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Serum procalcitonin (PCT): a valuable biochemical parameter for the post-mortem diagnosis of sepsis

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Abstract The aim of this prospective study was to investigate whether serum procalcitonin (PCT) can be used as a post-mortem marker of sepsis and to determine whether this biochemical parameter can be employed in the forensic elucidation of death due to sepsis. At least three blood samples were collected between 0.3 and 139 h post-mortem from sepsis-related fatalities (n = 8) and control individuals (n = 53, where death was due to various natural and unnatural causes). Additionally one ante-mortem blood sample was collected shortly before death from the patients in the sepsis group. In the sepsis group, serum PCT concentrations, determined by using an immunoluminometric assay, were elevated in all patients for the whole observation period, whereas in the control group serum PCT was not detectable in 94% of the cases. Measurement of PCT levels seems reasonable until at least approximately 140 h postmortem, depending on the ante-mortem levels. A linear regression model is presented that allows the serum PCT concentration of an individual at the time of death to be estimated on condition that at least two positive post-mortem PCT values have been determined. Ante-mortem PCT values correlated well with the predicted PCT values at the time of death in the sepsis group using the standardized PCT logarithms. According to the results of the present study, PCT is a valuable biochemical parameter for the post-mortem discrimination between sepsis and underlying non-septic causes of death.

Keywords Procalcitonin · PCT · Sepsis · Post-mortem · Diagnostics

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Introduction

Occasionally, when a well-documented medical history is not available for a deceased person, the post-mortem diagnosis of death due to sepsis can be a substantial challenge in forensic casework. Moreover, post-mortem blood cultures are most frequently contaminated by putrefaction processes and macromorphological autopsy findings such as buffy coat clots, oedema of the brain and lungs or spodogenous spleen tumescence as well as routine histological findings (e.g. tubulonecrosis of the kidneys, follicle necrosis of the spleen, periportal leucocyte infiltration of the liver) may have an infectious or non-infectious aetiology and are neither specific nor sensitive for recognizing sepsis-associated fatalities. Therefore other parameters are needed to establish a precise post-mortem diagnosis of death due to sepsis.

New biochemical parameters, such as procalcitonin (PCT) and the cytokines, have recently attracted attention as clinical markers of the systemic inflammatory response to sepsis and infection. PCT is the propeptide of calcitonin, is devoid of hormonal activity and consists of 116 amino acids with a molecular weight of 13 kD [12, 16]. The reference value of serum PCT concentrations in healthy individuals is below 0.5 ng/ml [2, 17]. Since the original publication by Assicot and co-workers [4], who demonstrated that serum PCT levels increase at the onset of bacterial infection and that serum PCT concentrations are correlated with the severity of sepsis, recent clinical studies have shown that PCT is a valid marker for the presence of bacterial infection in patients with severe sepsis [2, 6, 7, 9, 10, 11, 15, 25, 27].

The present prospective study was conducted to evaluate the potential role of PCT as a post-mortem marker of sepsis and to determine whether this biochemical parameter can be employed in the forensic elucidation of death due to sepsis.

Materials and methods

Blood samples

Post-mortem blood samples were collected by aspiration with a sterile needle and syringe from the femoral vein at defined time intervals between 0.3 and 139 h post-mortem (hpm) from the individuals included in both study groups and at least 3 post-mortem blood samples (maximum 5 samples) were obtained from each subject. Additionally, one ante-mortem venous blood sample from the patients included in the sepsis group which was collected shortly before death as part of the clinical routine in the intensive care unit (time of blood sampling within 1 and 3 h prior to death) was analysed. All blood samples were centrifuged immediately after collection at 3000 rpm for 10 min, the serum was separated and stored frozen at –80 °C prior to the immunoluminometric assay.

Study groups

The two study groups were formed according to whether there was an underlying septic condition as the cause of death based on the subjects medical records as well as autopsy findings. In each case the time of death was well defined by means of clinical monitoring and emergency physicians' records.

