Described here is a case report in which a patient suffered from severe heat stoke with subsequent development of multiple organ failure (MOF). The patient received hemodialysis with cold dialysate followed by high flow continuous hemodiafiltration (CHDF) therapy with cold dialysate, because this patient had been refractory to conventional cooling methods, including evaporative cooling methods, cold-water immersion methods, iced gastric lavage and cold blanket. As a result of the successful control of his temperature, he recovered from MOF 3 weeks after its onset. This case suggests that cold HD plus cold, high flow CHDF is preferred in severe heat stroke for the benefit of cooling the body temperature and for the treatment of its several potential complications.

CASE REPORT

A previously healthy 23-year-old male construction worker was presented to the emergency department (ED) of Keio University Hospital because of loss of consciousness at 13:15 hours on 5 July 2003. He had been in a closed workplace on the sixth floor of a building under construction. The ambient temperature was 28.1°C, the humidity was 53% and the wind velocity was 3.6 m/s at that time in that area. He began to work at 09:00 hours, and fainted abruptly at noon. He was initially sent to a nearby clinic, but refused intravenous fluid infusion therapy, and left the clinic after a short while. He was later found lying on the street with disturbance of consciousness, and transferred to the ED.

On arrival at the ED, the patient's airway was clear; he had spontaneous respiration at the rate of 32 breaths per min with oxygen saturation of 94% in room air. His pulse rate was 156 beats per min with regular rhythm. Although his arterial pulse was palpable, his blood pressure was not measurable. He was found to be comatose at grade 4 on the Glasgow Coma Scale (GCS; E1V1M2). The patient's core temperature measured inside the urinary bladder was 42.1°C. Physical examination showed a sluggish light reflex of bilateral pupils, a dry tongue and skin without sweat, a normal heart beat without a murmur or gallop, a normal respiratory sound, and a mildly distended abdomen. He was obese (approximately 90 kg in weight and 165 cm in height) with thick body hair and no rash. The color of his urine was dark brown. His electrocardiogram (ECG) showed ST elevation in I, II, III, aVL, aVF, and $V_{3\text{-}6}$, and a tall T wave in $V_{1\text{-}2}$. The echocardiogram showed diffuse hypokinesis with a 40% ejection fraction. His chest X-ray and computed tomography of the head were normal.

The blood gas analysis showed metabolic acidosis with an increased anion gap (Table 1). Urinalysis showed marked myoglobulinuria and proteinuria with granular casts. Hematuria was not detected. The patient was so dehydrated that his hemoglobin value was 16.7 g/dL and his hematocrit 49.5%. His white blood cell and platelet count were also high. The blood chemistry indicated hyperproteinemia (10.1 g/dL), hypernatremia (149.6 mEq/L) and markedly elevated levels of uric acid. All these data indicated his severely dehydrated state. Moderate hepatic and renal damage was evident. His electrolyte disturbance included hyperkalemia and hypocalcemia. The level of creatine phosphokinase (CPK) was markedly increased. Other laboratory data are summarized in Table 1.

After a diagnosis of heat stroke, 2 L of ice cold saline were infused intravenously. Active cooling was instituted with ice packs to the axillae, neck and

TABLE 1. *Laboratory data on arrival at the emergency room*

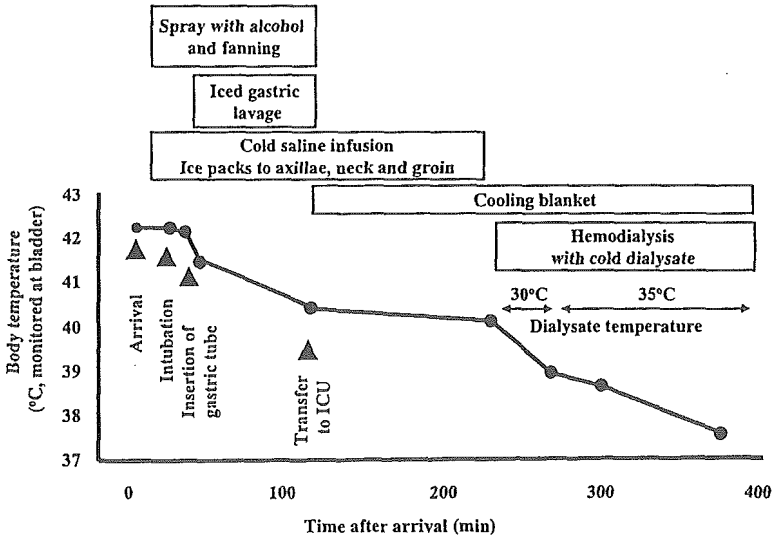
CBC	Biochemistry
WBC 21,800/μL	TP 10.1 g/dL
RBC 5.35 ×10⁶/μL	TC 289 mg/dL
Hb 16.7 g/dL	TB 0.8 mg/dL
Ht 49.5%	**BUN 20.7 mg/dL**
Plt 261 000/μL	**Creatinine 3.7 mg/dL**
Urinalysis	**UA 32.4 mg/dL**
color brown	Na 149.6 mEq/L
pH 6.0	**K 6.2 mEq/L**
Glu (±)	Cl 97 mEq/L
Pro(1+)	**Ca 5.5 mg/dL**
RBC 21–50	CRP 0.20 mg/dL
WBC 6–10	**LDH 704 IU/L**
Granular cast 1+	**AST 125 IU/L**
WBC cast 1+	**ALT 127 IU/L**
Coagulation and fibrinolysis	Amy 110 IU/L
APTT 25.7 s	**CPK 1337 IU/L**
PT-INR 1.46	**BS 160 mg/dL**
FNG 204 mg/dL	**NH3 63 mmol/L**
FDP 501 ng/mL	**TroponinT positive**
Blood gas analysis(O_2 6 L)	**Myoglobin (serum) 540000 ng/mL** (normal < 60)
pH 7.160	**Myoglobin (urine) 5750000 ng/mL**
Pa_{O_2} 95.8 mm Hg	ECG
Pa_{CO_2} 32.9 mm Hg	**ST elevation in I, II, III, aVL, aVF, and V3-6, tall T wave in V1-2**
HCO^{3-} 11.2 mEq/L	Echocardiogram
	Diffuse hypokinesis with a 40% ejection fraction.

Abnormal values are given in bold. AST, aspartate aminotransferase; ALT, alanine aminotransferase; Amy, amylase; APTT, activated partial thromboplastin time; BS, blood sugar; BUN, blood urea nitrogen; CBC, complete blood count; CRP, C-reactive protein; CPK, creatine phosphokinase; FDP, fibrin degradation products; FNG, fibrinogen; Glu, glucose; Hb, hemoglobin; Ht, hematocrit; LDH, lactate dehydrogenase; NH_3, ammonia; Plt, platelet; Pro (1+), protein (1+); PT-INR, prothrombin time-international normalized ratio; Pa_{O_2}, pressure of arterial oxygen; Pa_{CO_2}, pressure of arterial carbon dioxide; RBC, red blood cells; TP, total protein; TC, total cholesterol; TB, total bilirubin; UA, uric acid; WBC, white blood cells.

groin. Cold alcohol was applied to the patient's skin which was also fanned. A gastric lavage was undertaken several times using 2 L of iced saline (Fig. 1). Despite all these procedures, the patient's core temperature remained above 40°C. Because the systolic blood pressure was still lower than 60 mm Hg, an intravenous administration of dopamine hydrochloride was started and rapid infusion of ice-cold saline was continued in order to elevate the blood pressure. In the ED, 4 L of saline were infused in total. Because the patient remained comatose and his respiratory functions deteriorated, he was intubated and transferred to the intensive care unit (ICU).

The patient was covered with cold blankets but the speed of body temperature reduction slowed down (Fig. 1). We recognized his high body temperature had been refractory to conventional cooling procedures. We also suspected that acute renal failure (ARF) by rhabdomyolysis had developed and that we would need blood access for hemodialysis (HD) in the near future. We planned to set down a double-channel catheter and to carry out HD using low-temperature dialysate in order to wash out the patient's internal heat, but the patient's hemodynamic did not allow extracorporeal circulation. Saline infusion was continued and judging from the alteration of the levels of total protein, albumin, total cholesterol, hematocrit, hemoglobin, and sodium, depleted plasma volume levels were corrected (Fig. 1). At this stage, the patient's blood pressure rose to 124/82 mmHg (Fig. 1) so we could settle down a catheter and start cold HD. Initially, the temperature of dialysate was set at 30°C for rapid cooling, and after his body temperature had fallen below 39°C it was set at 35°C. Two hours after the beginning of cold HD, the patient's body temperature decreased to 38.4°C, his blood pressure stabilized, and the light reflexes of his bilateral pupils were restored (Fig. 1).

