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Serum procalcitonin as a marker of post-cardiac arrest syndrome and long-term neurological recovery, but not of early-onset infections, in comatose post-anoxic patients treated with therapeutic hypothermia☆

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ABSTRACT

Objective: To examine the relationship of early serum procalcitonin (PCT) levels with the severity of post-cardiac arrest syndrome (PCAS), long-term neurological recovery and the risk of early-onset infections in patients with coma after cardiac arrest (CA) treated with therapeutic hypothermia (TH).
Methods: A prospective cohort of adult comatose CA patients treated with TH (33 °C, for 24 h) admitted to the medical/surgical intensive care unit, Lausanne University Hospital, was studied. Serum PCT was measured early after CA, at two time-points (days 1 and 2). The SOFA score was used to quantify the severity of PCAS. Diagnosis of early-onset infections (within the first 7 days of ICU stay) was made after review of clinical, radiological and microbiological data. Neurological recovery at 3 months was assessed with Cerebral Performance Categories (CPC), and was dichotomized as favorable (CPC 1–2) vs. unfavorable (CPC 3–5).
Results: From December 2009 to April 2012, 100 patients (median age 64 [interquartile range 55–73] years, median time from collapse to ROSC 20 [11–30] min) were studied. Peak PCT correlated with SOFA score at day 1 (Spearman's $R = 0.44$, $p < 0.0001$) and was associated with neurological recovery at 3 months (peak PCT 1.08 [0.35–4.45] ng/ml in patients with CPC 1–2 vs. 3.07 [0.89–9.99] ng/ml in those with CPC 3–5, $p = 0.01$). Peak PCT did not differ significantly between patients with early-onset vs. no infections (2.14 [0.49–6.74] vs. 1.53 [0.46–5.38] ng/ml, $p = 0.49$).
Conclusions: Early elevations of serum PCT levels correlate with the severity of PCAS and are associated with worse neurological recovery after CA and TH. In contrast, elevated serum PCT did not correlate with early-onset infections in this setting.

1. Introduction

Post-cardiac arrest syndrome (PCAS) includes all clinical and biological manifestations secondary to global ischemia-reperfusion injury after cardiac arrest (CA).[1,2] The pathophysiology of PCAS is characterized by a number of acute mechanisms, mainly myocardial dysfunction, coagulopathy, adrenal insufficiency and a non-specific activation of systemic inflammatory response.[3–6] Systemic inflammatory response is an important pathological component of PCAS and involves a series of post-reperfusion related events, e.g. increased release of free oxygen radicals, complement-activation products, adhesion molecules and inflammatory cytokines. Elevated levels of circulating cytokines are observed in the acute phase (24–48 h) following CA in humans and are associated with worse outcome.[7] The intense systemic inflammatory response observed during PCAS shares many features with that observed after severe sepsis. Importantly, PCAS is increasingly recognized as an important determinant of outcome after CA.[8,9] However, the exact mechanisms of PCAS-related inflammatory response are only beginning to be elucidated and we still lack specific diagnostic and prognostic biomarkers in this setting.

Procalcitonin (PCT) – a 116-amino-acid peptide secreted from the thyroid parafollicular cells – is a biomarker of systemic inflammatory response.[10] Serum PCT levels are substantially increased

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during systemic infections, where other organs, such as liver and spleen, contribute to PCT release.[11] In critically ill patients, PCT has demonstrated higher accuracy than C reactive protein (CRP) in diagnosing sepsis[12–14] and is of great value in determining the initiation and the duration of antibiotic use in ICU patients with suspected severe pneumonia or bacterial infections.[15–17] Procalcitonin could therefore be a potentially useful biomarker in the setting of CA. Studies on patients with coma after CA primarily focused on the value of PCT to predict infections. Data are conflicting, some authors reporting that elevated PCT correlated with infections,[18] while others showed limited diagnostic value of PCT for early-onset pneumonia after CA and therapeutic hypothermia (TH).[19] Preliminary single-center studies also evaluated the prognostic value of PCT after CA and found elevated PCT levels were associated with worse outcome.[20–22] However, these studies were performed on a small number of patients, and some of them did not measure long-term outcome[20] or only evaluated PCT in the setting of comatose CA patients not treated with TH.[21]

To the best of our knowledge, no study simultaneously examined the value of PCT as a biomarker of PCAS, long-term neurological recovery and early-onset infections in patients with coma after CA treated with induced hypothermia. The aim of this study was to examine the diagnostic and the prognostic value of early (within 48 h) elevations of serum PCT in the setting of coma after CA and TH.

