Intensive Care Med (2010) 36:92–99
DOI 10.1007/s00134-009-1681-3

ORIGINAL

Nicolas Mongardon
Virginie Lemiale
Sébastien Perbet
Florence Dumas
Stéphane Legriel
Sylvie Guérin
Julien Charpentier
Jean-Daniel Chiche
Jean-Paul Mira
Alain Cariou

Value of procalcitonin for diagnosis of early onset pneumonia in hypothermia-treated cardiac arrest patients

Received: 31 July 2009
Accepted: 16 September 2009
Published online: 21 October 2009

This study was presented in part at the 37th Congress of the French Society for Critical Care (2008), Paris, France, and at the 22nd Congress of the European Society of Intensive Care Medicine (2009), Vienna, Austria.

Electronic supplementary material
The online version of this article (doi:10.1007/s00134-009-1681-3) contains supplementary material, which is available to authorized users.

N. Mongardon · V. Lemiale · S. Perbet · J. Charpentier · J.-D. Chiche · J.-P. Mira · A. Cariou
Medical Intensive Care Unit,
Cochin Hospital, AP-HP,
27 rue du Faubourg Saint-Jacques,
75679 Paris Cedex 14, France
e-mail: nmongardon@yahoo.fr

F. Dumas
Emergency Department, Hôtel Dieu Hospital, AP-HP, 1 place du Parvis Notre Dame, 75004 Paris, France

S. Legriel
Intensive Care Unit, Versailles Hospital Center, 177 rue de Versailles,
78157 Le Chesnay Cedex, France

S. Guérin
Department of Biochemistry,
Cochin Hospital, AP-HP, 27 rue du Faubourg Saint-Jacques,
75679 Paris Cedex 14, France

N. Mongardon · V. Lemiale · S. Perbet · F. Dumas · S. Guérin · J. Charpentier · J.-D. Chiche · J.-P. Mira · A. Cariou
Medical School, Paris Descartes University,
15 rue de l'Ecole de Médecine,
75270 Paris Cedex 06, France

F. Dumas · A. Cariou
Cardiovascular Research Center,
European Georges Pompidou Hospital,
INSERM U970, 56 rue Leblanc,
75015 Paris, France

J.-D. Chiche · J.-P. Mira
Cochin Institute, INSERM U567, CNRS UMR 8104, 22 rue Méchain,
75014 Paris, France

A. Cariou (✉)
Service de Réanimation Médicale, Centre Hospitalier Cochin-Saint Vincent de Paul,
27 rue du Faubourg Saint Jacques,
75014 Paris, France
e-mail: alain.cariou@cch.aphp.fr
Tel.: +33-1-58412501
Fax: +33-1-58412505

Abstract *Purpose:* Early onset pneumonia is frequently reported after cardiac arrest, despite the fact that therapeutic hypothermia and post-resuscitation disease manifestations make it difficult to diagnose. We aimed to assess the ability of serum procalcitonin (PCT) measurements to help diagnose pneumonia in this setting. *Methods:* Retrospective study of consecutive patients admitted to a single academic medical intensive care unit (ICU) for successfully resuscitated cardiac arrest (July 2006–March 2008). All patient files were reviewed to assess the development of pneumonia during the first 5 days of ICU stay. Serum PCT was measured at admission, days (D) 1, 2 and 3. *Results:* Among 132 patients included, pneumonia was diagnosed in 86, and antibiotics were initiated in 115 patients during the first 5 days. PCT was significantly higher in patients with pneumonia at D1 (4.58 vs. 1.03 ng/ml, $p = 0.017$), D2 (3.76 vs. 0.73, $p = 0.002$) and D3 (3.76 vs. 0.73, $p = 0.046$). Areas under the ROC curves were 0.59 at admission, 0.64 at D1, 0.68 at D2 and 0.63 at D3. Using a threshold of 0.5 ng/ml, negative predictive values were 39% at admission, 42% at D1 and 52% at D2, whereas positive predictive values were 72, 68 and 70%, respectively. Patients with post-resuscitation shock ($n = 66$) had significantly higher PCT levels than vasopressor-free patients from D1 to D3. *Conclusions:* The diagnostic value of PCT is poor after cardiac arrest and should not be performed to assess early onset pneumonia. The post-resuscitation disease itself could play a major role in this lack of specificity and predictive value.

Keywords Cardiac arrest · Hypothermia · Sepsis · Pneumonia · Procalcitonin · Biomarker

Introduction

Pneumonia is the most frequent infectious complication observed in patients successfully resuscitated from a cardiac arrest (CA). Up to one half of them will further develop a lower respiratory tract infection, mainly due to aspiration, which is associated with an increased mechanical ventilation duration and intensive care unit (ICU) length of stay [1–3]. Moreover, the use of therapeutic hypothermia is potentially associated with an increased incidence of infectious events. However, an accurate early diagnosis remains difficult to perform in this specific setting because of many confounding factors. First, clinical and biological signs of systemic inflammatory response syndrome (SIRS) can be provoked either by an authentic infection or by the "post-resuscitation disease" that mimics sepsis [4, 5]. Second, chest X-ray abnormalities are usual, but mostly related to pulmonary edema and/or atelectasia. Finally, routine use of therapeutic hypothermia deprives clinicians of major infectious criteria, like fever or white blood count (WBC) changes. All together, these confounding factors may explain that the usual clinical diagnostic approach is challenged in face of a common and potentially severe complication. Thus, physicians are dealing with a dilemma: waiting for clinical, radiological, biological evolution and bacteriological results (with the risk of degradation of an already severely ill patient) or treating any potential infection (with the risk of overusing antibiotics).