The patient's urine color became darker and urination ceased. The second blood chemical test at 16:00 hours showed the elevation of serum creatinine (4.7 mg/dL) and CPK (40 900 IU/L). Because rhabdomyolysis and resultant ARF were anticipated, continuous hemodiafiltration (CHDF) followed cold HD in the evening of the admission day (day 1). CHDF was carried out using a highly permeable polyacrylonitrile hollow fiber membrane (APF-10S, Asahi Medical Co., Tokyo, Japan); and the rate of the dialysate was set at high flow (18 000 mL/h, Fig. 2). The aim of using CHDF was to efficiently remove small molecular weight toxic substances including uric acid, in addition to large molecular weight substances such as myoglobin and cytokine, which are preferably removed by hemofiltration. In addition, the temperature of dialysate was kept at 35°C and



BP(mmHg)	Not measurable	124/82 mmHg	120/80 mmHg
TP (mg/dL)	10.1	7.2	5.6
Alb (mg/dL)	4.5	3.0	3.0
Na (mEq/L)	149.6	139.7	137.3
TC (mg/dL)	289	191	141
Hb (g/dL)	16.7	14.7	14.4

FIG. 1. Time course of body temperature and values indicating patient's body fluid volume Upper panel; the changes in patient's body temperature monitored at the bladder and the cooling techniques used for this patient. Note the speed of temperature fall plateaued despite several types of cooling techniques. Hemodialysis using cold dialysate at 30°C to 35°C resumed the patient's internal temperature reduction. Lower panel; the changes in the values indicating the patient's body plasma volume levels and his blood pressure. Judging from the changes of listed parameters, the rapid infusion of 4 L of ice-cold saline ameliorated dehydration to raise the blood pressure and stabilize the patient's circulation. This enabled us to start cold hemodialysis (HD). Alb, albumin; BP, blood pressure; Hb, hemoglobin; Ht, hematocrit; Na, sodium; TC, total cholesterol; TP, total protein.

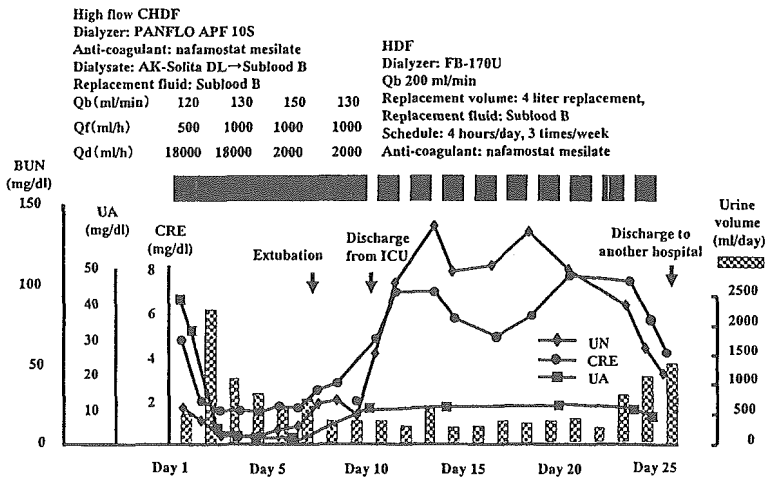
the high flow of cold dialysate prevented the further rise in body temperature.

From the second day, the patient's body temperature remained under 38.0°C, and the serum potassium level reached within the normal range by virtue of the cold blanket and cold, high flow CHDF. However, on day 2, the serum levels of CPK peaked at 337 700 IU/L, and serum myoglobin levels increased to 540 000 ng/mL (normal, <60 ng/mL). The patient was in a state of disseminated intravascular coagulation (DIC) with thrombocytopenia (26 000/μL), a prolonged prothrombin time (54%), and a decreased level of fibrinogen (124 mg/dL). Platelet transfusion and intravenous administration of gabexate mesilate, a serine proteinase inhibitor, were started and continued for 3 days. The patient was kept under treatment with cold, high flow CHDF, intravenous administration of antibiotics and parenteral nutrition. On day 3, the patient's levels of conciousness gradually improved and his blood pressure level was returned enough to normal to reduce the dose of dopamine from 15 to 3 μg/kg/min. On day 6, the patient was extubated without any complication. On day 7, CHDF was terminated and conventional hemodiafiltration (HDF) was begun. Conventional HDF was undertaken three times a week, for 4 h per session, for a total of 2 weeks. Because the patient's general condition improved and he recovered from DIC (CRP 7.53 mg/dL, FDP 404 ng/mL, PT-INR 0.92 and platelets 29 400/μL), he was discharged from ICU on day 10.

Regular intermittent HDF was continued for another week. The patient's conscious level returned to normal with a full score of GCS and he did not need oxygen supply on day 21. His renal function was partially restored (serum creatinine, 4.2 mg/dL) and his urine output was 1200 mL/day on day 23 (Fig. 2). His ECG and echocardiogram findings documented at the onset (Table 1) were normalized and his cardiac function was restored, although he still suffered from mild liver dysfunction (Fig. 2, serum AST and ALT, 66 and 100 IU/L, respectively). However, his general condition was good enough to be transferred to another hospital on day 26, mainly for the purpose of rehabilitation.

DISCUSSION

In the present case study, we describe a patient with severe heat stroke which was complicated by MOF including the failure of his kidney, liver, lung, heart, central nervous system and hematological system. Because extensive cooling with conventional methods failed to restore his body temperature, we decided to apply HD using cold dialysate (initially 30°C and later 35°C), followed by continuous hemodiafiltration (CHDF) with cold dialysate (35°C) at a high flow rate of 18 000 mL per hour. With the help of these therapeutic tools, we successfully controlled his body temperature and electrolyte balance, and continuously eliminated toxic substances including



	Day 1	Day 5	Day 10	Day 15	Day 20	Day 25
Consciousness (GCS)	E1V1M2		E4V4M6	E4V4M6	E4V4M6	E4V4M6
CPK (IU/L)	337700	620920	1945	1779	2000	1422
Myoglobin (ng/ml)(<60)	540000	43000	4200	9100	480	138
CRP (mg/dL)	16.60	24.69	7.56	3.94	2.74	1.94
FDP (ng/mL)	1137	404			514	119
AST (IU/L)	781	4807	692	198	120	66
ALT (IU/L)	256	1838	1032	432	190	100

FIG. 2. Clinical course of the patient with heat stroke. CHDF, continuous hemodiafiltration; HDF, hemodiafiltration; Qb, blood flow rate; Qd, dialysate flow rate; Qf, replacement fluid rate.

myoglobin and uric acid. We stress that hemodialysis or hemofiltration can be beneficial for the washout of thermal energy as well as for the elimination of toxic substances and for the normalization of electrolytes, acid-base balance, osmolarity and body fluid imbalances.

We had difficulty in cooling down the patient's body temperature by simple external cooling procedures. One possible reason for the resistance to therapy was attributed to his obese physique. Obesity is defined as one of the risk factors for heat stroke and it can block the temperature gradient between the skin and the body core (1). Another possible reason is that he was seriously dehydrated and cooled body fluid was not efficiently circulated inside the whole body. Because rapid cooling is critical for improving survival and minimizing end-organ damage (6), and conventional cooling techniques appeared to be inefficient and time-consuming, an internal cooling technique as well as the correction of dehydration should be considered in the early stages of heat stroke. In the present case, we initially utilized iced gastric lavage, which did not seem fully efficient. In heat stroke, redistribution of blood flow from the splanchnic circulation to the periphery causes gut ischemia, which can inhibit the efficient cooling of body core temperature. Rapid infusion of ice cold saline was also carried out, which was also not fully efficient because of the limitation in infusable volume. Finally, we initiated HD although it requires an invasive technique for blood access and sufficient blood pressure level. However, it can be followed by CHDF by using this blood access for the treatment of ensuing MOF. In this case, it took several hours to stabilize his hemodynamic state, which slightly delayed the initiation of extracorporeal circulation and the reduction in body temperature below 40°C. This might be a reason why it took approximately 3 weeks for the patient to recover from MOF and he still suffered from mild liver and renal dysfunctions. Cold HD should have been initiated in the very early stages of severe heat stroke.

One of the most serious complications of heat stroke is MOF which reportedly includes renal or hepatic failure, rhabdomyolysis, acute respiratory distress syndrome, DIC, neurological deficit, myocardial injury, intestinal ischemia, and pancreatic injury (1). This patient suffered from almost all these complications except for intestinal ischemia and pancreatic injury. His condition fulfilled the diagnostic criteria of MOF (7) and MOF indicates a poor prognosis in heat stroke. By virtue of cold, high flow CHDF, he recovered almost fully regarding neurological, respiratory, hematological and cardiac functions, although mild hepatic and renal failure still remained 3 weeks after the onset. It has already been reported that continuous hemofiltration and plasma exchange might improve survival in heat stroke (5). Ikeda et al. retrospectively reviewed five patients with heat stroke and found that three of five treated with CHDF plus plasmapheresis survived, whereas two patients treated with conventional therapy were dead within 3 days. There is some evidence that endotoxinemia and cytokines might be implicated in the pathogenesis of heat stroke (4) which resembles the pathophysiology of sepsis. Various studies have already shown that the removal of proinflammatory cytokines and interleukins by CHDF has the potential to improve a patient's clinical course in sepsis (8,9), although we did not measure the actual levels of these molecules of this patient before and after CHDF. Based on this background, it is quite reasonable to use CHDF in the treatment of heat stroke. Moreover, the novel strategy in this case was to use cold HD plus cold, high flow CHDF to wash out the patient's internal heat. Our case was more serious in terms of laboratory findings, conscious levels, and the numbers of affected end-organs than reported cases (5). High flow of cold dialysate increased the efficiency in heat exchange and contributed to the inhibition of a further rise in body temperature and progression of MOF, which had favorable effects in this severe clinical condition. In addition, previous reports suggested high-flow CHDF was efficient to treat hepatic encephalopathy (10) or tumor lysis syndrome complicated with severe hyperuricemia (11). In our case, severe hyperuricemia might deteriorate renal function. Liver failure and a high level of ammonium might also affect his condition. Because these small-molecular-weight substances are efficiently washed out mainly by hemodialysis, we believe cold CHDF was a better choice of therapy than the other modes of blood purification, including conventional CHDF, intermittent hemodialysis or hemofiltration for the purpose of cooling the body rapidly, the elimination of wide ranges of toxic substances, and maintaining the systemic circulation stability.