2. Methods

2.1. Patients

The subjects included in this single-center observational study were part of a prospective database of consecutive comatose patients successfully resuscitated from CA, admitted to the medical/surgical ICU of the Lausanne University Hospital, Lausanne, Switzerland, who were treated with TH and (1) had at least 2 serum PCT measurements in the acute phase (24–48 h) following CA and (2) survived at least 72 h from ICU admission. The approval for the study was obtained by the local Institutional Review Board, with waiver of informed consent since all interventions were part of standard patient care.

2.2. Post-resuscitation care

Therapeutic hypothermia was applied following a standardized written institutional algorithm, as described previously.[23,24] All patients were treated with mild TH to $33 \pm 1\,^{\circ}C$ for 24 h, irrespective of age, initial arrest rhythm, and post-resuscitation hemodynamic status. Cooling was started immediately after admission to the hospital. Therapeutic hypothermia was induced with ice-cold packs and intravenous ice-cold fluids and was maintained using a surface device with a computerized adjustment of patient temperature target (Arctic Sun®, Medivance, Inc., Louisville, CO). Midazolam (0.1 mg/kg/h) was used for sedation and fentanyl (1.5 μg/kg/h) for analgesia. Vecuronium (0.1 mg/kg boluses) or rocuronium (0.6 mg/kg) were administered to control shivering. Rewarming was achieved passively, and sedation-analgesia was stopped when the patient temperature was >35 °C. Patients were kept in a 30° semi-recumbent position; ventilation was set to target $PaCO_2$ between 35 and 45 mm Hg and PaO_2 of 80–100 mm Hg. Mean arterial pressure was kept greater than 65–70 mm Hg using volume resuscitation (mainly with isotonic solutions) and norepinephrine. Coronary angiography was performed on admission if ECG showed ST-elevation myocardial infarction.

2.3. Measurement of serum procalcitonin

PCT was measured using the ELFA method (VIDAS® BRAHMS PCT assay, bioMerieux Inc, Geneva, Switzerland) according to the manufacturer's instruction, with a detection limit of 0.05 ng/ml and an inter-plate variance of under 20%. Serum PCT was measured at day 1 and at day 2 from ICU admission. Peak PCT (corresponding to the highest PCT concentration) was used for data analysis.

Plasma CRP was also measured in all patients, using the Tinaquant® CRP method on a Modular P apparatus (Roche Diagnostics, Mannheim, Germany) by the Department of Pathology and Laboratory Medicine of the Lausanne University Hospital.

2.4. Post-resuscitation disease severity

To quantify the severity of PCAS, the SOFA score was used,[25] in line with recent clinical investigations on patients with coma after CA and TH.[26] For the purpose of this study, the SOFA score at day 1, calculated from ICU admission, was used.

2.5. Neurologic assessment and withdrawal of care

At least 36 h after CA, after rewarming at a core temperature >35 °C and off sedation, repeated neurologic examination, standard (20–30 min) EEG, and cortical somatosensory evoked potentials were performed. Patients with EEG evidence of status epilepticus were treated with IV antiepileptic drugs, discontinued if no clinical improvement was noted after at least 72 h. While physicians were not blinded to these results, PCT values were not used for the interdisciplinary decision on withdrawal of intensive care. This has been described previously,[27] and is based on a multimodal approach including at least 2 of the following (assessed in normothermia at least 48–72 h after CA): incomplete recovery of brainstem reflexes, early myoclonus, unreactive normothermic EEG, and bilaterally absent cortical somatosensory evoked potentials.