Reliable sepsis biomarkers could be helpful in this early recognition challenge. Among them, procalcitonin (PCT) has been shown to be superior to C-reactive protein (CRP) and is widely used as a marker of bacterial sepsis [6, 7]. Its kinetics are adapted to the critical care setting, with an early increase after septic injury and a fast decrease after infection control. Early detection in PCT increase could allow time sparing on usual criteria or culture of the endotracheal aspirates [8]. To our knowledge, only one study has investigated the value of PCT for diagnosis of ventilator-associated pneumonia in a small number of survivors of CA who did not receive therapeutic hypothermia [9]. Furthermore, there is a paucity of data about this marker in post-resuscitation shock management, which has recently been acknowledged as a cornerstone after CA resuscitation [10]. Thus, we designed this study to assess the ability of serum PCT measurements to detect early onset pneumonia after CA.

Materials and methods

Study setting and population

All consecutive patients over 18 admitted to our 24-bed medical ICU between July 2006 and March 2008 after a successfully resuscitated CA were studied. We reviewed retrospectively all medical records and data from our prospective ICU database, in which all CA survivor characteristics are registered according to the Utstein style [11]. The following variables were recorded prospectively for each patient: demographic data, clinical parameters, cause of CA, arrest location, no-flow and low-flow period, initial rhythm, Simplified Acute Physiology Score 2 (SAPS 2), hypothermia management, development of infection, major biological parameters and ICU mortality. Post-resuscitation shock was defined as a need for vasopressors (epinephrine or norepinephrine) lasting more than 6 h despite adequate fluid loading. Patient management was strictly standardized (see the Electronic Supplementary Material). Patients who died within the first 24 h, with a known infection prior to CA, with an extra-pulmonary infection developing within 5 days following admission and patients with missing data or incomplete samples were excluded.

Data analysis

All files were retrospectively reviewed by two independent investigators (NM and VL) in order to check the diagnosis of early onset pneumonia [P(+)] or not [P(−)] in the light of clinical, biological, microbiological and radiological data of the first 5 days of ICU stay. Each case of disagreement between prospective diagnosis and retrospective assessment was resolved by consensus between the investigators, with the help of a third expert (AC) if necessary. At the time of this assessment, investigators were blinded to CRP and PCT levels. According to commonly used criteria, early onset pneumonia was defined by the presence of a clinical compatible finding at auscultation and a new pulmonary infiltrate on chest X-ray (persistent for at least 48 h) associated with a positive quantitative culture of the endotracheal aspirates (threshold: 10^6 CFU/ml). In the absence of a bacteriological sample, the diagnosis was retained when the previous signs were associated with purulent endotracheal aspirates and hypoxemia ($PaO_2/FiO_2 < 200$) not explained by pulmonary edema or atelectasia. The main components of SIRS, i.e., body temperature, heart rate and WBC, were not considered since they are affected by hypothermia. Finally, the diagnosis of early onset pneumonia was considered when occurring within 5 days following ICU admission.

Blood sampling

All CRP and PCT dosages were performed in May 2008 by the same investigator (SG) by using blood samples collected at admission, day 1 (D1), day 2 (D2) and day 3 (D3). These samples were initially centrifuged and stored at −80°C within 4 h, as approved by our local institutional review board, as part of a serum collection. Analyses of

CRP were performed with a fully automated immunoturbidimetric assay (CRPLX, Modular PP®, Roche Diagnostic, Mannheim, Germany), with a low detection limit of 1 mg/ml. PCT concentrations were quantified with an immunofluorimetric assay (PCT sensitive, Kryptor®, Brahms, Berlin, Germany). Its analytical assay sensitivity was 0.02 ng/ml, according to the manufacturer.

Statistical analysis

Continuous variables were expressed as medians (with interquartile range), and categorical variables were reported as count and proportions, unless specified otherwise. Statistical significance of differences within and between groups was evaluated as follows: continuous variables with the *t* test or Wilcoxon rank sum test, as appropriate; categorical variables with the χ^2 test or the Fischer's exact test, as appropriate. Receiver-operating characteristic (ROC) curves were performed to assess the ability of PCT concentrations to identify early onset pneumonia. Statistical significance was defined as $p < 0.05$. Analyses were performed using Stata 7.0 software (Stata Corp., College Station, TX).

Results

During the 20-month study period, 245 patients were admitted after being successfully resuscitated from a CA. Forty-eight died within the first 24 h, and 54 other patients with missing data or incomplete samples were excluded. Furthermore, 11 patients presented an active infection at the moment of CA or experienced an extrapulmonary infection within 5 days following admission. Consequently, we included 132 consecutive patients.