Several reports have documented the application of blood purification for the treatment of heat stroke complicated with acute renal failure. The modalities were plasma exchange (12), peritoneal dialysis (13), continuous hemofiltration (14,15), and continuous hemofiltration plus plasma exchange (5). In most of these case reports, these modes were chosen because of the patient's unstable systemic circulation. In only one report, the authors discussed the effectiveness of blood purification in heat stroke for the treatment of

multiple organ damages (5). The beneficial effects of using cold dialysate in our modality have not been tested or discussed in the past. Heat stroke and its progression to multiorgan damages are caused by a complex interplay among acute physiological alterations associated with hyperthermia, the direct cytotoxicity of heat, and inflammatory response of the host. Therefore, continuous hemofiltration with cold dialysate in this report is a novel and ideal mode because it facilitates to wash out internal heat and remove inflammatory cytokines continuously at the same time.

In summary, we describe a case of heat stroke with MOF in which cold HD followed by cold, high flow CHDF had favorable effects. Probably because of the delay in the initiation of these aggressive cooling procedures, mild renal and hepatic dysfunctions still remained 3 weeks after the onset. These therapeutic sequences, as well as rapid normalization of circulatory volume, should be considered in the early treatment stage of severe heat stroke because the immediate body temperature normalization and support of organ function are the two main therapeutic keys to reduce the mortality of heat stroke (16).

REFERENCES

1. Bouchama A, Knochel JP. Heat stroke. *N Engl J Med* 2002;346:1978–88.
2. Shibolet S, Lancaster MC, Danon Y. Heat stroke: a review. *Aviat Space Environ Med* 1976;47:280–301.
3. Yeo TP. Heat stroke: a comprehensive review. *AACN Clin Issues* 2004;15:280–93.
4. Hammami MM, Bouchama A, Al-Sedairy S, Shail EAI, AlOhaly Y, Mohamed GE. Concentrations of soluble tumor necrosis factor and interleukin-6 receptors in heatstroke and heatstress. *Crit Care Med* 1997;25:1314–19.
5. Ikeda Y, Sakemi T, Nishihara G et al. Efficacy of blood purification therapy for heat stroke presenting rapid progress of multiple organ dysfunction syndrome: a comparison of five cases. *Intensive Care Med* 1999;25:315–18.
6. Grogan H, Hopkins PM. Heat stroke: implications for critical care and anaesthesia. *Br J Anaesth* 2002;88:700–7.
7. Asanuma Y, Sato T, Kotanagi H, Yamamoto Y, Nakae H. Treatment of multiple organ failure through sepsis by surgery and blood purification. *Ther Apher Dial* 2004;8:185–9.
8. Bellomo R, Tipping P, Boyce N. Continuous veno-venous hemofiltration with dialysis removes cytokines from the circulation of septic patients. *Crit Care Med* 1993;21:522–6.
9. Hirasawa H, Sugai T, Ohtake Y, Oda S, Matsuda K, Kitamura N. Blood purification for prevention and treatment of multiple organ failure. *World J Surg* 1996;20:482–6.
10. Kubota T, Sekido H, Takeda K et al. Acute hepatic failure with deep hepatic coma treated successfully by high-flow continuous hemodiafiltration and living-donor liver transplantation: a case report. *Transplant Proc* 2003;35:394–6.
11. Agha-Razii M, Amyot SL, Pichette V, Cardinal J, Ouimet D, Leblanc M. Continuous veno-venous hemodiafiltration for the treatment of spontaneous tumor lysis syndrome complicated by acute renal failure and severe hyperuricemia. *Clin Nephrol* 2000;54:59–63.
12. Kuroda M, Katsuki K, Uehara H et al. Successful treatment of fulminating complications associated with extensive rhabdomyolysis by plasma exchange. *Artif Organs* 1981;5:372–8.
13. Hart LE, Egier BP, Shimizu AG, Tandan PJ, Sutton JR. Exertional heat stroke: the runner's nemesis. *Can Med Assoc J* 1980;122:1144–50.
14. Sinha AK, Ghacha R, Youmbissi JT, Khursany IA. Classic heat stroke in a case of simple hypohydrosis with 'bad prognostic indicators' but a remarkable recovery. *Ren Fail* 2001;23:727–30.
15. Wang AY, Li PK, Lui SF, Lai KN. Renal failure and heatstroke. *Ren Fail* 1995;17:171–9.
16. Dematte JE, O'Mara K, Buescher J et al. Near-fatal heat stroke during the 1995 heat wave in Chicago. *Ann Intern Med* 1998;129:173–81.

A Case of Severe Heat Stroke With Abnormal Cardiac Findings

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SUMMARY

We document serial changes in the electrocardiogram (ECG) and myocardial markers in a case of severe heat stroke treated with cooling procedures. A 23-year-old comatose male with heat stroke was presented in the emergency room. The condition of the patient was complicated by hepatic failure, rhabdomyolysis, acute renal failure, and cardiac abnormalities. ECG revealed diffuse ST-T elevation; serum levels of myocardial markers were remarkably high and diffuse hypokinesis was observed on the echocardiogram. Cooling procedures, including applying cold vapor to the patient's skin, a gastric lavage with cold water, and an intravenous cold fluid infusion were not successful. Since multiple organ damage (heart, liver, central nervous system, and kidney) was evident, we utilized continuous hemodialysis and hemofiltration, using cold dialysate for efficient cooling. The patient recovered from the multiple organ damage and was removed from the intensive care unit 14 days after the onset. The cardiac abnormalities had normalized within several days without any damage to the myocardium. Q waves were not detected in any lead in the ECG. When interpreting ST-T elevation in the ECG of a heat stroke patient, caution should be used so as to not misdiagnose it as an acute myocardial infarction. (Int Heart J 2005; 46: 543-550)

Key words: Heat stroke, Electrocardiography, Multiple organ failure, Myocardium

HEAT stroke is an acute thermoregulatory failure that often results from exposure to high temperatures.[1)] The diagnosis of heat stroke is usually based on central nervous system dysfunction and a rectal temperature of 41°C or higher, as well as occasional multi-organ damage and dysfunction.[2,3)] Heat stroke can be exercise induced (exertional) or non-exercise induced (classic), and occurs when heat gain exceeds heat loss from the skin by radiation, convection, or evaporation.[4)]

Several cardiac complications have been documented in heat stroke cases,[5,6)] and certain nonspecific ECG changes, including ST-T elevation, have been described. ST-T elevation is rare in heat stroke and is sometimes attributed to cor-

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onary artery lesions.[7] Echocardiographic findings and myocardial marker levels in heat stroke have also been reported.[8] However, to the best of our knowledge, there have not been any reports concerning serial changes in ECG and myocardial marker levels after successful cooling.

In this paper, we report our observations on one patient with heat stroke who showed severe cardiac dysfunction. The ECG finding was diffuse ST-T elevation, which resembles that of acute myocardial infarction (AMI), although the affected leads in the ECG were unrelated to the territory of the coronary artery. The echocardiogram showed diffuse abnormal wall motion and no regional hypokinesis, which ruled out a diagnosis of AMI. The serum levels of myocardial markers were remarkably elevated. We continuously measured the ECG and serum myocardial markers, which detected a complete reversal of these abnormalities within a week. Q waves were not detected in any lead in the ECG. This case is unique because severe cardiac damage by heat stroke with ST elevation was reversed completely with aggressive cooling therapy and the serial changes in the ECG and serum cardiac specific markers were documented.

Case Report

A 23-year-old male construction worker was transferred to our emergency department because of loss of consciousness on July 5, 2003. He had been in a closed workplace on the 6th floor of a building under construction. The ambient temperature was 28.1°C, the humidity was 53%, and the wind velocity was 3.6 m/sec at that time in the area. He started work at 9:00 am, and fainted abruptly at noon; he was first sent to a nearby clinic. Without any reason, he refused to receive intravenous fluid supplementation and quickly left the clinic. He was later found lying on the street, and was transferred to our hospital at 1:15 pm.

On arrival, the patient was in a coma and the GCS scale was E1V1M2. Although his arterial pulse was palpable, his blood pressure was not measurable. His respiration rate was 32/min and the pulse was 156 beats/minute, which was regular. Core temperature measured inside the urinary bladder was 42.1°C. Physical examination revealed a sluggish bilateral light reflex, a dry tongue, skin without any sweat, a normal heart beat without a murmur or gallop, a normal respiratory sound, and a mildly distended abdomen. The ECG revealed ST elevation in leads I, II, III, aVL, aVF, and $V_{3\text{-}6}$, and a tall T wave in $V_{1\text{-}2}$ (Figure 1A). The echocardiogram showed diffuse hypokinesis with a 40% ejection fraction. A cardiologist commented that severe hypokinesis was evident in the apex of the left ventricle. A chest X-ray was normal and his brain CT scan did not detect anything harmful. The color of his urine was dark brown and the urinalysis results were marked "myoglobulinuria and proteinuria with granular casts". Hematuria