2.6. Outcome

Outcome was assessed prospectively for the entire cohort by scheduled follow-up interviews. Neurological recovery was assessed at 3 months using the Glasgow-Pittsburgh Cerebral Performance Categories (CPC), as described in our previous studies.[27,28] Accordingly, CPC 1 = full recovery, CPC 2 = moderate disability, discharged home and independent for daily activities, CPC 3 = severe disability, discharged to a rehabilitation facility and needing assistance, CPC 4 = vegetative state, and CPC 5 = death. Neurological recovery was subsequently dichotomized as favorable (CPC 1 and 2) and unfavorable (CPC 3–5). A CPC 5 was assigned to patients who remained comatose and died during hospital stay, because of complications or withdrawal of care.

2.7. Early infections

All patients' charts were retrospectively reviewed and detailed for evidence and type of infection by two authors (H.E. and N.B-H.). Each disagreement between prospective diagnosis and retrospective assessment was resolved by consensus (H.E., N.B-H. and M.O.). Infections were defined following commonly used criteria and according to previous studies on comatose CA patients treated with TH.[29] Pneumonia was defined by the presence of a new and persistent pulmonary infiltrate on chest radiography associated with either positive quantitative culture of the endotracheal aspirates, or, in the absence of bacteriologic sample, conjunction of purulent sputum and hypoxemia ($PaO_2/FIO_2 < 300$). Only early-onset

infections, occurring during the first 7 days from ICU admission, were considered for the present study. All patients included in this study received a 72-h antibiotic prophylaxis with i.v. amoxicilline-clavulanate: given the relatively high rate of pneumonia in this patient population, antibiotic prophylaxis was introduced as standard of care for the treatment of post-CA comatose patients in our unit since December 2009.

2.8. Data analysis

Data are expressed as medians (with interquartile range). Univariate analysis was conducted with the JMP Software 9.0 (SAS Institute Inc., Cary, NC, USA), using Wilcoxon's rank sum test for continuous variables and Fisher exact test for categorical variables. Correlations between variables were examined using non-parametric Spearman's rho (R) correlation coefficient. Statistical significance was set at $p < 0.05$.

3. Results

3.1. Patient characteristics

From December 2009 to April 2012, 120 patients were admitted for coma after CA. Twenty patients were excluded from the study because of incomplete PCT measurements ($n = 12$), early death within 72 h from ICU admission ($n = 6$), or lost to follow-up ($n = 2$). A total of 100 patients were analyzed (90 had out-of-hospital CA, 10 had in-hospital CA). Baseline characteristics of included patients are summarized in Table 1.

3.2. Associations between procalcitonin and post-cardiac arrest syndrome

Peak PCT over the first 48 h of CA was strongly correlated with SOFA score at day 1 (Spearman rho $R = 0.44$, $p < 0.0001$; Fig. 1). A significant correlation – although to a lesser extent – was also found between peak CRP and day 1 SOFA score ($R = 0.27$, $p = 0.007$, Fig. 1).

Table 1
Patient baseline characteristics.

Variable	Value
Patient number	100
Median age, years	64 (55–73)
Gender, female/male	22/78
Initial arrest rhythm	
Ventricular fibrillation	70
Asystole	17
Pulseless electrical activity	13
Time to ROSC, min	20 (11–30)
Cause of cardiac arrest	
Cardiac	79
Non-cardiac	21
Neurological examination at 3 days	
Motor response, present/absent	60/40
Brainstem reflexes, present/absent	69/31
Myoclonus, present/absent	7/93
Neurological recovery at 3 months	
Full recovery (CPC 1)	34
Moderate disability (CPC 2)	14
Severe disability (CPC 3)	6
Vegetative state (CPC 4)	0
Deceased (CPC 5)	46

Data are presented as median (interquartile range).
Abbreviations: CPC, cerebral performance categories; ROSC, return of spontaneous circulation.

