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Review article

Cerebral oximetry and return of spontaneous circulation after cardiac arrest: A systematic review and meta-analysis☆

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ABSTRACT

Aim: The prediction of return of spontaneous circulation (ROSC) during resuscitation of patients suffering of cardiac arrest (CA) is particularly challenging. Regional cerebral oxygen saturation (rSO_2) monitoring through near-infrared spectrometry is feasible during CA and could provide guidance during resuscitation.
Methods: We conducted a systematic review and meta-analysis on the value of rSO_2 in predicting ROSC both after in-hospital (IH) or out-of-hospital (OH) CA. Our search included MEDLINE (PubMed) and EMBASE, from inception until April 4th, 2015. We included studies reporting values of rSO_2 at the beginning of and/or during resuscitation, according to the achievement of ROSC.
Results: A total of nine studies with 315 patients (119 achieving ROSC, 37.7%) were included in the meta-analysis. The majority of those patients had an OHCA ($n = 225$, 71.5%; IHCA: $n = 90$, 28.5%). There was a significant association between higher values of rSO_2 and ROSC, both in the overall calculation (standardized mean difference, SMD −1.03; 95%CI −1.39,−0.67; $p < 0.001$), and in the subgroups analyses (rSO_2 at the beginning of resuscitation: SMD −0.79; 95%CI −1.29,−0.30; $p = 0.002$; averaged rSO_2 value during resuscitation: SMD −1.28; 95%CI −1.74,−0.83; $p < 0.001$).
Conclusions: Higher initial and average regional cerebral oxygen saturation values are both associated with greater chances of achieving ROSC in patients suffering of CA. A note of caution should be made in interpreting these results due to the small number of patients and the heterogeneity in study design: larger studies are needed to clinically validate cut-offs for guiding cardiopulmonary resuscitation.

1. Introduction

Despite improvements in the management of cardiopulmonary resuscitation (CPR) and of the post-resuscitation care, survival after cardiac arrest (CA) remains low. The rate of return of spontaneous circulation (ROSC) is low, especially among out-of-hospital (OH) CA;[1,2] moreover less than half of the patients admitted to a hospital after CA survive the six-month follow-up.[3]

The prediction of ROSC during resuscitation is challenging. To date there is no validated tool to aid physicians in deciding how long to prolong resuscitation efforts. The decision is often made mainly on clinical judgement alone. If ROSC is achieved, the main cause of death is neurological damage, resulting from both, the initial ischaemic insult and the subsequent reperfusion injury.[4,5]

Cerebral oximetry is a near-infrared spectrometry (NIRS) non-invasive technology approved by the US Food and Drug Administration allowing the monitoring of regional cerebral oxygen saturation (rSO_2) in accessible superficial brain cortex regions, which are also amongst the most vulnerable to ischaemic–hypoxic injury.[6] Values of rSO_2 have shown a correlation with those of jugular venous bulb oxygenation.[7,8]

The feasibility of rSO_2 monitoring in CA patients has already been demonstrated in several studies, investigating the cut-off

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values of rSO_2 that predict ROSC[9,10] and/or neurological outcome after CA.[11,12] Moreover, rSO_2 has been recently investigated as a tool to evaluate the quality of cardiopulmonary resuscitation (CPR).[13]

We undertook a systematic review of the available literature that evaluated rSO_2 to predict successful ROSC in patients suffering CA. We also conducted a meta-analysis with the hypothesis that ROSC was associated with higher rSO_2 values.

2. Methods

Our systematic review was based on the findings of a web-based literature search conducted using the NHS Library Evidence tool. A further manual search was conducted independently by two authors (FS and GS), exploring the list of references of the findings of the systematic search. We followed the approach suggested by the PRISMA statement for reporting systematic reviews and meta-analyses (Supplemental Digital Content–Appendix 1).[14] We attempted registration of the protocol of our systematic review and meta-analysis in the PROSPERO database; however since data extraction already started, the registration was not accepted.

Our hypothesis was that higher values of rSO_2, both at the first recorded value and the average value during resuscitation, would have been positively correlated with achievement of ROSC of CA patients.