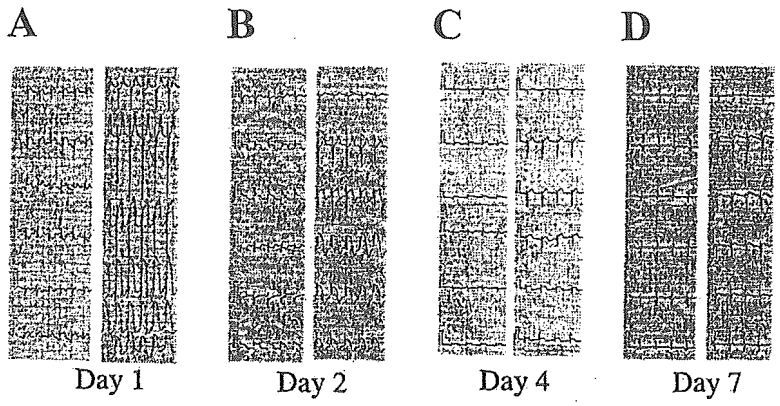

Figure 1. Serial changes in ECG findings in severe heat stroke.
ECG was measured when the patient was transferred to the emergency room (**A**). ST elevation in I, II, III, aVL, aVF, and V_{3-6}, and a tall T wave in V_{1-2} were observed, and still remained on day 2 (**B**). On day 4, these changes began to be normalized (**C**) and were completely normalized on day 7 (**D**).

was not detected. The hemoglobin value was 16.7 g/dL and the hematocrit was 49.5%. The white blood cell count was 21,800/mm^3 and the platelet count was 261,000/mm^3. The blood chemistry test results indicated that total protein was 10.1 g/dL; total bilirubin, 0.8 mg/dL; blood urea nitrogen, 20.3 mg/dL; creatinine, 3.7 mg/dL; and uric acid, 32.4 mg/dL. The sodium value was 149.6 mmol/L; potassium value, 6.2 mmol/L, calcium value, 5.5 mg/dL, and phosphorus value, 6.7 mg/dL. Lactate dehydrogenase was 704 IU/L; aspartate serine transferase, 125 IU/L; and aspartate lactate transferase, 127 IU/L. The level of creatine phosphokinase (CPK) was 1,337 IU/L. Blood gas analysis showed metabolic acidosis with an increased anion gap.

After a diagnosis of heat stroke with renal and hepatic dysfunction, 2 liters of ice-cooled saline were infused intravenously. Cold water was applied to the skin, which was also fanned. Gastric lavage was undertaken using 2 liters of iced saline, although the core temperature remained above 40°C. Because the systolic blood pressure was becoming lower than 60 mmHg, intravenous administration of dopamine was started to maintain the blood pressure. The patient was intubated and admitted to the intensive care unit.

The patient was then covered with cold blankets and extracorporeal circulation was started using cold dialysate at 36°C to reduce his internal temperature. Two hours after beginning the extracorporeal circulation, his body temperature decreased to 38.4°C, blood pressure rose to 120/60 mmHg, and the light reflexes of the bilateral pupils were restored to normal and prompt. His urine color

became darker and urination ceased. The second blood chemical test at 4:00 pm revealed the elevation of serum creatinine (4.7 mg/dL) and CPK (40,900 IU/L).

Because rhabdomyolysis was suspected, continuous hemodialysis and hemofiltration (CHDF) were started in the evening of the admission day (day 1). This was done in order to preserve intrinsic renal function and to remove myoglobin, uric acid, and other unknown substances that were considered to impair the level of consciousness or renal function. Since the second day, his body temperature had remained under 38.5°C, and the serum potassium level was within the normal limit by virtue of the cold blanket and CHDF. However, on day 2, the serum levels of CPK had peaked at 337,700 IU/L, and the patient entered a state of disseminated intravascular coagulation (DIC) with thrombocytopenia, a prolonged prothrombin time, and a decreased level of fibrinogen. Thrombocyte transfusion and intravenous administration of gabexate mesilate, a serine proteinase inhibitor, were started and continued for 3 days.

ECGs were performed and myocardial specific markers were continuously measured in order to follow cardiac dysfunction. The tall T wave disappeared on day 2; although the ST elevation observed on day 1 still remained (Figure 1B), it began to return to normal on day 4 (Figure 1C). On day 7, the ECG returned to a completely normal state (Figure 1D). The myocardial specific markers, MB-isoform of creatinine phosphokinase (CK-MB), and I-isoform of troponin (Trop-I) were serially measured (Figure 2). On day 1, the level of CK-MB was 43 ng/mL (normal; < 5 ng/mL), which had increased to 2,927 ng/mL on day 4. The level of Trop-I was 21.8 ng/mL (normal; < 0.5 ng/mL) on day 1, and had increased to 86.1 ng/mL on day 2. Both levels declined rapidly after reaching their peaks, which were paralleled with ECG changes. The echocardiogram findings on day 7 showed normal wall motion with an 80% ejection fraction without any segmental hypokinesis. Since the patient was still under controlled ventilation and the liver and kidney dysfunction persisted, neither a coronary angiogram nor venticulography or myocardial scintigraphy was performed.

The patient had been treated with CHDF, intravenous administration of antibiotics, and parenteral nutrition. On day 7, CHDF was terminated, and HDF was undertaken 3 times a week. On day 14, the ECG continued to be normal without a Q wave. The CK-MB and Trop-I levels were 42.3 ng/mL and 0.48 ng/mL, respectively. The total serum CPK level was decreased to 1,033 IU/L and his consciousness level returned to normal with a full score of GCS on day 21. Although the patient was still under regular HDF, his renal function was restored and his urine output was 1,200 mL/day on day 23. The patient was under rehabilitation on day 21. Since his renal and hepatic functions were improved, on day 25 his family requested that he be transferred to a hospital in his hometown, mainly for the purpose of rehabilitation. Although he had been well for a couple of days in

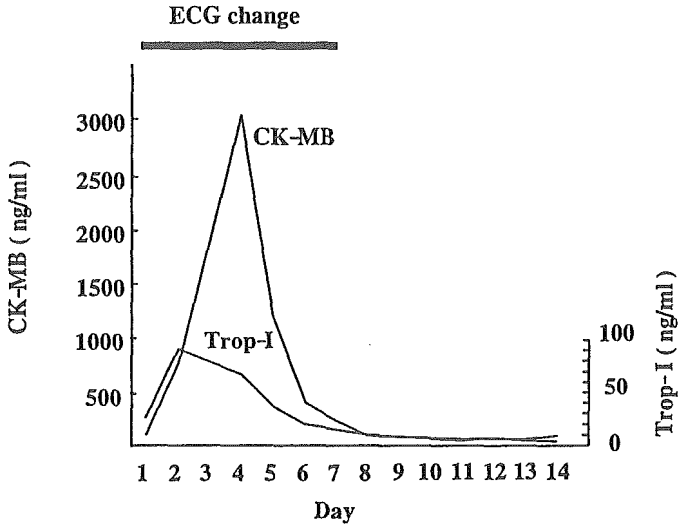

Figure 2. Changes in serum value of myocardial specific markers in severe heat stroke Serum levels of the MB-isoform of creatine phosphokinase (MB-CK) and I-isoform of troponin (Trop-I) were measured serially. The period when the ECG changes were observed is also indicated with a solid bar. MB-CK increased from 43 ng/mL up to a peak of 2927 ng/mL (normal; > 5 ng/mL) on day 4, while Trop-I increased from 21.8 ng/mL up to 86.1 ng/mL (normal; > 0.5 ng/mL) on day 2. Both levels declined rapidly after reaching their peaks, which paralleled the ECG changes.

that hospital, his condition worsened on August 4th due to an infection from the central venous catheter. He died on August 6th due to severe sepsis.

DISCUSSION

This severe heat stroke case was complicated by rhabdomyolysis, acute renal and hepatic failure, and DIC. We used cold blankets and extracorporeal circulation to rapidly reduce his temperature. With the help of CHDF, we successfully controlled his body temperature and mineral balance, and continuously eliminated toxic substances from his body, such as myoglobin, uric acid, and ammonium.

Among his several complications, the cardiac dysfunction was closely monitored and the serial changes in the ECGs were documented. ECG abnormalities and cardiac dysfunction in heat stroke have been reported before. Kew, *et al* documented 26 heat stroke patients with abnormal ECG in which they found prolonged Q-T intervals, ST-T changes, and T-wave abnormalities. They also reported 2 patients with ST elevation with changes localized to a territory of the

coronary artery. Other reports have described abnormal ECG findings, which included sinus tachycardia, a conduction defect, a prolonged Q-T interval, diffuse ST-T changes, and ST-T changes localized in a territory of the coronary artery. The prompt normalization of diffuse ST-T depression suggesting transient myocardial ischemia has been reported, and the increased oxygen demand due to high fever, tachycardia, and a significantly high cardiac output state, or hypotension, were considered to be causative factors in this abnormality.[6] Segmental ST-T elevation has also been reported in severe heat stroke cases. Garcia-Rubira, *et al* reported a 33-year-old victim of heat exhaustion who suffered from chest pain and whose ECG revealed new Q waves, suggesting myocardial infarction of the inferior wall.[7] Nevertheless, diffuse ST elevation in heat stroke unrelated to a territory of the coronary artery and that recovered without Q wave formation has not been reported.

The etiology of this diffuse ST-T elevation should be discussed. One factor that should be considered is diffuse coronary vasospasm induced by coronary endothelial damage. Bouchama, *et al* reported the elevation of the plasma concentration of circulating endothelin, intercellular adhesion molecule-1, and von Willebrand factor in 22 precooling heat stroke patients, which implied endothelial cell damage in these patients.[9,10] The pathophysiology of myocardial infarction due to coronary vasospasm is in part coronary endothelial dysfunction.[11] Although we did not measure these indicators during the treatment of our patient, the ensuing DIC was highly suggestive of diffuse endothelial damage, including in the coronary arteries which might cause coronary vasospasm.