1. Sepsis group: Patients (n = 8, 5 males, 3 females; individual ages 14–77 years, mean age 53 years) from the intensive care unit of the Department of Anaesthesiology, University Hospital Eppendorf, Hamburg, Germany, with a well documented medical history and diagnosis of sepsis in vivo according to the definition of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference [3] were included in this study group. The cause of death was multiple organ failure due to sepsis in all cases. Table 1 shows the individual clinical and biological characteristics of the patients.

2. Non-sepsis group: Autopsy cases (n = 53, 37 males, 16 females; age range 30–94 years, mean age 63 years) from the Institute of Legal Medicine, Hamburg, Germany, non-hospitalized cases with death due to various natural and unnatural causes, served as the control group. All individuals in this study group had no medical history of a septic condition prior to death and no other disease was found at autopsy except for the cause of death (myocardial infarction n = 12, myocardial insufficiency n = 9, intracerebral haemorrhage n = 3, malignant diseases n = 4, acute heroine intoxication n = 3, carbon monoxide poisoning n = 2, trauma/polytrauma n = 12, pulmonary embolism n = 4, drowning n = 2, hanging n = 2). Cardiopulmonary resuscitation was attempted in 22 cases. In none of these cases did the autopsy findings give any cause to suspect an underlying infectious disease and no post-mortem microbiological investigations were carried out.

Measurement of PCT

PCT levels were determined in 20 µl serum from each blood sample without prior knowledge of the origin, using a specific immunoluminometric assay (LUMItest PCT, B.R.A.H.M.S. Diagnostica, Berlin, Germany). The assay utilizes two monoclonal antibodies directed against the C-terminal catacalcin and mid-regional calcitonin sequences of PCT, respectively. The anti-catacalcin antibody is immobilized on the surface of the coated tube and the anti-calcitonin antibody is labelled using a luminescent acridine derivative. In brief, after incubation at room temperature for 2 h, the tubes were placed in a luminometer (Berthold LB952, EG&G Berthold, Wildbach, Germany). After injection of hydrogen peroxide and sodium hydroxide these substances react with the acridine derivative bound to the anti-calcitonin antibody, which emits light as it transforms into acridone. The emitted light intensity is directly proportional to the PCT concentration. The lower PCT detection limit of the assay is 0.3 ng/ml [17].

Analysis of data

The values given result from three independent luminometric measurements with a non-weighted averaging. Serum PCT levels related to post-mortem intervals were compared between and within individuals and evaluated for statistically significant differences with the Wilcoxon-Mann-Whitney test. To permit estimation of the post-mortem PCT values and thus to determine the serum PCT concentration at the time of death in order to compare these data with the authentic ante-mortem PCT values measured in the sepsis group, a linear regression model was used on the PCT logarithms.

Results

Serum PCT concentrations in the sepsis group

Serum PCT concentrations were elevated in all patients included in this study group for the whole observation period. In the ante-mortem blood samples PCT values ranged between 4.3 and 95.0 ng/ml. Post-mortem PCT concentrations ranged between 85.9 ng/ml and 1.2 ng/ml. In the early post-mortem interval, the highest PCT levels determined were 85.9 ng/ml (patient no. 1, 1.2 h post-mortem), 22.3 ng/ml (patient no. 3, 0.3 h post-mortem) and 16.2 ng/ml (patient no. 8, 6 h post-mortem). Peak PCT levels in the late post-mortem interval were found in patient no. 5 with 21.5 ng/ml (83.8 h post-mortem) and patient no. 1 with 13.2 ng/ml (111.6 h post-mortem). The time course of the post-mortem PCT values is presented in Fig. 1. Table 2 gives the serum PCT values of both, ante-mortem and post-mortem blood samples, the logarithms of PCT concentrations and the results of the linear regression analysis. The differences in the mean values for serum PCT were analysed for the patients and comparison of the

Table 1 Dual clinical and biological characteristics of the patients included in the sepsis group (*ICU* intensive care unit)