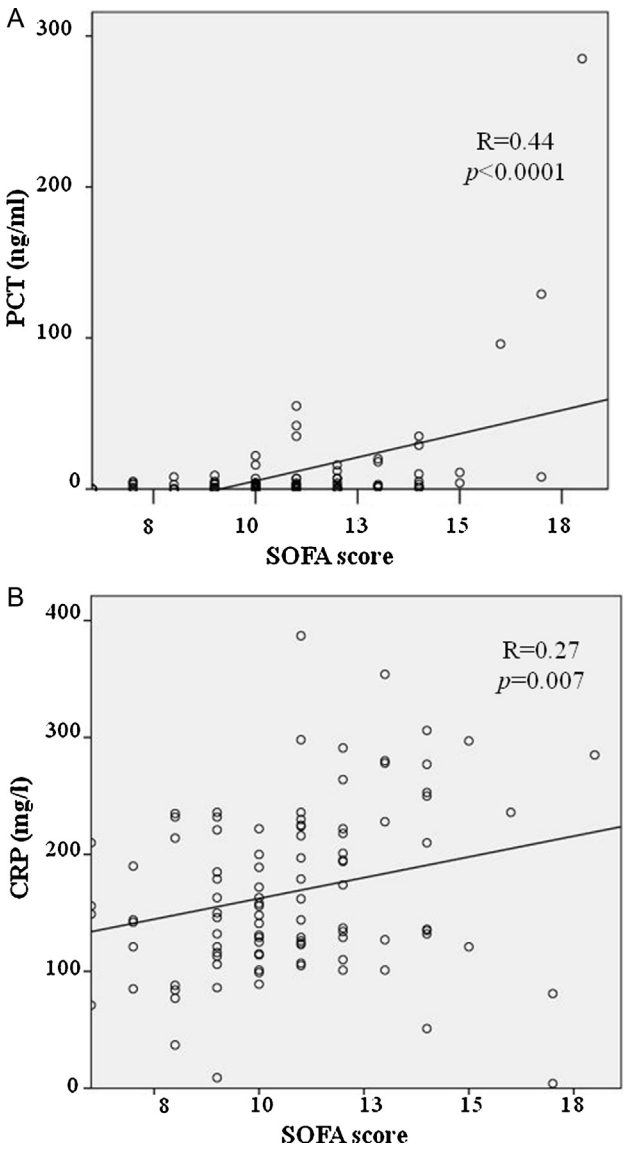

Fig. 1. Graphs showing the correlations of peak procalcitonin (PCT) and peak C reactive protein (CRP) with SOFA score at day 1 (R, non-parametric Spearman's correlation coefficient).

3.3. Early serum procalcitonin levels and 90-day neurological outcome after CA and TH

At 3 months, 48 patients (48%) had a favorable neurological recovery (CP 1 or 2) and 52 (52%) had an unfavorable outcome (6 had CPC 3 = severely disabled, 46 had CPC 5 = dead; no patient had a CPC 4 = vegetative state). In subjects who did not survive discharge, severe encephalopathy leading to withdrawal of care was the main etiology of death: only 4 patients died because of shock/multiple organ failure. As illustrated in Table 2, patients who had a favorable neurological recovery at 3 months had significantly lower early serum peak PCT (median 1.08 (0.35–4.45) ng/ml) than those who had an unfavorable outcome (CPC 3–5; median 3.07 (0.89–9.99) ng/ml, $p = 0.007$). A significant association was also found between peak PCT and mortality at 3 months (peak PCT 1.04 [0.35–3.93] ng/ml in survivors vs. 3.24 [1.03–10.0] ng/ml in non-survivors, $p = 0.001$). In addition, when looking to the dynamic of PCT over time (i.e. increase vs. decrease of PCT levels from day 1 to day 2), we found an increase of PCT from day 1 to day 2 was associated with a trend toward increased mortality, although this was

Table 2
Associations of peak procalcitonin (PCT) and peak C reactive protein (CRP) with 90-day neurological recovery.