Inclusion criteria were pre-specified according to the PICOS approach (Table 1). We excluded articles referring to the paediatric population. Since no randomized controlled studies addressing this subject were expected, a priori decision to include non-randomized prospective and retrospective clinical studies was made. Case series were included in the study if reporting at least five patients; series with a lower number of patients and single case reports were excluded.

The computerized search included MEDLINE (PubMed) and EMBASE, from inception until April 4th, 2015. The core search was structured by the combination of terms obtained from the following two groups. The first one included in alphabetical order: "cerebral oximetry", "near-infrared", "oxygen consumption", "spectrophotometry" and "spectroscopy". The second group consisted of the following: "cardiac arrest", "heart arrest", "resuscitation" and "return of spontaneous circulation". The search strategy was limited to clinical (human) studies and it is summarized in the Supplemental Digital Content – Appendix 2.

Two authors (FS and GS) independently searched these databases. Duplicates were initially filtered through automated software function and afterwards screened manually by three authors (FS, GS and CC). Study selection for determining the eligibility for inclusion in the systematic review and data extraction from the selected studies were performed independently by two reviewers (FS and GS). Discordances were resolved by involving another reviewer (MC) and/or by consensus. When needed, we contacted via email the corresponding authors for retrieving the largest amount of available data. Meta-analysis was performed independently by two experienced authors (CC and UB).

Table 1
"PICOS" approach for selecting clinical studies in the systematic search. NIRS = near-infrared spectrometry; ROSC = return of spontaneous circulation.

PICOS	
1. Participants	Cardiac arrest patients, including both in- and out-of-hospital setting
2. Intervention	Measurements of regional cerebral oxygen saturation via NIRS, either first recorded value or average value during resuscitation
3. Comparison	No comparison with other prognostication tool
4. Outcomes	Achievement of ROSC
5. Study design	Prospective and retrospective clinical studies; case series if reporting at least five patients

Language restrictions were applied: only articles published in English, Spanish, German, French or Italian were considered. Findings retrieved from EMBASE as conference abstract are reported only if published after August 2012 to allow a reasonable time for multiple peer-reviewed process. Two authors (CC and GS) independently assessed the methodological quality of the included studies using the Newcastle–Ottawa Assessment Scale (NOS) which is a tool recommended by the Cochrane collaboration for assessing the quality of non-randomized studies.[15] The scale has three main domains and assigns one point for each subset of assessment criteria within the selection and exposure domains. Studies can obtain up to two points within the comparability domain. We then classified studies as high risk (1–3 points), intermediate risk (4–5 points) and low risk of bias (6–9 points).

2.1. Statistical analysis

Continuous outcome differences were analyzed using an inverse variance model with a 95% confidence interval. Values are reported as standard mean difference (SMD), *P* values were two-tailed and considered significant if <0.05. The presence of statistical heterogeneity was assessed using the X^2 (Cochran *Q*) test. Heterogeneity was likely if $Q > df$ (degrees of freedom) suggested and confirmed if $P \leq 0.10$. Quantification of heterogeneity performed using I^2 statistic. Values of 0–24.9, 25–49.9, 50–74.9 and >75% were considered as none, low, moderate and high heterogeneity, respectively.[16] If heterogeneity was quantified as low or above, a random model was used. Two sensitivity analyses were planned excluding studies with high risk of bias and studies with high and intermediate risk of bias.

3. Results

The literature search with the above mentioned criteria produced 493 total findings, 138 on MEDLINE and 355 on EMBASE; 23 duplicates were removed via automatic software leaving a total of 470 publications.

We excluded 442 findings as judged to be not relevant to our search target, leaving potentially 28 studies. We manually identified three further duplicates and the manual search did not add further findings. Of the remaining 25 abstracts, 13 were excluded; 7 studies provided data on neurological outcome but not on ROSC, the other being reviews ($n = 2$) or letters to editor ($n = 4$).

A total of 12 articles remained for possible inclusion in the qualitative synthesis but only nine were included in the meta-analysis since one group of authors (Asim et al., *Am J Emerg Med*, 2014) did not have the NIRS data requested, the authors of one conference abstract did not provide the data requested (Bougle A et al., *Int Care Med*, 2014), and another conference abstract (Genbrugge et al., *Crit Care*, 2013) was a subset of a larger study published later[17] and included among the qualitative data analysis (Fig. 1).