No.	Gender	Age (years)	ICU (days)	Results of microbiology as identified by repeated blood cultures in vivo	Cause of sepsis
1	F	77	15	*Klebsiella pneumoniae*	Peritonitis (perforation of small bowel)
2	M	67	21	*Enterobacter cloacae*	Peritonitis (perforation of small bowel)
3	M	43	6	*Klebsiella oxytoca*	Peritonitis (abdominal gun shots)
4	M	57	3	*Enterococcus* sp., *Corynebacterium* sp.	Peritonitis (perforation of small bowel)
5	M	14	4	*Staphylococcus aureus*	Burn injury
6	F	58	11	*Escherichia coli*, *Enterococcus* sp.	Peritonitis (perforation of small bowel)
7	M	47	28	Coagulase-negative staphylococci	Liver failure following liver transplantation
8	F	64	18	*Streptococcus pneumoniae*	Oesophagogastrostomy

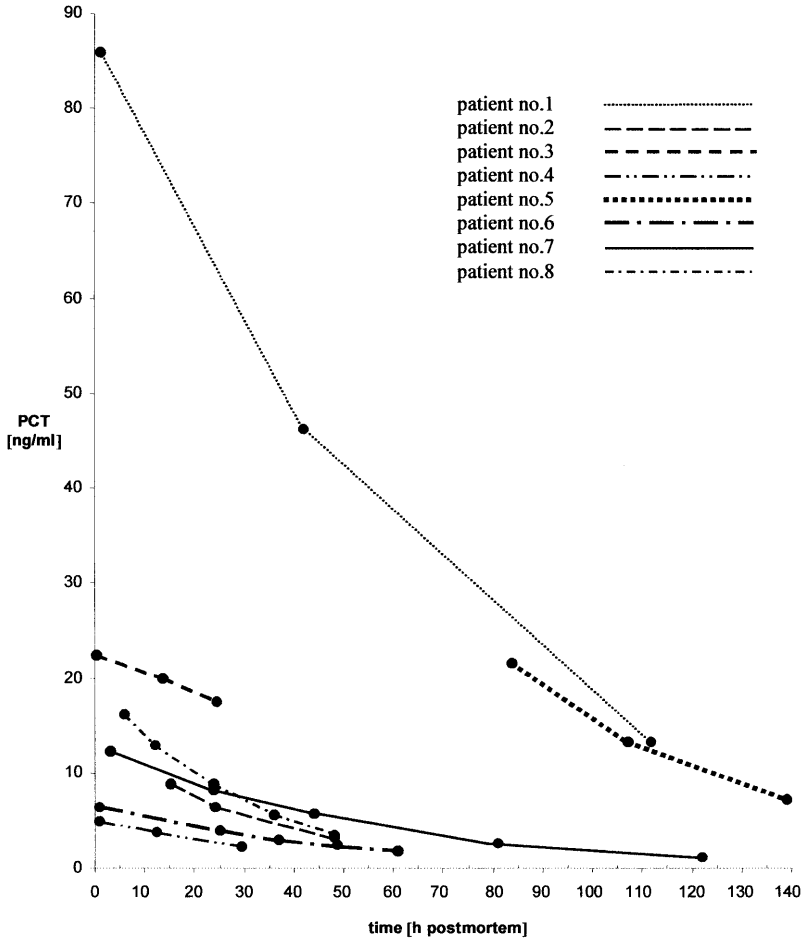

Fig. 1 Time course of serum PCT concentrations in the patients included in the sepsis group

parameters gender, age, number of days in intensive care and cause of sepsis revealed no significant differences of PCT levels. Figure 2 shows the results of the linear regression analysis of the post-mortem PCT values.

Serum PCT concentrations in the non-sepsis group

Serum PCT was not detectable in 50 (94%) of the cases included in the control group (data not shown), and PCT levels were just above the detection limit of the assay in only 3 cases, ranging between 0.4 and 0.6 ng/ml (Table 3). Cardiopulmonary resuscitation attempts had no influence on PCT levels.