The patient population had a median age of 60 (49–70) years, and 92 (69%) were men. CA occurred in the hospital for eight patients (6%). Most were cardiac etiologies (80 patients, 61%), followed by respiratory (31 patients, 23%) and neurological (6 patients, 4%) failures; the etiology was uncertain for 15 patients. The initial rhythm was asystole or pulseless electrical activity for 75 patients (57%) and ventricular tachycardia/fibrillation for 57 patients (43%). Hypothermia was instituted in all but one patient. The ICU mortality rate reached 55% (73 patients).

Early onset pneumonia was retrospectively established in 86 patients (65% of this population), with microbiological documentation in 72 patients. Responsible microorganisms are listed in the Electronic Supplementary Material. Antibiotherapy was initiated in 115 patients during the first 5 days of ICU stay: 98% of the patients were P(+), and 67% of the patients were retrospectively considered to be P(−) ($p < 0.001$). Characteristics of P(+) and P(−) patients are summarized in Table 1. Higher SAPS 2 and an increase in cardiac etiology in P(+) patients were the only significant differences.

Median serum PCT values in P(+) and P(−) patients were respectively (Fig. 1): 0.38 ng/ml (0.12–2.56) versus 0.18 (0.11–0.81) at admission ($p = 0.051$), 4.58 (0.77–21.86) versus 1.03 (0.45–4.68) at D1 ($p = 0.017$), 3.76 (0.82–25.6) versus 0.73 (0.4–4.4) at D2 ($p = 0.002$) and 3.76 (0.82–25.64) versus 0.73 (0.42–4.4) at D3 ($p = 0.046$). The PCT peak value was significantly higher in P(+) patients [5.9 (1.2–34.3) versus 1.6 (0.65–6.1) in

Table 1 Baseline admission characteristics and outcomes of patients admitted for successfully resuscitated cardiac arrest, classified according to presence [P(+)] or absence [P(−)] of early onset pneumonia

	P(+) ($n = 86$)	P(−) ($n = 46$)	*p*
Age (year)	60 [47–70]	60 [50–70]	0.9
SAPS II	67 [60–77]	62 [53–67]	0.004
No flow (min)	3 [0–10]	6 [1–10]	0.06
Low flow (min)	15 [5–20]	15 [6–23]	0.95
Shockable rhythm, *n* (%)	40 (47%)	17 (37%)	0.16
Cardiac etiology, *n* (%)	58 (68%)	22 (48%)	0.02
Therapeutic hypothermia, *n* (%)	85 (99%)	46 (100%)	0.46
Temperature (°C)			
Admission	36 [34.7–37.1]	35.4 [34.5–36.5]	0.17
Day 1	32.7 [32.9–34]	33.3 [32.9–34]	0.83
Day 2	37.5 [37–37.9]	36.9 [36.2–37.8]	0.06
Day 3	37.8 [37.3–38.1]	37.8 [37–38]	0.22
Post-resuscitation shock, *n* (%)	44 (51%)	22 (48%)	0.72
Renal replacement therapy, *n* (%)	33 (38%)	17 (37%)	0.89
ICU mortality, *n* (%)	47 (55%)	25 (54%)	0.9

No flow was defined as the time elapsed from collapse to initiation of cardiopulmonary resuscitation and low flow as the duration of cardiopulmonary resuscitation. Both intervals were estimated by the physician of the emergency mobile unit for out-of-hospital CA or by the physician of the rapid response unit for in-hospital CA. Data are expressed as median (with interquartile range) or absolute value (%)

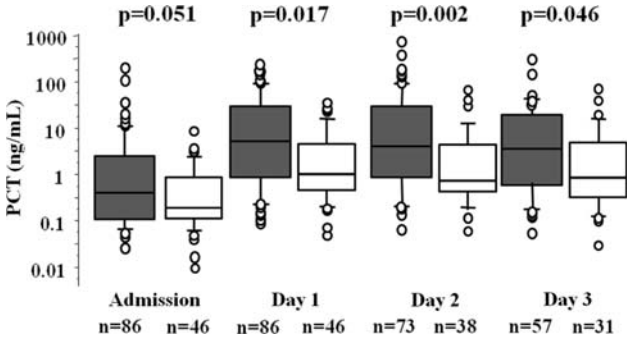

Fig. 1 Serum PCT levels on admission, D1, D2 and D3 in patients experiencing early onset pneumonia [P(+), *grey boxes*] or not [P(−), *white boxes*]. PCT levels are expressed in box plot forms (median, interquartile range). Values are expressed in ng/ml according to a logarithmic scale

P(−) patients ($p < 0.001$)]. The areas under the ROC curves of PCT for identification of early onset pneumonia were 0.59 (95% CI 0.49–0.69) at admission, 0.64 (95% CI 0.54–0.74) at D1, 0.68 (95% CI 0.57–0.79) at D2 and 0.63 (95% CI 0.49–0.76) at D3 (Fig. 2). Considering the kinetics of this biomarker, we also assessed the diagnostic value of the delta between PCT level measured at admission and PCT levels measured at D1 and D2. The areas under the curves of the delta were respectively 0.62 and 0.5 for admission D1 and for D1–D2. Predictive values of PCT to diagnose pneumonia were poor, despite determination of a threshold of 0.5 and 5 ng/ml (Table 2).