All nine studies included in this meta-analysis were non-randomized observational studies published in peer-reviewed journals. We did not find evidence of retrospective studies or case series. No systematic-reviews and meta-analysis have assessed this topic as yet.

Of the nine findings included in the data for meta-analysis, five studies evaluated out-of-hospital CA (OHCA) patients only,[10,17–20] other two studies included only patients presenting with in-hospital CA (IHCA),[13,21] and two studies included both OHCA and IHCA populations.[9,22] Different devices have been used in these studies (Table 2). Unfortunately, none of the studies reported the exact time between the CA and the first detected rSO_2 value; moreover, no study reported a multivariable analysis including

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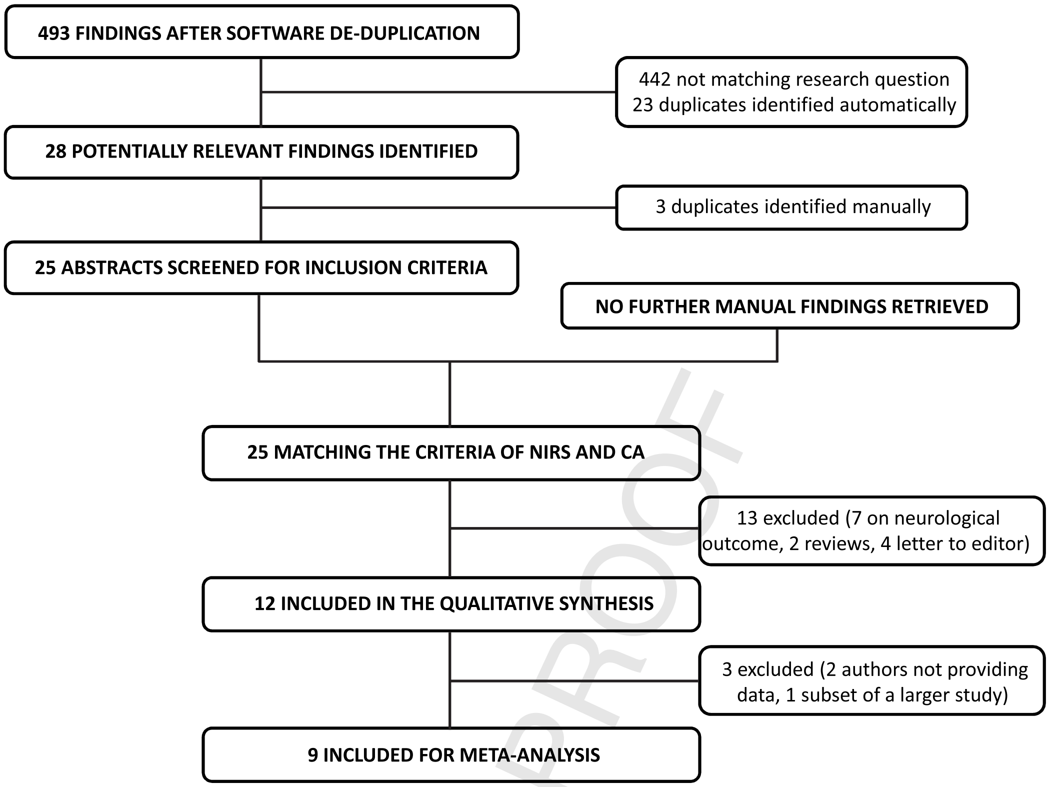

Fig. 1. Flowchart of the systematic search and of the qualitative synthesis for meta-analysis.

Table 2
Population included in the selected studies for meta-analysis and device used for monitoring cerebral oximetry. IHCA: in-hospital cardiac arrests; OOHCA: out-of-hospital cardiac arrests.