Calculation of serum PCT concentration at the time of death

According to our results, the serum PCT concentration of an individual at the time of death can be estimated using a linear regression model with the logarithmic PCT values on condition that at least two post-mortem PCT values above the detection limit have been determined at different time points post-mortem.

The post-mortem PCT values measured in the sepsis group of the present series (Fig. 3) can be compared with post-mortem PCT values determined in future investigations according to the following formula by using the standardized PCT logarithms:

$$\frac{f(t)}{f(0)} = \frac{m \cdot t + b}{b} = \frac{m}{b} \cdot t + 1$$

where t is post-mortem interval (h), m is slope and b is offset, also for the PCT logarithm at time of death.

Comparison of ante-mortem and post-mortem serum PCT concentrations

On condition that at least two positive post-mortem PCT values have been determined, the inverse logarithm of b can be calculated, thus enabling the "predictive" PCT value at $t = 0$ (time of death) to be estimated for a subject. Thereafter the predictive PCT value can be compared with the (real) ante-mortem PCT value. In the present study, the ante-mortem serum PCT values, derived from blood samples collected shortly before death, correlated well with the predictive PCT values at the time of death in seven out of the eight cases in the sepsis group by using the standardized PCT logarithms (Table 2). In one case (patient no. 5, Table 2) a divergence of 16.8 ng/ml between the estimated predictive PCT value (111.8 ng/ml) and the ante-mortem

Table 2 Serum PCT concentrations, PCT logarithms and results of linear regression analysis in ante-mortem and post-mortem blood samples in the sepsis group (*a.m.* ante-mortem, *p.m.* post-mortem)

Patient no.	Blood sample (a.m./p.m.)	Time (h)	PCT (ng/ml)	PCT logarithm (ng/ml)	Slope (*m*)	Offset (*b*)
1	a.m.	1.0	82.2	4.4		
	p.m.	1.2	85.9	4.5	-1.71×10^{-2}	90.2
		41.9	46.2	3.8		
		111.6	13.2	2.6		
2	a.m.	1.6	10.5	2.4		
	p.m.	15.2	9.0	2.2	-3.05×10^{-2}	13.8
		24.1	6.4	1.9		
		48.2	3.2	1.2		
3	a.m.	3.4	21.0	3.1		
	p.m.	0.3	22.3	3.1	-9.90×10^{-2}	22.5
		13.6	20.0	3.0		
		24.6	17.5	2.9		
4	a.m.	0.9	4.3	1.5		
	p.m.	1.0	4.9	1.6	-2.63×10^{-2}	5.1
		12.6	3.8	1.3		
		29.4	2.4	0.9		
5	a.m.	1.4	95.0	4.6		
	p.m.	83.8	21.5	3.1	-1.98×10^{-2}	111.8
		107.2	13.2	2.6		
		139.0	7.2	2.0		
6	a.m.	1.8	5.4	1.7		
	p.m.	1.0	6.4	1.9	-2.04×10^{-2}	6.5
		25.0	3.9	1.4		
		36.9	3.0	1.1		
		48.7	2.5	0.9		
		60.9	1.9	0.6		
7	a.m.	3.0	10.4	2.3		
	p.m.	3.0	12.2	2.5	-1.97×10^{-2}	13.1
		24.0	8.2	2.1		
		44.0	5.7	1.7		
		81.0	2.7	1.0		
		122.0	1.2	0.2		
8	a.m.	3.0	16.7	2.8		
	p.m.	6.0	16.2	2.8	-3.50×10^{-2}	20.0
		12.0	12.9	2.7		
		24.0	8.8	2.3		
		36.0	5.6	1.7		
		48.0	3.7	1.3		

PCT value (95 ng/ml) was found; this patient showed the highest ante-mortem PCT concentration in the present series.