CRP levels and WBC values were not significantly different between the patients with and without pneumonia (Table 3). Areas under the ROC curves of CRP were poorly informative, with a value of 0.55 (95% CI 0.41–0.66) at admission, 0.51 (95% CI 0.39–0.64) at D1, 0.50 (95% CI 0.37–0.64) at D2 and 0.50 (95% CI 0.37–0.63) at D3 (not shown).

A post-resuscitation shock was observed in 66 patients and in a similar proportion between P(+) and P(−) patients. PCT levels were higher in patients with shock than in vasopressor-free patients at admission ($p = 0.09$), at D1 ($p < 0.001$), at D2 ($p < 0.001$) and at D3 ($p = 0.03$) (Table 4). In the subgroup of patients with shock, positive and negative predictive values of PCT were low whatever the cut-off value (Table 2).

We also examined PCT concentrations in patients requiring renal replacement therapy ($n = 50$), which was performed with intermittent hemodialysis. They exhibited significantly higher PCT levels from admission to D3 (Table 4). Those requiring dialysis were strongly linked with the development of post-resuscitation shock; 70% ($n = 46$) of patients with shock required dialysis, and 92% ($n = 46$) of patients receiving renal replacement therapy were vasopressor-dependent ($p < 0.0001$).

Discussion

To our knowledge, this is the first study designed to evaluate the potential usefulness of PCT determination for diagnosis of early onset pneumonia in successfully resuscitated CA patient undergoing therapeutic hypothermia. We found that PCT was significantly higher in patients with confirmed pneumonia in the early post-

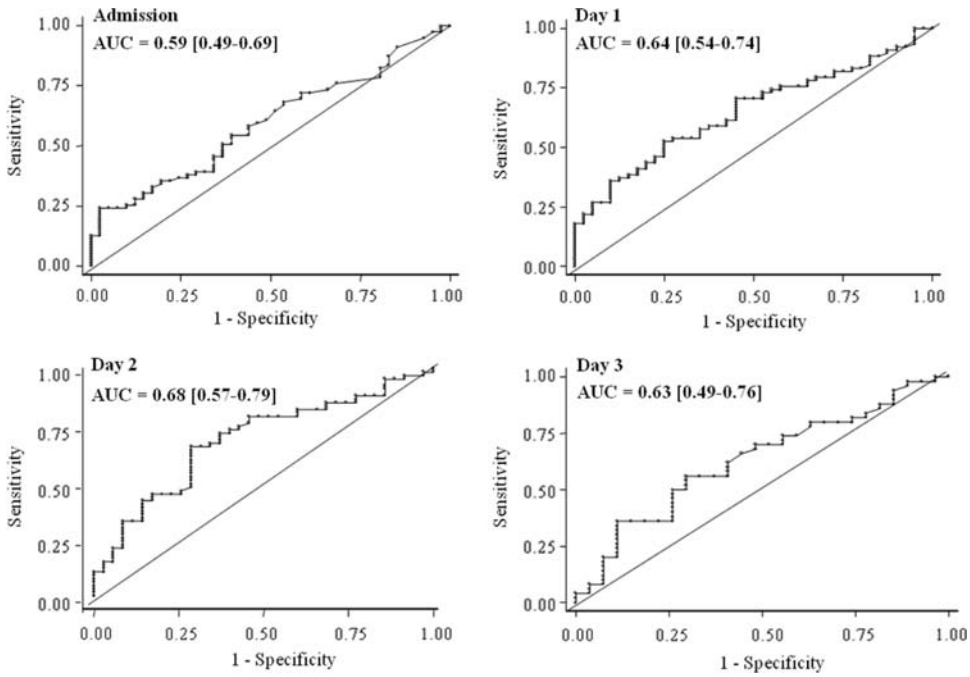

Fig. 2 ROC curves comparing the ability of PCT concentrations to identify early onset pneumonia at admission, D1, D2 and D3

Table 2 Predictive values of PCT to diagnose early onset pneumonia according to two different thresholds in all patients and in patients with post-resuscitation shock

	Positive predictive value (%)	Negative predictive value (%)
All patients ($n = 132$)		
PCT threshold = 0.5 ng/ml		
Admission	72	39
Day 1	68	42
Day 2	70	52
PCT threshold = 5 ng/ml		
Admission	94	39
Day 1	78	42
Day 2	70	44
Patients with shock ($n = 66$)		
PCT threshold = 0.5 ng/ml		
Admission	65	35
Day 1	72	71
Day 2	72	40
PCT threshold = 5 ng/ml		
Admission	100	36
Day 1	77	48
Day 2	78	37

Table 3 C-reactive protein (CRP) and white blood count (WBC) in the presence [P(+)] or absence [P(−)] of early onset pneumonia