Variable	90 day neurological recovery		
	Favorable (CPC 1–2) $n = 48$ patients	Unfavorable (CPC 3–5) $n = 52$ patients	P value
Peak PCT (ng/ml)	1.08 (0.35–4.45)	3.07 (0.89–9.99)	0.01
Peak CRP (mg/l)	132 (111.5–219.5)	172 (127.5–224.5)	0.19
SOFA score at day 1	10 (range 6–17)	11 (range 6–18)	0.31

Data are presented as median (interquartile range), except when otherwise stated.
Abbreviation: CPC, cerebral performance categories.

not statistically significant (75% increase in PCT in non-survivors vs. 55% in survivors, $p = 0.09$).

In contrast, as shown in Table 2, no correlation was found between peak CRP and 3-month neurological outcome (peak CRP 132 [111.5–219.5] mg/l in patients with CPC 1–2 vs. 172 [127.5–224.5] mg/l in those with CPC 3–5, $p = 0.19$). Similarly, we did not find a significant correlation between SOFA score at day 1 and 3-month neurological recovery (Table 2).

3.4. Procalcitonin and early-onset infections after CA and TH

A total of 56 patients (56%) were diagnosed with early (within 7 days) infections. Among infectious episodes, the majority of patients (49, 87.5%) had early-onset pneumonia, while in the remaining 7 patients infections were due to bacteremia ($n = 5$) or urinary tract infection ($n = 2$). 34% of patients had visibly aspirated on admission. Microbiological diagnosis was made in 31/56 infectious episodes. Peak PCT did not differ significantly between patients with infections ($n = 56$: peak PCT 2.14 [0.49–6.74] ng/ml) and those who did not have infections ($n = 44$: peak PCT 1.53 [0.46–5.38] ng/ml, $p = 0.49$, Table 3). Similarly, no significant difference in peak CRP was found between the two groups (peak CRP 150 [121–224] mg/l in patients with infections vs. 152.5 [115.3–220.3] mg/l in those without infections, $p = 0.82$, Table 3).

4. Discussion

The main findings of this study are that peak serum PCT over the first 24–48 h from ICU admission correlates with the severity of PCAS and is associated with 90-day neurological outcome of post-CA coma. In contrast, PCT appears unreliable to predict early-onset infections after CA and TH.

4.1. Procalcitonin as a marker of PCAS

Post-cardiac arrest syndrome is frequent in comatose CA patients and is an important determinant of outcome.[8,9] At present there is no specific diagnostic or prognostic biomarker of PCAS in patients with coma after CA. Here, we identify – in a relatively large cohort of comatose CA treated with induced hypothermia – early serum PCT as a strong marker of PCAS. We found a close correlation between peak PCT and day 1 SOFA score, which is recognized as the optimal clinical score to quantify the severity of PCAS.[26] From the pathophysiological standpoint this reinforces the notion that systemic inflammatory response is a major determinant of PCAS.[3,7] Although CRP also correlated with day 1 SOFA score, this correlation was much greater for PCT, thereby indicating that PCT is a more specific biomarker in this context. Our findings might have important clinical implications. First, early elevation of serum PCT levels after CA might identify patients at higher risk for cardio-circulatory failure and PCAS-related organ dysfunction and death. Second, and consequently, our data support the concept that PCT might help to discriminate comatose post-CA patients that, in addition to TH, may potentially benefit from more aggressive vaso-active therapy[30–32] or artificial organ support.[33,34]

4.2. Procalcitonin as a complementary biomarker of outcome after cardiac arrest and TH

Since the introduction of TH, prognostication of coma after CA has become a more difficult challenge that requires a multimodal approach, including clinical examination, electrophysiological tests and blood biomarkers.[35] Relying on one single test alone is not recommended, given the potential of false prediction. At present, among prognostic serum biomarkers, neuron specific enolase[36,37] and soluble 100-beta[38] have been most studied. However, these biomarkers are not available everywhere and carry a relatively high rate of false prognostic prediction.[35] Here, we show that serum PCT – a biomarker that is nowadays widely available in the ICU setting – is associated with worse long-term neurological recovery in comatose CA patients treated with induced hypothermia. An increase of PCT from day 1 to 2 was further associated with increased mortality. Interestingly, elevated plasma CRP was not associated with outcome, thereby suggesting that PCT may be a more reliable and specific marker of prognosis after CA. Furthermore, the SOFA score at day 1 did not correlate with 90-day outcome. Altogether, our findings suggest that PCT is a potential good candidate as a biomarker of disease severity and prognosis of CA and support the concept that – pending further confirmatory studies – PCT may be incorporated in future multimodal algorithms for the prognostication of post-CA coma.