Discussion

In living patients, serum PCT concentrations show a good correlation with the severity of sepsis and PCT is used as a diagnostic parameter in the clinical monitoring of severe bacteria-induced sepsis and multi-organ dysfunction syndrome [1, 2, 7, 10, 13, 15, 17, 25, 27]. Viral infections, autoimmune disorders, allergic reactions and local bacterial infections do not induce PCT, hence PCT can be used in the living for the differential diagnosis of bacterial and non-bacterial inflammation and to differentiate between sepsis and systemic inflammatory response syndrome of non-infectious origin [13, 17, 18]. During septic episodes PCT levels measured in vivo are above 2 ng/ml and in severe sepsis may even rise above 100 ng/ml, whereas in non-infected individuals the serum concentration is below 0.5 ng/ml [17]. The results of the present study carried out using post-mortem blood samples show that the serum PCT concentration can be considered as a valuable diagnostic tool to distinguish sepsis-associated fatalities from underlying non-septic causes of death post-mortem.

Apart from the immunohistochemical detection of an enhanced pulmonary expression of different cellular adhesion molecules, such as P-selectin [20], E-selectin [32],

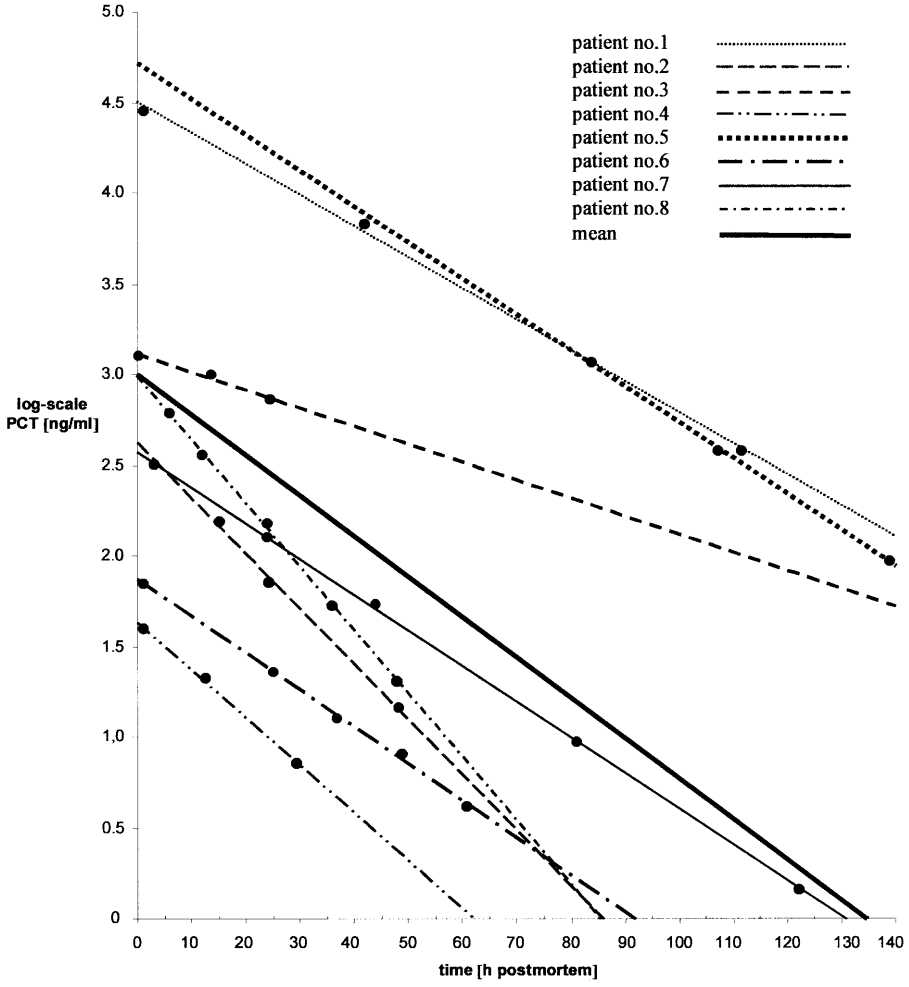

Fig. 2 Serum PCT concentrations in the sepsis group as determined by linear regression analysis