	P(+) ($n = 86$)	P(−) ($n = 46$)	p
CRP (mg/ml)			
Admission	2.3 [1.2–15.4]	2.8 [1.2–5.4]	0.68
Day 1	49.3 [18.1–110.4]	50.4 [20.6–105.4]	0.94
Day 2	137.8 [91.1–180.9]	139.9 [84.4–202.2]	0.42
Day 3	172 [84.7–205.7]	170 [91.7–198.5]	0.95
WBC (10^9/l)			
Admission	14.2 [11.2–20.9]	15.1 [10.7–19.8]	0.78
Day 1	12.5 [8.9–16.3]	12.6 [8.5–16.4]	0.93
Day 2	11.1 [8.5–14.6]	11.7 [9.1–14.1]	0.92
Day 3	10.8 [8.1–14.1]	11.5 [8.9–14.8]	0.54

Data are expressed as median (with interquartile range)

resuscitation period. However, sensitivity, specificity, and positive and negative predictive values of PCT were quite poor and barely superior to CRP, despite attempts to remove potential flaws in this setting. PCT cut-off values for the diagnosis of infection in critically ill patients are still to be determined, ranging from 0.44 ng/ml [12] to 9.7 ng/ml [13], according to the medical or surgical ICU setting, as well as the severity of the septic insult. As a result, we calculated the diagnostic value according to a low (0.5 ng/ml) or high (5 ng/ml) threshold. This failed to improve diagnostic utility. PCT kinetics have been proposed to circumvent the drawback of assigning a specific threshold [12, 14]. However, in our study, the use of PCT kinetics between admission, D1 and D2 did not significantly improve the diagnostic accuracy of this biomarker. As renal dysfunction affects many of survivors of CA and is known to interfere with the diagnostic accuracy of PCT [15], we investigated this specific point. Renal replacement therapy was used as a surrogate of acute kidney injury [16] and was associated with significantly higher PCT concentrations. However, patients requiring renal therapy were also likely to present post-resuscitation shock, thus making it difficult to distinguish the respective role of acute kidney injury, hemodialysis and shock on PCT levels.

Our results contrast with the recent increasing use of PCT, which is widely reported as a useful biomarker of infection in critically ill patients in many indications: to diagnose infection [7, 17], to guide the antibiotic treatment decision [18, 19] or duration [20]. Moreover, PCT was also proposed to predict outcome by examining the absolute values [21], or kinetics [22].

The high rate of antibiotic initiation in our cohort, especially in patients without confirmed pneumonia, is noteworthy. Early overuse of antibiotics may be explained by clinical, biological and radiological confounding factors in survivors of CA treated with therapeutic hypothermia, added to the preoccupation of missing a septic insult in such severe patients. This reinforces the need for complementary tools to improve diagnosis of early onset pneumonia and justifies our study using PCT in this context. However, to our knowledge, only four studies have investigated the interest of PCT after CA, and none of them focused on the PCT value in aspiration pneumonia. Fries et al. [23] studied PCT concentrations in the first 3 days in 23 patients, showing that they were higher in patients with impaired neurological outcome. Remarkably, neither infection nor SIRS was diagnosed in their population. Post-resuscitation shock was also not a clearly-defined entity. These authors recently proposed an investigation

Table 4 Serum PCT levels in the subgroups of patients with or without post-resuscitation shock and renal replacement therapy requirements

	Post-resuscitation shock ($n = 66$)	No post-resuscitation shock ($n = 66$)	p	Renal replacement therapy ($n = 50$)	No renal replacement therapy ($n = 82$)	p
Admission	0.45 [0.11–3.16]	0.19 [0.11–0.69]	0.09	1.0 [0.15–3.68]	0.2 [0.11–0.81]	0.017
Day 1	6.66 [2.28–25.67]	0.95 [0.4–3.09]	<0.001	9.58 [3.58–35.66]	1.02 [0.41–4.86]	<0.001
Day 2	6.58 [1.78–27.38]	0.82 [0.43–3.12]	<0.001	11.52 [3.23–37.55]	0.82 [0.42–4.21]	<0.001
Day 3	5.2 [1.08–19.6]	0.95 [0.31–3.67]	0.03	5.61 [1.42–19.6]	0.95 [0.29–5.2]	0.003

Values are expressed in ng/ml as median (with interquartile range)

of inflammatory biomarkers, including PCT, after CA treated with hypothermia [24]. They draw the same conclusion on the relationship between a high PCT level and impaired neurological evolution. Unfortunately, a high infection rate may have influenced the marker measurements. In line with our study, Oppert et al. [9] reported that an elevated PCT value greater than 1 ng/ml diagnosed pneumonia with a sensitivity of 100% and a specificity of 75% during the first week. Interestingly, elevation of PCT preceded the pneumonia diagnosis with a median of 2 days, but the study was performed in only 28 patients, extended to late-onset pneumonia with a debatable definition of pneumonia and without daily measurement of this marker or exclusion of extrapulmonary infections. Consequently, results of these three studies do not allow any firm conclusion about the diagnostic value of PCT after CA. Finally, Adib-Conquy et al. [25] compared PCT values in patients experiencing cardiac surgery, CA or sepsis. In 54 CA survivors without infection, they showed that PCT levels in patients who died from refractory post-resuscitation shock overlapped those measured in septic patients. Moreover, PCT was higher in patients who ultimately died from neurological failure than in survivors. Even if the authors did not report PCT levels in patients with infection or with post-resuscitation shock, post-CA patients exhibited high levels of PCT (median concentrations of 0.43, 2.19 and 2.4 ng/ml at admission, D1 and D2). Notably, these values are slightly above the concentrations observed in our P(−) cohort. This could be explained by the fact that all patients reaching ICU were included (even those who died in the early ICU period), preventing from getting the time to rule out infectious complications. The authors concluded that PCT was more likely a marker of severe inflammation than infection.