The state of so-called Tako-Tsubo cardiomyopathy is another possible causative mechanism. This disease entity is characterized by transient left ventricular dysfunction with chest symptoms and ECG changes similar to those of AMI but is associated with normal findings on coronary angiography.[12] This disease is often misdiagnosed as AMI[13] and is usually accompanied by preceding psychological stress or pre-existing clinical conditions, such as a subarachnoidal hemorrhage,[14] pheochromocytoma,[15] and syndrome malin.[16] Recently, Ogura, *et al* compared ECG findings between Tako-Tsubo cardiomyopathy and AMI, and reported that the longer QTc interval and the absence of abnormal Q waves in the anterior leads and reciprocal changes in the inferior leads could help to distinguish Tako-Tsubo cardiomyopathy from AMI.[17] Although a definite diagnosis by coronary angiography was lacking in this case, considering similar ECG findings, easy reversibility of cardiac function, and the pre-existing stressful condition of exposure to high ambient temperature, the cardiac abnormality probably resembled the state of Tako-Tsubo cardiomyopathy. The prominent impaired wall motion in the apex region observed when he was transferred to the emergency room may reflect the typical abnormalities seen in Tako-Tsubo cardiomyopathy.

The etiology of Tako-Tsubo cardiomyopathy has not yet been elucidated, but stunned myocardium from multiple coronary spasms and direct myocardial toxicity by catecholamines have been suggested. Although we did not measure the circulating levels of catecholamines, the sympatho-adrenal system is reported to be activated in patients with heat stroke.[18] Therefore, it is possible that activation of the sympathetic nerve system may have caused the cardiac abnormalities in this case.

We documented the serial changes in several myocardial specific marker levels, which indicated severe damage to the myocardium by heat attack. In parallel to the ECG change and the echocardiographic findings, their levels declined after successful cooling. The follow-up of serum myocardial markers in heat stroke has been reported. Kew, *et al* analyzed the isozyme of LDH and found that 69% of heat stroke patients showed elevated LDH levels whose isozyme patterns were indicative of a myocardial origin.[5] On the other hand, Costrini, *et al* did not find elevated levels of the MB fraction of CK in any of their 13 heat stroke patients.[19] The difference may be attributable to the severity of exposure of the myocardium to a high temperature and/or the severity of myocardial ischemia. Our data showed extraordinarily high levels of these markers; a 580-fold increase for CK-MB and a 170-fold increase for troponin I above the upper normal. Although the decreased renal excretory function modified these values, these data indicated the presence of severe myocardial damage in our case.

In summary, we have described a case of severe heat stroke in which the ECG revealed diffuse ST-T elevation and the echocardiogram proved diffuse hypokinesis. Serum myocardial markers were significantly elevated. These were normalized within several days without any damage to the myocardium. No Q waves were detected after ECG normalization. Proper treatment with cooling, fluid supplementation, and CHDF may help to prevent the prolonged cardiac damage. Diffuse vasospasm and/or catecholamine toxicity in the myocardium could be considered as underlying factors for cardiac complications in heat stroke. When interpreting ST-T elevation in the ECG of a heat stroke patient, it is important to be aware that this change is not always related to a coronary lesion. Caution must be exercised so as to not misdiagnose it as AMI, because, like in this case, cooling may be sufficient treatment.

REFERENCES

1. Bouchama A, Knochel JP. Heat stroke. N Engl J Med 2002; 346: 1978-88. (Review)
2. Clowes GH Jr, O'Donnell TF Jr. Heat stroke. N Engl J Med 1974; 291: 564-7. (Review)
3. Knochel JP. Environmental heat illness. An eclectic review. Arch Intern Med 1974; 133: 841-64.
4. Shibolet S, Lancaster MC, Danon Y. Heat stroke: a review. Aviat Space Environ Med 1976; 47: 280-301. (Review)

5. Kew MC, Tucker RB, Bersohn I, Seftel HC. The heart in heatstroke. Am Heart J 1969; 77: 324-35.
6. Akhtar MJ, al-Nozha M, al-Harthi S, Nouh MS. Electrocardiographic abnormalities in patients with heat stroke. Chest 1993; 104: 411-4.
7. Garcia-Rubira JC, Aguilar J, Romero D. Acute myocardial infarction in a young man after heat exhaustion. Int J Cardiol 1995; 47: 297-300.
8. al-Harthi SS, Nouh MS, al-Arfaj H, Oaraquish A, Akhter J, Nouh RM. Non-invasive evaluation of cardiac abnormalities in heat stroke pilgrims. Int J Cardiol 1992; 37: 151-4.
9. Bouchama A, Hammami MM, Haq A, Jackson J, al-Sedairy S. Evidence for endothelial cell activation/injury in heatstroke. Crit Care Med 1996; 24: 1173-8.
10. Giustolisi R, Musso R, Cacciola E, Cacciola RR, Russo M, Petralito A. Abnormal plasma levels of factor VIII/ von Willebrand factor complex in myocardial infarction--expression of acute phase reaction or index of vascular endothelium damage? Thromb Haemost 1984; 51: 408.
11. Kugiyama K, Ohgushi M, Motoyama T, *et al.* Nitric oxide-mediated flow-dependent dilation is impaired in coronary arteries in patients with coronary spastic angina. J Am Coll Cardiol 1997; 30: 920-6.
12. Dote K, Sato H, Tateishi H, Uchida T, Ishihara M. Myocardial stunning due to simultaneous multivessel coronary spasms: a review of 5 cases. J Cardiol 1991; 21: 203-14. (Japanese)
13. Kurisu S, Sato H, Kawagoe T, *et al.* Tako-tsubo-like left ventricular dysfunction with ST-segment elevation: a novel cardiac syndrome mimicking acute myocardial infarction. Am Heart J 2002; 143: 448-55.
14. Pollick C, Cujec B, Parker S, Tator C. Left ventricular wall motion abnormalities in subarachnoid hemorrhage: an echocardiographic study. J Am Coll Cardiol 1988; 12: 600-5.
15. Yamanaka O, Yasumasa F, Nakamura T, *et al.* "Myocardial stunning"-like phenomenon during a crisis of pheochromocytoma. Jpn Circ J 1994; 58: 737-42.
16. Kawabata M, Kubo I, Suzuki K, Terai T, Iwama T, Isobe M. "Tako-Tsubo cardiomyopathy" associated with syndrome malin: reversible left ventricular dysfunction. Circ J 2003; 67: 721-4.
17. Ogura R, Hiasa Y, Takahashi T, *et al.* Specific findings of the standard 12-lead ECG in patients with 'Takotsubo' cardiomyopathy: comparison with the findings of acute anterior myocardial infarction. Circ J 2003; 67: 687-90.
18. al-Hadramy MS, Ali F. Catecholamines in heat stroke. Mil Med 1989; 154: 263-4.
19. Costrini AM, Pitt HA, Gustafson AB, Uddin DE. Cardiovascular and metabolic manifestation of heat stroke and severe heat exhaustion. Am J Med 1979; 66: 296-302.

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ORIGINAL ARTICLE

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Multicenter prospective study of procalcitonin as an indicator of sepsis

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Abstract The clinical significance of serum procalcitonin (PCT) for discriminating between bacterial infectious disease and nonbacterial infectious disease (such as systemic inflammatory response syndrome (SIRS)), was compared with the significance of endotoxin, β-D-glucan, interleukin (IL)-6, and C-reactive protein (CRP) in a multicenter prospective study. The concentrations of PCT in patients with systemic bacterial infection and those with localized bacterial infection were significantly higher than the concentrations in patients with nonbacterial infection or noninfectious diseases. In addition, PCT, endotoxin, IL-6, and CRP concentrations were significantly higher in patients with bacterial infectious disease than in those with nonbacterial infectious disease ($P < 0.001$, $P < 0.005$, $P < 0.001$, and $P < 0.001$, respectively). The cutoff value of PCT for the discrimination of bacterial and nonbacterial infectious diseases was determined to be 0.5 ng/ml, which was associated with a sensitivity of 64.4% and specificity of 86.0%. Areas under the receiver operating characteristic curves (POCs) were 0.84 for PCT, 0.60 for endotoxin, 0.77 for IL-6, and 0.78 for CRP in the combined group of patients with bacterial infectious disease and those with nonbacterial infectious disease, and the area under the ROC for PCT was significantly higher than that for endotoxin ($P < 0.001$). In patients diagnosed with bacteremia based on clinical findings, the positive rate of diagnosis with PCT was 70.2%, while that of blood culture was 42.6%. PCT is thus essential for discriminating bacterial infection from SIRS, and is superior in this respect to conventional serum markers and blood culture.

Key words Procalcitonin · Bacterial infection · Sepsis · SIRS

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Introduction

Although the monitoring of parameters of infectious diseases, such as body temperature, heart rate, respiratory rate, leukocyte count, and C-reactive protein (CRP) concentration has been routinely performed, these parameters often provide information that is inadequate for the discrimination of bacterial and nonbacterial infections and for diagnosis. Blood culture is a very specific and confirmatory method for the detection of septicemia, but test results are not available within 24 h; physicians must, in the meantime, decide whether the patient needs antibiotic treatment. In addition, the sensitivity of blood culture is low.[1] For patients with a slight possibility of bacterial infection, physicians tend to prescribe antibiotics so as not to miss severe infections such as septicemia. A rapid and reliable test to rule out bacterial infections would thus be very useful for knowing the suitable indications for antibiotics, and this could also have an impact on both the length of hospital stay and total medical costs.[2,3]

Procalcitonin (PCT) is a 13-kDa 116-amino acid prohormone of calcitonin. Under physiological conditions, hormonally active calcitonin is produced and secreted in the C cells of the thyroid gland after the specific intracellular proteolytic processing of the prohormone PCT. Calcitonin is secreted into the circulation, and its plasma half-life is only a few minutes. In 1993, Assicot et al.[4] reported increased PCT concentrations in patients with sepsis and infection. Further clinical studies indicated that bacterial inflammation and sepsis, but not viral infections or autoimmune disorders, could induce high concentrations of serum PCT.[5–8] The origin of PCT in these conditions is thought to be extrathyroidal.[4] In severe bacterial infections or sepsis, specific proteolysis fails, and high concentrations of the precursor protein of PCT accumulate in plasma.[9] Nylen et al.[10] suggested a biological role of PCT as a mediator of inflammation. PCT has a half-life of approximately 24–30 h in the circulation.[9] However, all of the reports described above originate from Europe, and there could be ethnic differences between European populations and the Japanese population. Therefore, a multicenter, prospective study was carried out in Japan to assess the diagnostic efficiency of PCT in distinguishing bacterial infection from other infectious diseases, systemic inflammatory response syndrome (SIRS), and related conditions.