Table 3 Patients' characteristics and post-mortem PCT values in the three cases with PCT levels above the detection limit of the assay in the non-sepsis group

Gender	Age (years)	Cause of death as determined by autopsy	Time of blood sampling (hpm)	PCT (ng/ml)
Female	94	Myocardial insufficiency	10.5	0.4
			31.9	0.4
			58.4	0.4
Male	87	Polytrauma	0.8	0.5
			24.1	0.4
			48.3	0.4
Male	70	Intracerebral haemorrhage	1.5	0.6
			24.7	0.6
			48.6	0.5

VLA-4 and ICAM-1 [31] in sepsis-induced lung injury, there are no defined post-mortem markers for death caused by sepsis. These immunohistochemical investigations are not routinely used in forensic casework and as a result, clinical data and morphological findings that are to a great extent unspecific remain the diagnostic criteria in the post-mortem diagnosis of death due to sepsis [26, 28, 30, 33].

In a variety of forensic studies, the post-mortem determination of biochemical parameters has been recognized as useful in establishing the post-mortem diagnosis of the underlying cause of death, e.g. the autopsy diagnosis of diabetes mellitus based on biological compounds in vitreous humour or cerebrospinal fluid [14, 23, 24], the elucidation of sudden cardiac death and acute myocardial infarction by the estimation of plasma lipids, apolipoproteins or cardiac troponin I [8, 21, 22, 34] and the detection of acetone and HbA1 in blood to support the diagnosis of ketoacidosis and lactoacidosis as the cause of death in chronic alcoholics [5]. However, the present prospective study assessing the course of serum PCT levels in sepsis-associated fatalities, is the first to deal with the post-mortem diagnosis of sepsis with the aid of a biochemical parameter.