Interestingly, we also found that patients with post-resuscitation shock had higher PCT levels, suggesting that PCT could be a marker of the systemic response following CA that correlates with clinical severity. SIRS, which is commonly observed in these patients, could explain the lack of predictive value and specificity of PCT after CA. This hypothesis is supported by similar observations performed in other settings known to provide SIRS. For instance, Geppert et al. [26] reported than high concentrations of PCT were also encountered in cardiogenic shock, suggesting that hypoperfusion provoked by myocardial and endothelial dysfunctions could be a supplementary cause of elevated PCT. In fact, SIRS occurs very early in the course of resuscitated CA and with a variable intensity [5]. Post-resuscitation disease is also characterized by immunologic, endothelial and cardiovascular dysfunctions sharing many features with sepsis. The main hypothesis is related to the activation of endotoxin and cytokine pathways [27]. Endotoxin, which is a strong trigger for PCT synthesis [28], is released as a consequence of splanchnic hypoperfusion and bloodstream translocation in nearly half of post-CA patients. Furthermore, high levels of pro-inflammatory cytokines may also participate in the non-infectious increase in PCT level [27, 29]. As suggested by two recent meta-analyses, PCT cannot accurately differentiate sepsis from other non-infectious causes of SIRS and precludes the recommendation for its routine use as a tool for septic screening, especially following CA [30, 31]. The pro-inflammatory, non-infectious pattern of PCT elevation prevents its use in this setting.

Even if performed in a large cohort of post-CA patients, some limitations of our study deserve careful consideration. First, we considered a retrospective single-institution cohort. However, all analyzed data were prospectively collected, and the monocentric design led to a homogeneous strategy. Second, diagnosis of early onset pneumonia lacks a consensus strategy, which may over- or underestimate the true incidence. We should admit that our findings regarding PCT levels might have been different if diagnosis had relied on other criteria. Nevertheless, we employed a robust methodology to minimize this risk as all files were reviewed by two separate investigators who were unaware of the biomarker levels. The CPIS score, widely used in the assessment of pneumonia in mechanically ventilated patients, cannot be used in survivors of CA. This is because it takes into account the temperature and WBC [32], which are both artificially modified by therapeutic hypothermia. Furthermore, its lack of diagnostic accuracy has been emphasized [33, 34]. The routine use of quantitative culture of endotracheal aspirates in our patients can also be discussed. However, the best microbiological tool is still a matter of debate, and its discussion is beyond the scope of this manuscript. Third, we did not include patients who died within the first 24 h as refractory shock is the main cause of early death in this setting [35]. We can speculate that PCT, as a marker of the inflammatory response, would have been very high in this population whatever the infectious status and would have reinforced our results. Moreover, it increased our ability to confirm or exclude infection, whatever the source. Fourth, the utility of PCT was evaluated as a single parameter. We did not determine if the combination of PCT level with clinical, biological and radiological data would improve the diagnostic value. In the same way, one may argue that comparing the PCT levels of the suspected ($n = 115$) with the non-suspected patients ($n = 17$) would have more closely reflected daily use of this biomarker; realistically, this would have more dramatically impaired its real accuracy by mixing confirmed and refuted pneumonias. Finally, this study was performed in patients undergoing therapeutic hypothermia. The relationship between inflammatory cytokines or biomarkers and the effect of therapeutic hypothermia is controversial [24, 36]. In our cohort, there was no significant difference in hypothermia use between the P(+) and P(−) groups, so that it did not prevent comparison. Fries et al. [24] demonstrated that hypothermia blunted the PCT

elevation in patients with bad neurological outcome, whereas it did not affect levels in patients with good recovery. Interpretation of this finding is limited by the small number of patients and by the observational study design, making it difficult to precise the impact of hypothermia on PCT concentrations. As a result, our conclusions cannot be extrapolated to patients not undergoing therapeutic hypothermia. Moreover, as implementation of therapeutic hypothermia is still low [37] despite compelling evidence [10], further studies should involve patients undergoing therapeutic hypothermia or not to reflect more real-life practices.

To conclude, in patients successfully resuscitated from CA, serum PCT levels measured during the first 3 days were significantly higher in patients with early onset pneumonia. However, this biomarker was associated with a poor sensitivity, specificity, and positive and negative predictive values. At this time, PCT levels should not be used to assess early onset pneumonia after CA undergoing therapeutic hypothermia. Post-resuscitation shock, which is present in a large subset of these patients, could contribute to the PCT elevation and may affect its diagnostic accuracy.

Acknowledgments We are indebted to Nathalie Marin, PharmD, for substantial help in blood sample management. We thank Nancy Kentish-Barnes and Alex Dyson for critical reading of the manuscript.

Conflict of interest statement The authors have not disclosed any potential conflicts of interest. Financial support was provided solely from departmental resources. Brahms donated procalcitonin kits without any access to data management. The company had no role in the study design, manuscript writing or decision to submit the manuscript for publication.