Study	Population	NIRS device used
Ahn 2013	50 pts (36 IHCA; 14 OHCA)	Equanox 7600, Nonin Medical, Inc., Plymouth, MN, USA
Fukuda 2014	69 pts (OHCA)	INVOS 5100, Covidien, Boulder, CO, USA
Genbrugge 2015	49 pts (OHCA)	Equanox Advance, Nonin Medical, Inc., Plymouth, MN, USA
Koyama 2013	15 pts (OHCA)	Hamamatsu Photonics, Hamamatsu-Shi, Shizuoka, Japan
Meex 2013	14 pts (5 IHCA; 9 OHCA)	FORE-SIGHT (CAS Medical Systems, Branford, CT, USA) and Equanox Advance (Nonin Medical, Inc., Plymouth, MN, USA)
Parnia 2012	15 pts (IHCA)	INVOS Somanetics, Troy, USA
Parnia 2014	34 pts (IHCA)	Equanox, Nonin, Plymouth, MI, USA INVOS, Covidien, Mansfield, MA, USA
Schewe 2014	10 pts (OHCA)	Equanox 7600, Nonin Medical, Inc., Plymouth, MN, USA
Singer 2014	59 pts (OHCA)	Equanox, Nonin, Plymouth MI, USA

other variables influencing outcomes of CA patients. Risk of bias assessment using the NOS considered two studies as high risk of bias,[19,21] another study as intermediate risk,[22] with the remaining studies regarded as low risk[9,10,13,17,18,20] (Supplemental Digital Content–Appendix 3).

3.1. Cerebral oximetry and ROSC

A total of 315 patients (number of patients per study ranging from 14 to 69 patients) were included in the selected studies for meta-analysis. Of these, 119 achieved ROSC (37.7%) while 196 (61.8%) did not. The majority of patients included suffered of OHCA ($n = 225$, 71.5%; IHCA: $n = 90$, 28.5%).

Only one study reported rSO_2 data both at the initial recording ("earliest point possible"–device always easily available) and the mean value during the resuscitation period.[9]

Four studies provided data on initial values of NIRS in OHCA patients: one study recorded data immediately at the arrival of medical emergency team to the OHCA,[17] one reported values gathered from rSO_2 sensor applied to the right forehead of both IHCA and OHCA patients at the beginning of resuscitation,[22] while two Japanese studies provided rSO_2 data promptly measured at Emergency Department arrival.[18,19] The remaining four studies recorded the average rSO_2 value from the initial recording until the CPR was ended (ROSC vs death).[10,13,20,21]

ROSC was associated with significantly higher values of rSO_2 compared to the population that did not achieve ROSC. Values of rSO_2 were significantly higher overall (SMD −1.03; 95%CI −1.39, −0.67; $p < 0.001$), in the subgroup of studies providing initial values during resuscitation (SMD −0.79; 95%CI −1.29, −0.30; $p = 0.002$) and in the subgroup of studies evaluating the averaged value during CPR (SMD −1.28; 95%CI −1.74, −0.83; $p < 0.001$) (Fig. 2). There was moderate heterogeneity in the subgroup of initial rSO_2 values ($I^2 = 55\%$) and low heterogeneity in the subgroup of average rSO_2 values during resuscitation ($I^2 = 33\%$), resulting in an overall moderate heterogeneity ($I^2 = 52\%$).

Two sensitivity analyses were conducted: the first one included only studies with low risk of bias and the second one included both studies at low and intermediate risk of bias. In both analyses the overall and the subgroups yielded same significant association between higher values of rSO_2 and ROSC.

The overall mean was calculated from the values of single studies with consideration for their size. For the subgroup reporting the initial rSO_2 value, we found that patients achieving ROSC had a mean of 32.7% vs 25.4% in those not achieving ROSC. Similarly, for studies reporting the average value during resuscitation, patients