Subjects, materials, and methods

Subjects

Serum specimens were collected prospectively by seven Japanese hospitals from October 2000 through December 2001. All patients gave their informed consent according to the regulations of each hospital. Two hundred and forty-five patients diagnosed with infectious diseases, suspected of having infectious diseases, and diagnosed with noninfectious diseases were enrolled in the study, with the addition of 20 healthy volunteers. Inclusion criteria were more than one of the following results: (1) body temperature less than 36°C or more than 37.5°C; (2) white blood cell count less than 4000 or more than 9000/mm^3; and (3) elevated CRP greater than 0.3 mg/dl. The patients were divided into five groups by the results of blood culture.

Systemic bacterial infection group

In this group, at least one blood culture was positive for pathogenic bacteria. A causative bacterium was identified by the physicians in charge. Coagulase-negative *Staphylococcus* spp. and *Bacillus* spp. may or may not have been considered as pathogenic bacteria, depending on the judgment of physicians in charge.

Localized bacterial infection group

In this group, there was clinical evidence of local infection, defined as positive culture(s) of nonblood specimens, such as spinal fluid, ascites, pleural fluid, sputum, bronchoalveolar lavage, urine, and pus, and/or the presence of a clinical focus of infection, such as fecal peritonitis, a wound with purulent discharge, or pneumonia. Also included in this group were patients with positive serological antibody tests for *Mycoplasma*, *Chlamydia*, and *Streptolysin*.

Nonbacterial infection group

In this group, viral or fungal infection was diagnosed by cultures or serum antibody titers.

Suspected bacterial infection group

In this group, the physician in charge suspected a bacterial infection but could not confirm it by laboratory testing. This group was not included in the statistical analysis.

Noninfectious disease group

In this group, blood culture or other specimens were negative. In addition, there was no clear clinical evidence of bacterial infection and the physician in charge did not suspect it.

The healthy volunteers were not included in the statistical analysis.

The average, median, and range of age in the 176 patients in the four groups shown in Table 1 (102 men and 74 women) were 37.3, 47.5, and 0.1–92 years, respectively. The numbers of patients with systemic bacterial infection, localized bacterial infection, nonbacterial infection, suspected bacterial infection, and noninfectious disease, and the healthy volunteers were 20, 70, 26, 69, 60, and 20, respectively. Data analysis was performed for the groups with systemic bacterial infection, localized bacterial infection, nonbacterial infection, and noninfectious disease. Table 1 summarizes the underlying diseases for these four groups.

PCT assay

Serum PCT concentrations were measured by immunoluminometric assay (LUMI test PCT; Brahms Diagnostica, Berlin, Germany).[11] The luminometer used was an Autolumat LB953 (Berthord, Bad Wildbad, Germany).

Serological assays

Endotoxin and (1–3)-β-D-glucan (β-D-glucan) were measured by kinetic turbidimetric *Limulus* tests; the Wako Endotoxin-single test, and Wako β-Glucan test (Wako Pure Chemical Industries, Osaka, Japan).[12–14] The serum interleukin (IL)-6 concentration was determined by enzyme-linked immunosorbert assay (ELISA; human IL-6 ANALYZA Immunoassay Kit; TECHNE, Minneapolis, MN, USA). Other conventional markers were tested and blood cultures were performed at each hospital using commercially available kits and instruments.

Table 1. Patients' underlying diseases

Underlying disease		PCT value (ng/ml)			
		Systemic and localized bacterial infection groups combined		Nonbacterial infection and Non-infectious group combined	
	n	*n*	Range	*n*	Range
Circulatory disease	38	10	0–10.08	28	0–1.70
Respiratory disease	10	5	0–21.04	5	0–0.42
Gastroenterological disease	14	11	0.60–373.46	3	0–0.91
Hepatobiliary disease	7	4	0–205.79	3	0–0.41
Renal disease	3	2	2.02–212.18	1	0.33
Neurological disease	3	3	0–7.98	0	–
Diabetes mellitus	7	6	0.34–82.29	1	0
Malignant disease	6	3	0.42–1.73	3	0
Trauma	15	10	0–82.48	5	0–0.38
Burns	7	7	0–34.53	0	–
Kawasaki disease	12	1	4.89	11	0–1.91
Others	17	7	0–20.59	10	0–8.72
None	37	21	0–93.29	16	0–3.67
Total	176	90		86	

Statistical analysis

The statistical significances of differences were determined using the Mann-Whitney *U*-test and receiver operating characteristic (ROC) analysis, carried out with StatFlex Ver. 5.0 (AHTEKKU, Osaka, Japan). *P* values of less than 0.05 were considered significant.

Results

Serum PCT, endotoxin, β-D-glucan, IL-6, and CRP concentrations in patient groups

The patterns of distribution of PCT, endotoxin, IL-6, and CRP concentrations in the systemic bacterial infection group, localized bacterial infection group, nonbacterial infection group, and noninfectious disease group are shown in Fig. 1. The median ages of the patients with nonbacterial and suspected bacterial infections were lower than those of the other groups (Table 2). Previous studies have reported that there were no differences in PCT values by age,[15,16] with the exception of neonates.[17] Table 3 summarizes serum concentrations of PCT, endotoxin, IL-6, and CRP in patients in the five groups and in the healthy volunteers. Table 4 shows statistical analysis using the criteria for the diseases. Serum PCT concentrations were significantly higher in both the systemic bacterial infection and localized bacterial infection groups than in both the nonbacterial infection and noninfectious disease groups ($P < 0.05$). Serum PCT concentrations did not differ significantly between the systemic bacterial infection and localized bacterial infection groups ($P = 0.770$). The systemic bacterial infection and localized bacterial infection groups were therefore combined as the bacterial infectious disease group. In the same fashion, no significant difference in serum PCT concentration was observed between the nonbacterial infection group and the noninfectious disease groups ($P = 0.174$), and the nonbacterial infection and noninfectious disease groups were therefore combined as the nonbacterial infectious disease group. The patterns of distribution of PCT, endotoxin, IL-6, and CRP concentrations for these two groups are shown in Fig. 2. Serum PCT, endotoxin, IL-6, and CRP concentrations were significantly higher in the bacterial infectious disease group than in the nonbacterial infectious disease group ($P < 0.001$, $P < 0.005$, $P < 0.001$, and $P < 0.001$).

Cutoff value and diagnostic accuracy of serum PCT concentration

Table 5 shows the sensitivity, specificity, positive predictive values, and negative predictive values for the serum markers. When 0.5 ng/ml was used as the cutoff value for PCT, the sensitivity, specificity, positive predictive value, and negative predictive value were 64.4%, 86.0%, 82.9%, and 69.8%, respectively. Figure 3 presents the receiver operating characteristic curves of four serum markers used to discriminate the bacterial infectious disease group from the nonbacterial infectious disease group. The area under the receiver operating characteristic curve (AUC) for PCT was 0.84, which was significantly higher than that for endotoxin (0.60; $P < 0.001$), and tended to be higher than those for IL-6 (0.77; $P = 0.22$) and CRP (0.78; $P = 0.32$).

Sensitivities of serum markers for the type of infection

Table 6 shows the sensitivities of PCT, endotoxin, β-D-glucan, IL-6, and CRP with regard to the type of infection determined by culture. The difference in PCT serum con-