4.3. Procalcitonin is not a reliable marker for early infection after cardiac arrest and TH

Despite antibiotic prophylaxis was given to the entire cohort, 56% of patients had infectious complications, and the majority had pneumonia. Although the rate of infections in our study was slightly inferior to that recently reported by other groups,[19,29,39] it underlines the importance of infectious complications in the context of post-CA coma. Early infections after CA are an important determinant of patient prognosis,[40] thereby underscoring the need to identify a reliable diagnostic biomarker in this setting. Here, we found that peak PCT during the first 24–48 h from CA was not associated with a higher rate of early infections in comatose CA patients treated with induced hypothermia. Previous data were conflicting, some authors reporting elevated PCT correlated with infections,[18] while others showed limited diagnostic value of PCT for early-onset pneumonia after CA and TH.[19] Similarly to PCT, elevated CRP levels also were not associated with an increased risk of infections. Our data strongly suggest that elevated blood PCT and CRP levels are unreliable to predict early-onset infections after CA and TH.

4.4. Study limitations

There are several limitations to this study. First, although the sample-size was relatively large ($n = 100$) and the cohort was homogeneous and treated with a standardized algorithm of post-resuscitation care and TH, the data were single-center. Additional studies are required to further confirm our findings. We believe multicenter trials are warranted to examine the diagnostic and the

Table 3
Associations of peak procalcitonin (PCT) and peak C reactive protein (CRP) with early-onset infections.

Variable	Early-onset (within 7 days from ICU admission) infections		
	Infections $n = 56$ patients	No infections $n = 44$ patients	P value
Peak PCT (ng/ml)	2.14(0.49–6.74)	1.53 (0.46–5.38)	0.49
Peak CRP (mg/l)	150 (121–224)	152.5 (115.3–220.3)	0.82

prognostic value of PCT in patients with coma after CA and TH. Second, although we found a significant relationship between peak PCT during the first 24–48 h from CA and 3-month neurological outcome, this association must be considered preliminary and will need future confirmation by larger studies. Furthermore, such studies will be necessary to more precisely determine the predictive value of PCT in this setting: given the limited number of patients studied, we judged that trying and answer this specific question was too preliminary at this stage. Despite such limitation, we still believe our findings that PCT appears to be a strong prognostic marker of post-CA coma are important from the clinical standpoint. Third, it is important to underline that this study was not designed to determine whether PCT was useful in identifying post-CA sepsis. Particularly, the definitions used to diagnose infection did not include SIRS criteria. Furthermore, PCT has been more validated as a marker of existing infection and to guide antibiotic therapy, rather than a marker to predict infection. Finally, while PCT was not used to confirm the diagnosis of infection, clinicians were not blinded to PCT values. Altogether, having these important limitations in mind, based on our observation, we can only conclude that PCT may not be a good marker to follow existing infection in the context of CA, since post-CA syndrome itself is associated with increased PCT values. This is an important message for the clinicians who care for these patients, and indeed are in line with previous reports.[19] Another limitation of our study is that we did not evaluate the dynamics and trends of PCT elevations during the early course of CA more in details, as sample intervals were limited to 24 and 48 h in the majority of our cohort. This was primarily because the sampling of PCT was integrated into our standardized algorithm of care, and as it is the case in other critically ill patients at our institution, PCT was sampled no more than once per day.

5. Conclusions

In our single-center cohort of patients with coma after cardiac arrest and therapeutic hypothermia we found that early elevations of serum procalcitonin at 24–48 h from ICU admission strongly correlate with the severity of PCAS and are significantly associated with long-term patient prognosis. In contrast, elevated serum PCT was not associated with early-onset infections in this setting.