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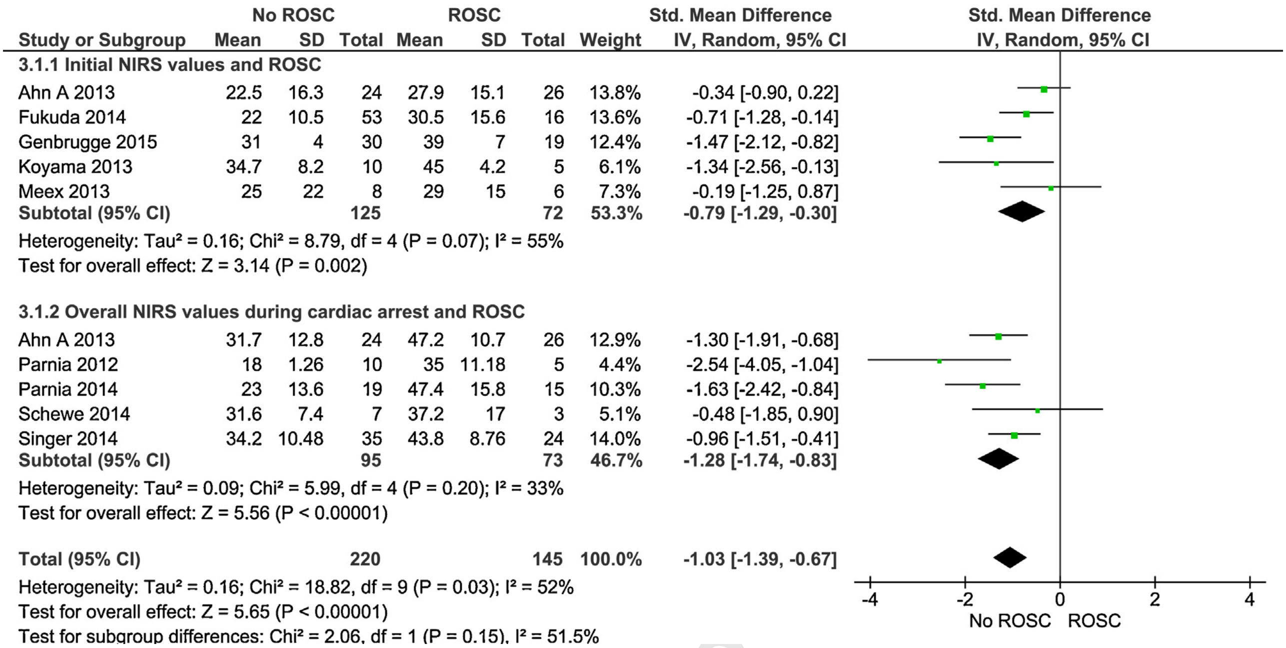

Fig. 2. Near-infrared spectrometry (NIRS) values and achievement of return of spontaneous circulation (ROSC) vs non-ROSC. Standard mean difference (95% CI) for prediction of ROSC is showed for the subgroups of studies providing data on initial NIRS values, for studies using the average NIRS values during resuscitation, and overall. The study by Ahn et al. (2013)[9] is the only one providing data on initial and during resuscitation NIRS values.

who achieved ROSC had a mean rSO_2 value of 44.9% vs 29.4% in those not achieving ROSC.

4. Discussion

This meta-analysis showed a significant association between higher values of rSO_2 and ROSC following CA. This finding is not unexpected, since higher values of cerebral oxygenation are likely to indicate a better coronary perfusion pressure (CorPP) during resuscitation. In fact, a correlation between cerebral and coronary perfusion pressure has been demonstrated.[23] Paradis et al. reported that a CorPP >15 mmHg has to be maintained with CPR in order to achieve ROSC.[24] However, there is no clinical available method for measuring CorPP in the resuscitation setting, and cerebral oxygenation could be considered as a reasonable surrogate. The application of NIRS sensors on the forehead of unconscious patients is feasible although it may require the presence of an additional operator to avoid delays in CPR. Importantly, rSO_2 can be used in the absence of pulsatile flow and it is currently used for cerebral monitoring during cardiac surgery with cardiopulmonary bypass.[25] Moreover, rSO_2 has been investigated also to assess cerebral auto-regulation in patients undergoing cardiopulmonary bypass,[26] sepsis[27] and in-post CA patients,[28] and it has been used in several other scenarios investigating regional tissue perfusion.

Among other predictors of ROSC during resuscitation, the end tidal CO_2 ($etCO_2$) is the most extensively studied since its detection relies on the presence of blood flow in the pulmonary circulation. Current evidence supports a strong correlation between steep increase in $etCO_2$ during resuscitation and the presence of ROSC.[29] However, $etCO_2$ is dependent on effective minute ventilation and is also influenced by the administration of vasoactive drugs.[30,31] Interestingly, in a recent conference abstract Engel et al. showed that the initial, the overall, the last five-minutes and the final value of rSO_2 correlated better with ROSC than the respective values of $etCO_2$.[32] The $etCO_2$ has been also used as a tool for evaluation of the efficacy of chest compressions, and in this regards also rSO_2 is currently investigated for its correlation with the efficacy of resuscitation. One study has shown a poor correlation between rSO_2 values and quality of CPR; indeed improving the CPR technique after an episode of low-quality CPR did not significantly increase the rSO_2 values.[33] On the contrary a recent conference abstract found a strong correlation between depth of chest compression and rSO_2 values.[34] However these two studies enrolled only nine and eight patients respectively and the results of such small study populations should be interpreted with caution.

