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Critical illness polyneuropathy: a new iatrogenically induced syndrome after cardiac surgery?[1]

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Abstract

Objective: Critical illness polyneuropathy (CIP) is a newly described severe complication after open heart surgery leading to tetraplegia for weeks to months. The purpose of the study was to gather further information on critical illness polyneuropathy developing in patients after cardiac surgery and to evaluate the hypothetical risk factors possibly related to the onset of this neurological disorder. **Methods:** From July 1994 to October 1995, 7 out of 1511 patients undergoing open heart surgery developed critical illness polyneuropathy, which was diagnosed on the basis of electromyographic and nerve conduction features. The only common clinical finding was an intensive care unit (ICU) stay beyond seven days, therefore a similar group of 37 patients staying longer than seven days in the intensive care unit during the same period of time was evaluated and retrospectively compared to the 7 patients developing critical illness polyneuropathy. Univariate analysis of several traits was performed to evaluate possible risk factors. **Results:** 4 Out of 7 patients in the CIP group died, all due to multiple organ failure, in contrast to 3/37 patients in the control group, again due to multiple organ failure. Patients developing CIP were staying significantly longer in the ICU (62 ± 3 versus 14 ± 8 days, $P < 0.01$) and had a significantly longer time on ventilator support (50 ± 28 versus 7 ± 13 days, $P < 0.01$) The incidence of sepsis was significantly higher in the CIP group than in the control group (85.7 versus 10.8%, $P < 0.01$). Compared to the control group the proportion of patients receiving corticosteroids (100 versus 10.8%, $P < 0.01$) and increased dosages of epinephrine and norepinephrine was higher in the CIP group (85.7 versus 35.1%, $P < 0.05$). Furthermore, the proportion of patients requiring chronic venovenous hemodiafiltration was significantly elevated in the CIP group (85.7 versus 5.4%, $P < 0.01$). **Conclusions:** CIP, despite it's benign nature due to it's spontaneous remission in patients who survive, is a disturbing complication following cardiac surgery which is associated with high mortality, a prolonged stay in the ICU, as well as an extended time on ventilator support. Interventions like chronic hemodiafiltration, the application of corticosteroids and the administration of high doses of catecholamines are more frequent in patients with CIP. Whether this indicates a causal relationship remains to be elucidated. © 1997 Elsevier Science B.V.

Keywords: Critical illness polyneuropathy; Intensive care unit; Sepsis; Multiple organ failure; Cardiac surgery

1. Introduction

Talking to senior cardiac surgeons, they do not recall any patients, besides the very small number with cerebrovascular ischemia, showing the clinical features of flaccid quadriplegia, hyporeflexia and muscular atrophy which lead to difficulty in weaning the patient off the ventilator and to a prolonged stay from weeks to

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months in the intensive care unit (ICU). As we know from other surgical specialities this neurological complication occurs in 50–70% of patients suffering from sepsis throughout the postoperative course during their stay in the ICU. It has been proposed that this syndrome may be part of the final common pathway of sepsis, multiple organ dysfunction syndrome and multiple organ failure [4].

In order to define and to characterize this syndrome more precisely, a number of electromyographic and neurographic studies were performed which revealed axonal damage which predominantly affected motor neurones resulting in denervation, decreased compound action potential with normal nerve conduction velocities and normal distal latencies [3,6,12].

The cause of this polyneuropathy remains unclear, and few advances have been made in understanding it. Considering the clinical, electromyographical and pathological facts, this neurological disorder is defined as critical illness polyneuropathy (CIP) with predominantly motor-axonal dysfunction, with acute onset after development of respiratory insufficiency in a setting of systemic inflammatory response and multiple organ dysfunction [4,12,14]. CIP has not been considered a problem in cardiac surgery ICUs until recently when it has been observed in patients who have undergone cardiac surgical procedures [1,19].

Recently we observed some patients showing neurological symptoms consistent with the clinical features of CIP. The difficulty in weaning them off the ventilator prolonged their stay in the ICU. Assuming that this neurological syndrome may complicate cardiac operations, a screening electromyographic study was performed to determine the incidence of CIP in our ICU. A retrospective study was initiated in order to evaluate possible risk factors contributing to the onset of CIP in patients after cardiac surgery.

2. Patients and methods

From July 1994 to October 1995 1511 adult patients were admitted to our ICU after open heart surgery.

Cardiopulmonary bypass was established with moderate to mild systemic hypothermia (26–30°C) with flow rates of 2.0–2.4 l/min per m^2 and a mean arterial pressure of 40–50 mmHg. A left ventricular vent was placed through the right pulmonary vein. Crystalloid cold cardioplegic solution was used and the heart was cooled with 4°C cold saline solution externally repeated, if necessary, to ensure the absence of ventricular electrocardiographic or mechanical activity throughout the operation. Cardiopulmonary bypass was not discontinued until the rectal temperature had reached 35°C.

2.1. Electromyographic and nerve conduction studies

After institutional approval and informed consent had been obtained from each patient's next of kin, patients who required prolonged mechanical ventilation beyond 3–5 days were included in the study. All patients enrolled underwent neurological examination and electrodiagnostic studies including neurographic and electromyographic studies [4,10] at the bedside using a Dantec Cantata™ instrument (Dantec, Copenhagen, Denmark). Nerve conduction studies play a key part in confirming the presence of peripheral neuropathy and assist in determining whether the underlying pathology is axonal degeneration or demyelination [16]. When muscles are denervated, spontaneous fibrillations and positive sharp waves are recorded in resting muscles on needle electromyography (EMG). Thus, EMG is the main ancillary test to confirm the presence of axonal degeneration [13], especially in patients in whom clinical examination of the peripheral nervous system is not diagnostic [4]. Data were gathered on days 5–7 after the onset of mechanical ventilation, and repeated weekly within the first month and on a 2-week schedule over the next 2 months. Thereafter, a 3-week schedule was used if the patient was still in our ICU. All measurements are standard procedures, as described in detail by Kimura [13] and McLeod [16].