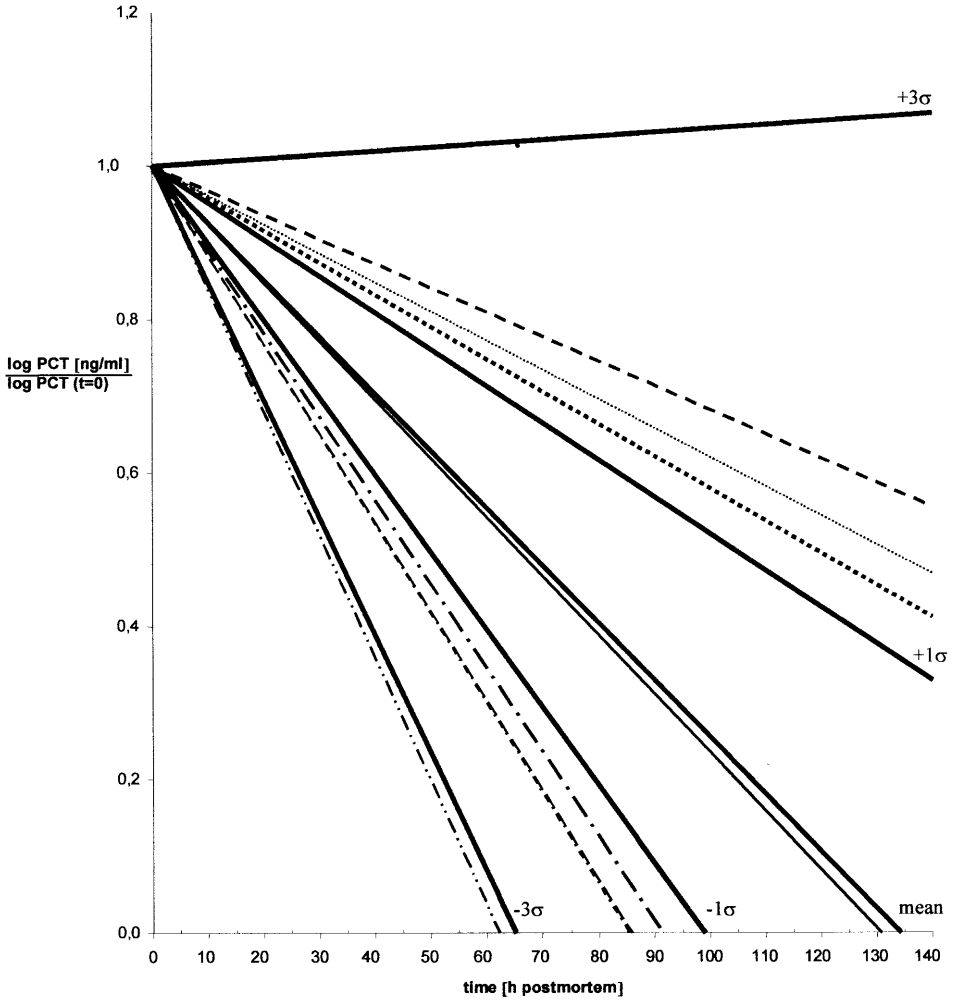

Fig. 3 Normalized PCT logarithms of the patients included in the sepsis group: standard deviation and mean

Compared to other potential biochemical post-mortem markers of sepsis, PCT has several advantages. In contrast to proinflammatory cytokines, such as tumour necrosis factor-α or interleukin-6 which circulate in the blood with a half-life between minutes and a few hours [29], PCT has a half-life of 25–30 h [17]. Furthermore, in comparison to cytokines, PCT is a very stable protein ex vivo, even at room temperature and PCT concentrations do not differ in arterial and venous blood samples from living persons [19]. In addition, repeated freezing and thawing of the blood samples does not significantly influence PCT concentrations in these specimens [17, 19]. PCT exhibits a high stability against haemolysis at different conditions of storage [17, 19] and post-mortem blood samples can be rapidly investigated by using the immunoluminometric assay employed in the present study. Hence quantification of post-mortem PCT has the potential to be routinely employed in questioned cases of potentially sepsis-associated fatalities and thus to contribute in diminishing a small number of otherwise unresolved deaths in forensic autopsy practice.

Our findings suggest that for the forensic elucidation of death due to underlying sepsis, measurement of PCT levels seems reasonable until at least approximately 140 h post-mortem, depending on the ante-mortem levels in the case in question. According to our results, when the cause of death of a deceased is presumed to be sepsis-related, the serum PCT concentration at the time of death ("predictive" PCT level) can be estimated on condition that two positive post-mortem PCT values (above the detection limit of the assay) have been determined. In our series, in the overwhelming majority of the cases included in the sepsis group the ante-mortem PCT values correlated well with the predictive PCT values at the time of death using the standardized PCT logarithms (Table 2). A considerable divergence between both values was found in only one case. Due to the fact that this patient expressed by far the highest ante-mortem PCT concentration in the present series, we assume that in cases with very high PCT concentrations prior to death, a substantial divergence between the predictive PCT value (calculated on the basis of post-mortem PCT determination) and the real ante-mortem PCT value should be taken into consideration. Even so, this does not influence the possibility of facilitating the post-mortem diagnosis of a sepsis-related fatality based on the results of post-mortem PCT determination in such cases.

In order to compare the graphs of the different patients in the sepsis group, the PCT values were standardized to

the PCT levels at the time of death (Fig. 3). This enables post-mortem PCT values from future studies to be compared to the post-mortem PCT values measured in the sepsis group of the present series.

The current study represents a first study of serum PCT as a biochemical parameter for the post-mortem diagnosis of sepsis. Further studies are required to include hospital patients with a well-known medical history as control individuals and also to put the main focus on the comparison between autopsy findings and post-mortem PCT levels in cases where clinically the diagnosis of a possible sepsis was raised but the patient died prior to the final diagnosis. Moreover, further investigations are needed to determine post-mortem PCT concentrations in different body fluids, arterial blood samples and in serum specimens taken from sites more peripheral than the femoral region. In conclusion, the results of the present study indicate that the determination of serum PCT from femoral venous blood samples is a valuable tool for the post-mortem discrimination between sepsis and non-septic underlying causes of death.

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