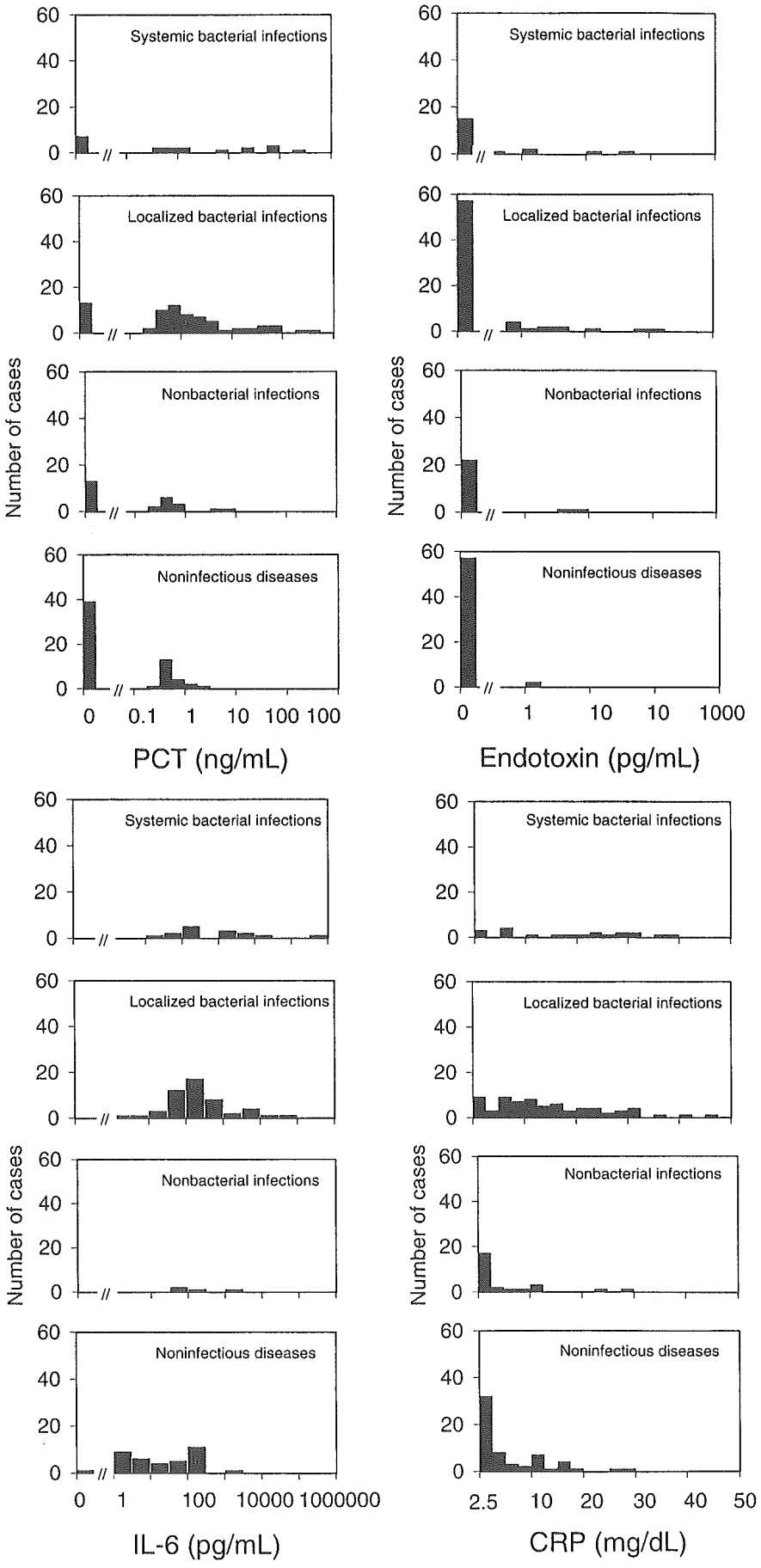

Fig. 1. Distribution patterns of procalcitonin (*PCT*), endotoxin, interleukin-6 (*IL-6*) and C-reactive protein (*CRP*) in patients with systemic bacterial infections, localized bacterial infections, nonbacterial infections, and noninfectious diseases

Table 2. Patient demographics

	n	Sex	Age (years)
		Male/Female	Median (range)
Systemic bacterial infection	20	7/13	58 (1–81)
Localized bacterial infection	70	44/26	53 (0.1–92)
Nonbacterial infection	26	13/13	4 (0.1–72)
Suspected bacterial infection	69	45/24	5 (0.1–85)
Noninfectious disease	60	38/22	48 (0.1–87)
Healthy volunteers	20	16/4	22 (22–27)

Table 3. Serum concentrations of PCT, endotoxin, IL-6 and CRP in patients with systemic bacterial infection, localized bacterial infection, nonbacterial infection, suspected bacterial infection, and noninfectious diseases, and healthy volunteers

	n	PCT (ng/ml)	Endotoxin (pg/ml)	IL-6 (pg/ml)	CRP (mg/dl)
		Median (range)	Median (range)	Median (range)	Median (range)
Systemic bacterial infection	20	0.66 (0.00–212.18)	0.0 (0.0–39.4)	199.5 (22.3–592 000.0)	20.0 (0.1–38.2)
Localized bacterial infection	70	0.94 (0.00–373.46)	0.0 (0.0–135.4)	141.2 (1.6–38 922.0)	11.9 (0.2–46.7)
Nonbacterial infection	26	0.16 (0.00–8.72)	0.0 (0.0–7.0)	152.6 (54.3–2 550.0)	1.9 (0.3–28.4)
Suspected bacterial infection	69	0.38 (0.00–85.93)	0.0 (0.0–29.1)	17.1 (10.3–1 086.0)	2.5 (0.1–26.8)
Noninfectious disease	60	0.00 (0.00–1.91)	0.0 (0.0–1.3)	17.1 (0.0–1 350.0)	2.1 (0.0–28.1)
Healthy volunteers	20	0.00 (0.00–0.00)	0.0 (0.0–0.6)	1.8 (1.5–4.5)	0.1 (0.0–0.1)

Table 4. Statistical analysis according to the disease criteria

	p value			
	PCT	Endotoxin	IL-6	CRP
Systemic bacterial infection vs localized bacterial infection	0.770	0.469	0.131	0.244
Systemic bacterial infection vs nonbacterial infection	0.026	0.149	0.317	<0.001
Systemic bacterial infection vs noninfectious disease	<0.001	0.004	<0.001	<0.001
Localized bacterial infection vs nonbacterial infection	<0.001	0.323	0.766	<0.001
Localized bacterial infection vs noninfectious disease	<0.001	0.011	<0.001	<0.001
Nonbacterial infection vs noninfectious disease	0.174	0.317	0.104	0.756

centrations between Gram-negative and Gram-positive bacterial infections was not significant (13.79 ± 28.18 ng/ml for Gram-negative and 9.91 ± 35.20 ng/ml for Gram-positive bacterial infections; $P = 0.673$). The sensitivity of PCT for mixed Gram-negative and Gram-positive bacterial infections was 64.3% (9/14 cases). The sensitivities of PCT and endotoxin for Gram-negative bacterial infections in systemic infections were 100% (3/3) and 67% (2/3), respectively. On the other hand, the sensitivities of PCT and endotoxin for localized Gram-negative bacterial infections were 50% (6/12) and 0% (0/12), respectively. In a patient with confirmed fungal infection, the PCT result was negative, below the cutoff value. Four of 24 samples from patients with viral infections (16.7%) exhibited PCT concentrations exceeding the cutoff value. One patient with malaria showed a high PCT concentration, of 8.7 ng/ml.

Sensitivity of serum PCT compared with blood culture

The sensitivities of serum PCT and blood culture were compared in the combined systemic bacterial infection group and the localized bacterial infection group. The sensitivity of PCT was 70.2% (33/47 cases) in this combined group, but it was 42.6% (20/47 cases) for blood culture.

Discussion

Sepsis can be difficult to distinguish from other, noninfectious, conditions in critically ill patients admitted with clinical signs and symptoms of various acute inflammatory diseases. This issue is of paramount importance, given that therapies and outcomes differ greatly between patients with and those without bacterial sepsis. Blood culture is the most reliable method of detecting bacterial infections. However, more than 3 days is required to obtain results, and the positive detection rate is low. Although CRP and IL-6 have been suggested to be good indicators of sepsis, elevated CRP and IL-6 concentrations can also be found following surgical procedures and in patients with nonbacterial or noninfectious inflammation alone. Thus, there is an unmet need for clinical tools that distinguish bacterial infections from other inflammatory diseases.

The diagnostic and prognostic importance of PCT in severe inflammatory diseases was first reported for a series of patients with burns, in 1992.[18] Serum PCT values were less than 0.1 ng/ml in healthy individuals, but were markedly increased, mostly as a result of induced extrathyroidal production, in patients with severe infection. However, the roles of PCT and the origin of its production, as well as the