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Conflict of interest statement

The authors have no conflict of interest to declare.

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.2013.01.029.

References

1. Mongardon N, Dumas F, Ricome S, et al. Postcardiac arrest syndrome: from immediate resuscitation to long-term outcome. Ann Intensive Care 2011;1:45.
2. Negovsky VA. Postresuscitation disease. Crit Care Med 1988;16:942–6.
3. Adrie C, Laurent I, Monchi M, Cariou A, Dhainaou JF, Spaulding C. Postresuscitation disease after cardiac arrest: a sepsis-like syndrome? Curr Opin Crit Care 2004;10:208–12.
4. Adrie C, Monchi M, Laurent I, et al. Coagulopathy after successful cardiopulmonary resuscitation following cardiac arrest: implication of the protein C anticoagulant pathway. J Am Coll Cardiol 2005;46:21–8.
5. Gando S, Nanzaki S, Morimoto Y, Kobayashi S, Kemmotsu O. Out-of-hospital cardiac arrest increases soluble vascular endothelial adhesion molecules and neutrophil elastase associated with endothelial injury. Intensive Care Med 2000;26:38–44.
6. Laurent I, Monchi M, Chiche JD, et al. Reversible myocardial dysfunction in survivors of out-of-hospital cardiac arrest. J Am Coll Cardiol 2002;40:2110–6.
7. 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.
8. Adrie C, Cariou A, Mourvillier B, et al. Predicting survival with good neurological recovery at hospital admission after successful resuscitation of out-of-hospital cardiac arrest: the OHCA score. Eur Heart J 2006;27:2840–5.
9. Laver S, Farrow C, Turner D, Nolan J. Mode of death after admission to an intensive care unit following cardiac arrest. Intensive Care Med 2004;30:2126–8.
10. Becker KL, Snider R, Nylen ES. Procalcitonin in sepsis and systemic inflammation: a harmful biomarker and a therapeutic target. Br J Pharmacol 2010;159:253–64.
11. Assicot M, Gendrel D, Carsin H, Raymond J, Guilbaud J, Bohuon C. High serum procalcitonin concentrations in patients with sepsis and infection. Lancet 1993;341:515–8.
12. Brunkhorst FM, Eberhard OK, Brunkhorst R. Discrimination of infectious and noninfectious causes of early acute respiratory distress syndrome by procalcitonin. Crit Care Med 1999;27:2172–6.
13. de Kruif MD, Limper M, Gerritsen H, et al. Additional value of procalcitonin for diagnosis of infection in patients with fever at the emergency department. Crit Care Med 2010;38:457–63.
14. Uzzan B, Cohen R, Nicolas P, Cucherat M, Perret GY. Procalcitonin as a diagnostic test for sepsis in critically ill adults and after surgery or trauma: a systematic review and meta-analysis. Crit Care Med 2006;34:1996–2003.
15. Bouadma L, Luyt CE, Tubach F, et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. Lancet 2010;375:463–74.
16. Schuetz P, Christ-Crain M, Thomann R, et al. Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. JAMA 2009;302:1059–66.
17. Stolz D, Smyrnios N, Eggimann P, et al. Procalcitonin for reduced antibiotic exposure in ventilator-associated pneumonia: a randomised study. Eur Respir J 2009;34:1364–75.
18. Oppert M, Reinicke A, Muller C, Barckow D, Frei U, Eckardt KU. Elevations in procalcitonin but not C-reactive protein are associated with pneumonia after cardiopulmonary resuscitation. Resuscitation 2002;53:167–70.
19. Mongardon N, Lemiale V, Perbet S, et al. Value of procalcitonin for diagnosis of early onset pneumonia in hypothermia-treated cardiac arrest patients. Intensive Care Med 2010;36:92–9.
20. Fries M, Kunz D, Gressner AM, Rossaint R, Kuhlen R. Procalcitonin serum levels after out-of-hospital cardiac arrest. Resuscitation 2003;59:105–9.
21. Hayashida H, Kaneko T, Kasaoka S, et al. Comparison of the predictability of neurological outcome by serum procalcitonin and glial fibrillary acidic protein in postcardiac-arrest patients. Neurocrit Care 2010;12:252–7.
22. Stammet P, Devaux Y, Azuaje F, et al. Assessment of procalcitonin to predict outcome in hypothermia-treated patients after cardiac arrest. Crit Care Res Pract 2011;2011:631062.
23. Benz-Woerner J, Delodder F, Benz R, et al. Body temperature regulation and outcome after cardiac arrest and therapeutic hypothermia. Resuscitation 2012;83:338–42.
24. Cueni-Villoz N, Devigili A, Delodder F, et al. Increased blood glucose variability during therapeutic hypothermia and outcome after cardiac arrest. Crit Care Med 2011;39:2225–31.
25. Vincent JL, de Mendonca A, Cantraine F, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study, Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. Crit Care Med 1998;26:1793–800.
26. Rittenberger JC, Tisherman SA, Holm MB, Guyette FX, Callaway CW. An early, novel illness severity score to predict outcome after cardiac arrest. Resuscitation 2011;82:1399–404.