Although we calculated a mean value averaging the findings of the retrieved studies, a receiver curve operator cannot be calculated with the available data. Before approaching conclusions, it seems reasonable to wait for larger and homogeneous studies that may provide a sensitivity/specificity values for prediction of ROSC during resuscitation of CA patients. Moreover, rSO_2 is mainly a trend monitoring technique and change over time may be more important prognostic value. Indeed, we think that future studies should look principally at variations of the rSO_2 values during CPR.

The values of rSO_2 have been also used for prognostication of survival and neurological outcome of patients successfully resuscitated after CA. Both Ito et al.[11] and Storm et al.[12] found significantly higher rSO_2 values at hospital arrival in patients with good neurological outcome, with mean rSO_2 values in patients with Cerebral Performance Category (CPC) scale 1–2 of 56 and 68%, respectively, as compared with rSO_2 in patients with CPC 3–5 of 20 and 58%, respectively. However, a recent conference abstract (Bougle A et al., *Int Care Med*, 2014) reported no difference in rSO_2 between CPC 1–2 (62%) and CPC 3–5 (58%) patients.

Other studies evaluated the differences in rSO_2 values after ROSC according to survival after CA with opposite findings. Indeed, Ahn et al. found significantly higher average rSO_2 values in survivors during the first 24 h post-CA, although this difference was not significant for the period between the 24th and the 48th hour.[35] Another study found no difference in rSO_2 values between survivors and non-survivors during maintenance of therapeutic hypothermia after CA.[36] However, neither of the two studies provided data according to the CPC scale, recognized standard for the outcome assessment after CA. Unfortunately these four studies and one conference abstract presents large differences in the design and outcome analyzed, and therefore a meta-analysis on the rSO_2 value

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in predicting long-term outcome of patients resuscitated from CA would be meaningless.

This meta-analysis has several limitations. First, no studies provided a multivariate analysis and therefore we cannot exclude the effects of several confounders such as age, primary causes of CA, rhythm at presentation, site of CA, witnessed CA or not, bystander CPR, duration of resuscitation, etc. Moreover the time delay between CA and the first application of the NIRS probe was not available which may greatly influence the first recorded rSO_2 value. In this context, it is worth highlighting that two studies were conducted in Japan[18,19] where emergency medical personnel are not allowed to terminate resuscitation out of the hospital, increasing the heterogeneity in the results of the meta-analysis. Second, all the studies included are fairly small range of 15–69 patients and were single centre based. Third, different devices have been used to measure cerebral oximetry in the retrieved studies, leading to a possible bias due to the different calibration and algorithms of each device. Indeed, NIRS monitoring is applied on a heterogeneous vascular bed (arteries, veins and capillary networks) and non-vascular tissue, making NIRS sensor analysis subject to limitations and confounding factors. These mainly includes: interference of extra-cerebral tissue and spatial resolution between and superficial brain tissue,[37] differences in the cerebral arterial/venous blood partitioning[37] (usually estimated in the ratio of 30/70%),[38] the effect of blood- and tissue- derived chromophores (i.e. conjugated bilirubin).[39] There are multiple devices available in the market and they use different algorithms to deal with these confounding factors potentially introducing variability in clinical practice.[40]

5. Conclusions

Higher initial and average values of regional cerebral oxygen saturation are associated with greater chances of achieving return of spontaneous circulation in patients with cardiac arrest. Large multicentre studies using multivariate analysis are needed to assess the performance and predictive values of regional cerebral oxygen saturation as a diagnostic tool to predict successful resuscitation.

Conflict of interest statement

All the authors declare no conflict of interest with regards of this topic. No authors received funding for undertaking this project.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.resuscitation.2015.06.023

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