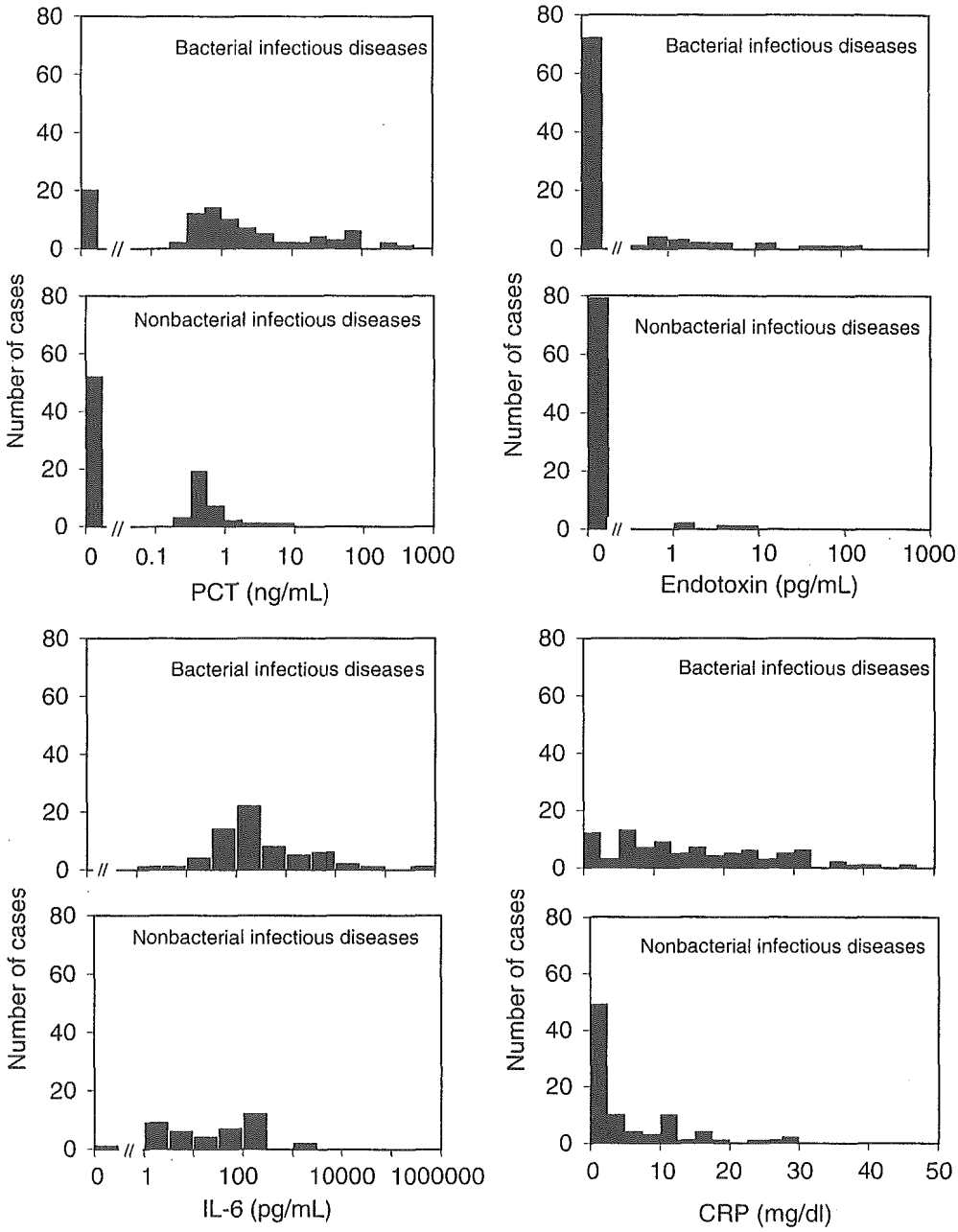

Fig. 2. Distribution patterns of PCT, endotoxin, IL-6, and CRP in patients with bacterial infectious diseases and those with nonbacterial infectious diseases

Table 5. Sensitivity, specificity, positive predictive value and negative predictive value of PCT, endotoxin, IL-6, and CRP in patients with bacterial infectious diseases and those with nonbacterial infectious diseases

	Cutoff value	Sensitivity	Specificity	Positive predictive value	Negative predictive value
PCT	0.5 ng/ml	64.4% (58/90)	86.0% (74/86)	82.9% (58/70)	69.8% (74/106)
PCT	2.0 ng/ml	34.4% (31/90)	97.7% (84/86)	93.9% (31/33)	58.7% (84/143)
Endotoxin	1.0 pg/ml	14.6% (13/89)	95.2% (79/83)	76.5% (13/17)	51.0% (79/155)
IL-6	10 pg/ml	96.9% (63/65)	39.0% (16/41)	71.6% (63/88)	88.9% (16/18)
IL-6	100 pg/ml	70.8% (46/65)	65.9% (27/41)	76.7% (46/60)	58.7% (27/46)
CRP	0.3 mg/dl	97.8% (88/90)	9.3% (8/86)	53.0% (88/166)	80.0% (8/10)
CRP	5.0 mg/dl	83.3% (75/90)	68.6% (59/86)	73.5% (75/102)	79.7% (59/74)

mechanism underlying PCT induction, are still not well known. Recent findings suggest that sources of PCT may include hepatic cells and monocytes/macrophages.[19,20] PCT is consistently increased after endotoxin injection, suggesting an association of endotoxin with septic shock and high PCT serum concentration.[21] Tumor necrosis factor (TNF) and IL-6 concentrations peaked before the appearance of PCT, suggesting that proinflammatory cytokines may play a

Table 6. Sensitivity of PCT, endotoxin, β-D-glucan, IL-6, and CRP with respect to the type of infection

Type of infection	PCT	Endotoxin	β-D-glucan	IL-6	CRP
	0.5 ng/ml	1.0 pg/ml	11 pg/ml	100 pg/ml	5 mg/dl
Gram-negative infection	65.2% (15/23)	21.7% (5/23)	17.4% (4/23)	58.8% (10/17)	87.0% (20/23)
Gram-positive infection	61.0% (25/41)	7.5% (3/40)	16.2% (6/37)	69.0% (20/29)	85.4% (35/41)
Mixed Gram-negative and -positive infection	64.3% (9/14)	21.4% (3/14)	16.7% (2/12)	72.7% (8/11)	71.4% (10/14)
Mixed bacterial and fungal infections	87.5% (7/8)	25.0% (2/8)	57.1% (4/7)	83.3% (5/6)	100.0% (8/8)
Fungal infection	0.0% (0/1)	0.0% (0/1)	100.0% (1/1)	0.0% (0/1)	100.0% (1/1)
Mycoplasmal infection	0.0% (0/1)	0.0% (0/1)	0.0% (0/1)	–	0.0% (0/1)
Viral infection	16.7% (4/24)	4.5% (1/22)	0.0% (0/19)	50.0% (1/2)	20.8% (5/24)
Malarial infection	100.0% (1/1)	100.0% (1/1)	0.0% (0/1)	100.0% (1/1)	100.0% (1/1)

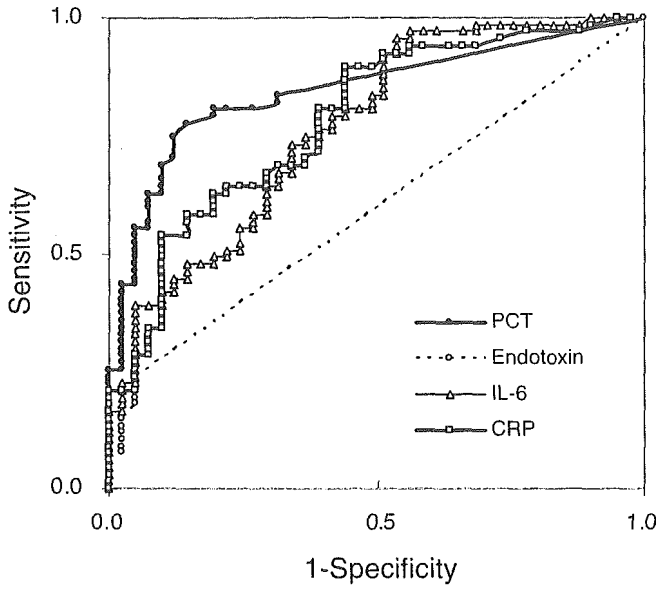

Fig. 3. Receiver operating characteristic curves (ROCs) of serum parameters (PCT, endotoxin, IL-6, and CRP) in patients with bacterial infectious diseases and those with non-bacterial infectious diseases

role in inducing PCT release.[22] Many studies have established that the determination of serum PCT concentrations can be used to differentiate bacterial from viral infections and to identify bacterial infections in patients admitted to intensive care units because of systemic inflammatory response syndrome (SIRS). Some studies have compared the diagnostic value of PCT with those of other parameters of inflammation, such as CRP and cytokine concentrations.[23,24] Thus, we conducted a prospective, multicenter study in patients diagnosed with or suspected of having infections. We obtained a cutoff value of 0.5 ng/ml for the PCT concentration, with acceptable sensitivity and high specificity. When assessed in 90 patients diagnosed with localized bacterial infectious disease and 86 patients diagnosed with nonbacterial infectious disease, the sensitivity, specificity, positive predictive value, and negative predictive value of PCT were 64.4%, 86.0%, 82.9%, and 69.8%, respectively. Al-Nawas et al.[25] showed that PCT determination in adult patients with sepsis had a lower specificity

Table 7. Sensitivity of PCT and blood culture in patients with systemic bacterial infections and localized bacterial infections

	n	PCT	Blood culture
Systemic bacterial infections	20	11 (55.0%)	20 (100%)
Localized bacterial infections	70	47 (67.1%)	0 (0.0%)
Blood culture negative	27	22 (81.5%)	0 (0.0%)
Blood culture not performed	43	25 (58.1%)	No test

(79%) and higher negative predictive value (78%), but lower sensitivity (60%) and positive predictive value (61%) than in our study, as above. The study by Liaudat et al.[26] intended to evaluate PCT concentration as an early predictive marker of bacteremia. In their hospital, where the prevalence of bacteremia was 8%, they found that PCT evaluation had a negative predictive value of 96%. Gendrel et al.[5] pointed out that low PCT serum concentrations in bacteremic patients may be due to previous administration of antibiotics. In the present study, 17 of 32 patients with bacterial infectious disease with a PCT concentration of less than 0.5 ng/ml had received antibiotics within 2 days of the testing. With the diagnostic criteria of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference,[27] we classified 18 of these 32 patients as having non-SIRS ($n = 6$) or sepsis ($n = 12$), but none of them were classified as having severe sepsis. The AUC for PCT differed significantly from that for endotoxin, and tended to be higher than those for IL-6 and CRP. PCT is specific for bacterial infectious disease, but CRP and IL-6 may have elevated values in patients with SIRS.

The sensitivity of PCT was compared with respect to the classification of bacteria. No significant difference was observed for PCT serum concentrations between Gram-negative and Gram-positive bacterial infections, similar to already published data.[26]

The study by Assicot et al.[4] indicated that patients with viral infection had normal or only slightly increased concentrations of PCT. In the present study, 4 of 24 patients with viral infection had PCT concentrations higher than 0.5 ng/ml, and the mean PCT concentration in the viral infection group was 0.36 ± 0.76 ng/ml, while the highest concentration was 3.67 ng/ml.

PCT yielded negative results in one patient with fungal infection. The sensitivity of PCT for mixed bacterial and