References

1. Rello J, Vallés J, Jubert P, Ferrer A, Domingo C, Mariscal D, Fontanals D, Artigas A (1995) Lower respiratory tract infections following cardiac arrest and cardiopulmonary resuscitation. Clin Infect Dis 21:310–314
2. Gajic O, Festic E, Afessa B (2004) Infectious complications in survivors of cardiac arrest admitted to the medical intensive care unit. Resuscitation 60:65–69
3. Tsai MS, Chiang WC, Lee CC, Hsieh CC, Ko PC, Hsu CY, Su CP, Chen SY, Chang WT, Yuan A, Ma MH, Chen SC, Chen WJ (2005) Infections in the survivors of out-of-hospital cardiac arrest in the first 7 days. Intensive Care Med 31:621–626
4. Negovsky VA (1988) Postresuscitation disease. Crit Care Med 16:942–946
5. Adrie C, Laurent I, Monchi M, Cariou A, Dhainaut JF, Spaulding C (2004) Postresuscitation disease after cardiac arrest: a sepsis-like syndrome? Curr Opin Crit Care 10:208–212
6. Simon L, Gauvin F, Amre DK, Saint-Louis P, Lacroix J (2004) Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis. Clin Infect Dis 39:206–217. Erratum in: Clin Infect Dis 2005; 40:1386–1388
7. Uzzan B, Cohen R, Nicolas P, Perret GY (2006) 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 34:1996–2003
8. Harbarth S, Holeckova K, Froidevaux C, Pittet D, Ricou B, Grau GE, Vadas L, Pugin J, Geneva Sepsis Network (2001) Diagnostic value of procalcitonin, interleukin-6, and interleukin-8 in critically ill patients admitted with suspected sepsis. Am J Respir Crit Care Med 164:396–402
9. Oppert M, Reinicke A, Müller C, Barckow D, Frei U, Eckardt KU (2002) Elevations in procalcitonin but not C-reactive protein are associated with pneumonia after cardiopulmonary resuscitation. Resuscitation 53:167–170
10. Neumar RW, Nolan JP, Adrie C, Aibiki M, Berg RA, Böttiger BW, Callaway C, Clark RS, Geocadin RG, Jauch EC, Kern KB, Laurent I, Longstreth WT Jr, Merchant RM, Morley P, Morrison LJ, Nadkarni V, Peberdy MA, Rivers EP, Rodriguez-Nunez A, Sellke FW, Spaulding C, Sunde K, Vanden Hoek T (2008) Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A consensus statement from the International Liaison Committee on Resuscitation (American Heart Association, Australian and New Zealand Council on Resuscitation, European Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Asia, and the Resuscitation Council of Southern Africa); the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; and the Stroke Council. Circulation 118:2452–2483
11. Jacobs I, Nadkarni V, Bahr J, Berg RA, Billi JE, Bossaert L, Cassan P, Coovadia A, D'Este K, Finn J, Halperin H, Handley A, Herlitz J, Hickey R, Idris A, Kloeck W, Larkin GL, Mancini ME, Mason P, Mears G, Monsieurs K, Montgomery W, Morley P, Nichol G, Nolan J, Okada K, Perlman J, Shuster M, Steen PA, Sterz F, Tibballs J, Timerman S, Truitt T, Zideman D, International Liason Committee on Resusitation (2004) Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries. A statement for healthcare professionals from a task force of the international liaison committee on resuscitation (American Heart Association, European Resuscitation Council, Australian Resuscitation Council, New Zealand Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa). Resuscitation 63:233–249
12. Charles PE, Kus E, Aho S, Prin S, Doise JM, Olsson NO, Blettery B, Quenot JP (2009) Serum procalcitonin for the early recognition of nosocomial infection in the critically ill patients: a preliminary report. BMC Infect Dis 9:49
13. Clec'h C, Fosse JP, Karoubi P, Vincent F, Chouahi I, Hamza L, Cupa M, Cohen Y (2006) Differential diagnostic value of procalcitonin in surgical and medical patients with septic shock. Crit Care Med 34:102–107

