oxygen delivery to the brain. Indeed, hypothermia has negative hemodynamic effects by slowing metabolism and directly depressing myocardial function.22 Patients can developed hypovolemia in consequence of an augmentation of urine output (also called cold diuresis).23 Afterload is also raised through the release of catecholamines, leading to an increase of arterial resistance.22 As a result of all these mechanisms, cardiac output is decreased.22 Finally, it has been reported that, in patients with pre-existent coronary artery disease, coronary vasconstriction may occur during hypothermia,24 because of an endothelial dysfunction, and worsen oxygen delivery to heart. Then, whether to apply or not such a strategy in these patients remains a matter of debate, especially since the results of the TTM2 trial in which the authors found discordant results in the subgroup of patients suffering cardiovascular failure at admission.

One strength of our study is the prospective and consecutive inclusion of patients and collection of data, in a multicentric randomized trial, increasing the validity of our result. However, we acknowledge that our study has several limitations. First, it was a non-prespecified post hoc analysis, and the study may have lack of power to identify association between variables and outcome. Second, some patients died during the period of analysis and hemodynamic data collection introducing a survival bias. However, the primary cause of death was withdrawal of care related to anoxic brain damage (64% of death), and we tried to limit this bias performing a competitive risk analysis, and expect the bias to be minimal. Third, the haemodynamic impact of TTM could have been more accurately evaluated using vasopressors and inotropic support doses over time as well as sedation doses. Unfortunately, these information were not collected in the HYPERION trial. While we believe this could have improved our findings, cardiovascular SOFA is a reliable tool used to evaluate one-point as well as longitudinal cardiovascular data. Finally, patients who developed circulatory failure after TTM were not analyzed as shocked patient, which can introduce a selection bias. However, we considered that this situation must not be considered as a post cardiac arrest syndrome but is due to other etiologies (sepsis, ventilator associated pneumonia, hemorrhage).

### Conclusion

Circulatory failure is frequent after CA with non-shockable rhythm survivors admitted to the ICU. Severity of circulatory failure at admission and TTM strategy were associated with worse long-term neurological outcome and a delay in the timing of resolution of circulatory failure.

### Conflict of Interest

Dr. Lascarrou reports consulting fees from BD and Zoll. None of the other authors has any conflicts of interest to disclose.

### Acknowledgements

None.

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Credit Author Statement

Matthieu Petit and Guillaume Geri conceptualized the study.
Acquisition of data: Jean-Baptiste Lascarrou, Hamid Merdji, Gwenhael Colin and Alain Cariou acquired the data.
Matthieu Petit and Guillaume Geri did the formal analysis of the data.
Matthieu Petit and Guillaume Geri wrote the manuscript.
All authors reviewed the manuscript. critical revision of the manuscript for important intellectual content: all authors.
Obtained funding: Jean-Baptiste Lascarrou obtained obtained funding for the original study.
Study was supervised by Guillaume Geri.

Appendix B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resplu.2022.100271.

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