27. Rossetti AO, Oddo M, Logroscino G, Kaplan PW. Prognostication after cardiac arrest and hypothermia: a prospective study. Ann Neurol 2010;67:301–7.
28. Rossetti AO, Urbano LA, Delodder F, Kaplan PW, Oddo M. Prognostic value of continuous EEG monitoring during therapeutic hypothermia after cardiac arrest. Crit Care 2010;14:R173.
29. Mongardon N, Perbet S, Lemiale V, et al. Infectious complications in out-of-hospital cardiac arrest patients in the therapeutic hypothermia era. Crit Care Med 2011;39:1359–64.
30. Kern KB, Hilwig RW, Berg RA, et al. Postresuscitation left ventricular systolic and diastolic dysfunction. Treatment with dobutamine. Circulation 1997;95:2610–3.
31. Tennyson H, Kern KB, Hilwig RW, Berg RA, Ewy GA. Treatment of post resuscitation myocardial dysfunction: aortic counterpulsation versus dobutamine. Resuscitation 2002;54:69–75.
32. Tsai MS, Huang CH, Chang WT, et al. The effect of hydrocortisone on the outcome of out-of-hospital cardiac arrest patients: a pilot study. Am J Emerg Med 2007;25:318–25.
33. Laurent I, Adrie C, Vinsonneau C, et al. High-volume hemofiltration after out-of-hospital cardiac arrest: a randomized study. J Am Coll Cardiol 2005;46:432–7.
34. Megarbane B, Leprince P, Deye N, et al. Emergency feasibility in medical intensive care unit of extracorporeal life support for refractory cardiac arrest. Intensive Care Med 2007;33:758–64.
35. Oddo M, Rossetti AO. Predicting neurological outcome after cardiac arrest. Curr Opin Crit Care 2011;17:254–9.
36. Cronberg T, Rundgren M, Westhall E, et al. Neuron-specific enolase correlates with other prognostic markers after cardiac arrest. Neurology 2011;77:623–30.
37. Rossetti AO, Carrera E, Oddo M, Early EEG. correlates of neuronal injury after brain anoxia. Neurology 2012;78:796–802.
38. Rundgren M, Karlsson T, Nielsen N, Cronberg T, Johnsson P, Friberg H. Neuron specific enolase and S-100B as predictors of outcome after cardiac arrest and induced hypothermia. Resuscitation 2009;80:784–9.
39. Perbet S, Mongardon N, Dumas F, et al. Early-onset pneumonia after cardiac arrest: characteristics risk factors influence on prognosis. Am J Respir Crit Care Med 2011;184:1048–54.
40. Mongardon N, Max A, Bougle A, et al. Epidemiology and outcome of severe pneumococcal pneumonia admitted to intensive care unit: a multicenter study. Crit Care 2012;16:R155.