14. Luyt CE, Combes A, Reynaud C, Hekimian G, Nieszkowska A, Tonnellier M, Aubry A, Trouillet JL, Bernard M, Chastre J (2008) Usefulness of procalcitonin for the diagnosis of ventilator-associated pneumonia. Intensive Care Med 34:1434–1440
15. Amour J, Birenbaum A, Langeron O, Le Manach Y, Bertrand M, Coriat P, Riou B, Bernard M, Hausfater P (2008) Influence of renal dysfunction on the accuracy of procalcitonin for the diagnosis of postoperative infection after vascular surgery. Crit Care Med 36:1147–1154
16. Bellomo R, Kellum JA, Ronco C (2007) Defining and classifying acute renal failure: from advocacy to consensus and validation of the RIFLE criteria. Intensive Care Med 33:409–413
17. Müller B, Harbarth S, Stolz D, Bingisser R, Mueller C, Leuppi J, Nusbaumer C, Tamm M, Christ-Crain M (2007) Diagnostic and prognostic accuracy of clinical and laboratory parameters in community-acquired pneumonia. BMC Infect Dis 7:10
18. Christ-Crain M, Stolz D, Bingisser R, Müller C, Miedinger D, Huber PR, Zimmerli W, Harbarth S, Tamm M, Müller B (2006) Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial. Am J Respir Crit Care Med 174:84–93
19. Stolz D, Christ-Crain M, Bingisser R, Leuppi J, Miedinger D, Müller C, Huber P, Müller B, Tamm M (2007) Antibiotic treatment of exacerbations of COPD: a randomized, controlled trial comparing procalcitonin-guidance with standard therapy. Chest 131:9–19
20. Nobre V, Harbarth S, Graf JD, Rohner P, Pugin J (2008) Use of procalcitonin to shorten antibiotic treatment duration in septic patients: a randomized trial. Am J Respir Crit Care Med 177:498–505
21. Krüger S, Papassotiriou J, Marre R, Richter K, Schumann C, von Baum H, Morgenthaler NG, Suttorp N, Welte T, CAPNETZ Study Group (2007) Pro-atrial natriuretic peptide and pro-vasopressin to predict severity and prognosis in community-acquired pneumonia: results from the German competence network CAPNETZ. Intensive Care Med 33:2069–2078
22. Luyt CE, Guérin V, Combes A, Trouillet JL, Ayed SB, Bernard M, Gibert C, Chastre J (2005) Procalcitonin kinetics as a prognostic marker of ventilator-associated pneumonia. Am J Respir Crit Care Med 171:48–53
23. Fries M, Kunz D, Gressner AM, Rossaint R, Kuhlen R (2003) Procalcitonin serum levels after out-of-hospital cardiac arrest. Resuscitation 59:105–109
24. Fries M, Stoppe C, Brücken D, Rossaint R, Kuhlen R (2009) Influence of mild therapeutic hypothermia on the inflammatory response after successful resuscitation from cardiac arrest. J Crit Care 24:453–457
25. Adib-Conquy M, Monchi M, Goulenok C, Laurent I, Thuong M, Cavaillon JM, Adrie C (2007) Increased serum levels of soluble triggering receptor expressed on myeloid cells 1 and procalcitonin after cardiac surgery and cardiac arrest without infection. Shock 28:406–410
26. Geppert A, Steiner A, Delle-Karth G, Heinz G, Huber K (2003) Usefulness of procalcitonin for diagnosing complicating sepsis in patients with cardiogenic shock. Intensive Care Med 29:1384–1389
27. Adrie C, Adib-Conquy M, Laurent I, Monchi M, Vinsonneau C, Fitting C, Fraisse F, Dinh-Xuan AT, Carli P, Spaulding C, Dhainaut JF, Cavaillon JM (2002) Successful cardiopulmonary resuscitation after cardiac arrest as a "sepsis-like" syndrome. Circulation 106:562–568
28. Dandona P, Nix D, Wilson MF, Aljada A, Love J, Assicot M, Bohuon C (1994) Procalcitonin increase after endotoxin injection in normal subjects. J Clin Endocrinol Metab 79:1605–1608
29. Geppert A, Dorninger A, Delle-Karth G, Zorn G, Heinz G, Huber K (2006) Serum concentrations of interleukin-6, organ failure, vasopressor support, and successful coronary revascularization in predicting 30-day mortality of patients with cardiogenic shock complicating acute myocardial infarction. Crit Care Med 34:2035–2042
30. Tang BM, Eslick GD, Craig JC, McLean AS (2007) Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: systematic review and meta-analysis. Lancet Infect Dis 7:210–217
31. Jones AE, Fiechtl JF, Brown MD, Ballew JJ, Kline JA (2007) Procalcitonin test in the diagnosis of bacteremia: a meta-analysis. Ann Emerg Med 50:34–41
32. Pugin J, Auckenthaler R, Mili N, Janssens JP, Lew PD, Suter PM (1991) Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and nonbronchoscopic "blind" bronchoalveolar lavage fluid. Am Rev Respir Dis 143:1121–1129
33. Luyt CE, Chastre J, Fagon JY (2004) Value of the clinical pulmonary infection score for the identification and management of ventilator-associated pneumonia. Intensive Care Med 30:844–852
34. Schurink CA, Van Nieuwenhoven CA, Jacobs JA, Rozenberg-Arska M, Joore HC, Buskens E, Hoepelman AI, Bonten MJ (2004) Clinical pulmonary infection score for ventilator-associated pneumonia: accuracy and inter-observer variability. Intensive Care Med 30:217–224
35. Laver S, Farrow C, Turner D, Nolan J (2004) Mode of death after admission to an intensive care unit following cardiac arrest. Intensive Care Med 30:2126–2168
36. Callaway CW, Rittenberger JC, Logue ES, McMichael MJ (2008) Hypothermia after cardiac arrest does not alter serum inflammatory markers. Crit Care Med 36:2607–2612
37. Wolfrum S, Radke PW, Pischon T, Willich SN, Schunkert H, Kurowski V (2007) Mild therapeutic hypothermia after cardiac arrest—a nationwide survey on the implementation of the ILCOR guidelines in German intensive care units. Resuscitation 72:207–213