For sensory measurements, sensory nerve action potentials (SNAP's) were recorded from the second digit after stimulation of the median nerve using ring electrodes. For each measurement, 20 responses were averaged. Compound muscle action potentials (CMAPs) were recorded with surface electrodes from the abductor pollicis brevis muscle following supramaximal stimulation of the median nerve at the wrist and elbow. Likewise, the ulnar nerve was stimulated, and the responses were recorded from the abductor digiti minimi muscle. The amplitudes of compound action potentials (CMAP's and SNAP's) were measured as the peak-to-peak voltage following distal stimulation. Nerve conduction velocity was calculated according standard procedures, and neuromuscular transmission was assessed by repetitive stimulations of 3 and 30 Hz.

At least one proximal and one distal arm muscle were examined by needle-EMG using a concentric needle electrode. Abnormal spontaneous activity, as shown in the presence of fibrillation potentials and positive sharp waves in resting muscles, was graded on a scale of 0–3, where 0 is normal, 1 mild, 2 moderate, and 3 severe [11]. Patients with grade 2–3 denervations were considered to have definite CIP. Those with grade 1 denervations were deemed to have mild neuropathy that would not account substantially for weaning failure [12].

2.2. Design of the retrospective study

The only common finding in the patients who developed CIP was a stay beyond seven days in our ICU. Therefore, we created a control group including all adult patients staying seven days or longer in the ICU in the same period of time. The patients of the control group were retrospectively compared to the group of patients developing CIP. In order to identify possible risk factors contributing to the onset of CIP the following items were evaluated.

2.3. Systemic inflammatory response syndrome and sepsis

Systemic inflammatory response syndrome (SIRS) and sepsis were defined according to the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference [5]. Patients with SIRS had to fulfil more than one of the following criteria independent of it's cause: (1) a body temperature above 38 or below 36°C; (2) a heart rate greater than 90 beats/min if other reasons like hypovolemia were excluded. If the patient was not being ventilated: (3) tachypnea, manifested by a respiratory rate greater than 20 breaths/min, or hyperventilation, as indicated by a $PaCO_2$ of less than 32 mmHg; and (4) an alteration in the white blood cell count, such as a count greater than 12 000/mm^3, a count less than 4000/mm^3, or the presence of more than 10% immature neutrophils. All these changes should represent an acute change from the baseline in the absence of other known causes for such abnormalities, such as chemotherapy, drug induced neutropenia, and leukopenia.

Sepsis was defined as SIRS due to an infection [5].

2.4. Application of corticosteroids

If the diagnosis of SIRS or sepsis was ascertained, hydrocortisone was applied in order to attenuate the systemic inflammatory response by an initial bolus of 100 mg i.v. followed by a permanent infusion of 300 mg hydrocortisone/24 h for a period of three days [6]. The dosage was expressed as the total amount of corticosteroids/kg body weight. In the case of organ transplantation a triple therapy was performed including cyclosporine, azathioprine and prednisolone.

2.5. Application of nondepolarising neuromuscular blocking agents

If possible, we avoided the application of nondepolarising neuromuscular blocking agents, especially as we never applied these agents as a permanent infusion. If necessary we injected pancuronium or vecuronium in repetitive cycles of a 4 or 8 mg bolus. Vecuronium was used in the early postoperative course whereas pancuronium was applied in the later course in order to minimize the total amount of nondepolarising neuromuscular blocking agents. The total amount of these agents was expressed as mg/kg body weight.

2.6. Application of aminoglycosides

Our standard protocol of antibiotic therapy did not include the application of aminoglycosides. The perioperative prophylaxis consisted of the application of three doses of 1.5 g cefuroxime. If there was an indication to use aminoglycosides we administered 4 to 6 mg netilmicinsulfate/kg body weight. The total amount applied during the stay in our ICU was again expressed as mg netilmicinsulfate/kg body weight.

2.7. Hemodynamic status

The definition of the hemodynamic status was based on the catecholamine support and it was classified in the following two categories: status I: patients receiving less than 8 μg/kg body weight dopamine and/or less than 6 μg/kg body weight dobutamine and/or less than 0.1 μg/kg body weight epinephrine and/or less than 0.1 mg/kg body weight norepinephrine. Status II: patients requiring higher doses of these catecholamines.

2.8. Chronic venovenous hemodiafiltration

In the case of acute renal insufficiency with an urine output of less than 0.5 ml/kg body weight per h, increased serum levels of creatinine (>2.0 mg/dl), urea (>200 mg/dl) and potassium (>6.0 mmol/l), the continuous venovenous hemodiafiltration was initiated. It was established by an indwelling sheldon catheter placed into the right or left femoral vein. The hemofiltration was discontinued when the patient resumed a sufficient urine output (>0.5 ml/kg body weight/h) with decreasing serum levels of creatinine (less than 2.0 mg/dl), urea (less than 40 mg/dl) and potassium (less than 5.0 mmol/l).

At the preoperative examination each patient was classified according to the four categories of the New York Heart Association, the left ventricular end diastolic pressure was recorded. The duration of cardiopulmonary bypass was also noted.

2.9. Statistical analysis

All values are expressed as mean $\pm$ S.D. Statistical analysis was performed using the χ^2 test and Student's t-test to assess the differences between the two groups. All $P < 0.05$ were considered to indicate statistical significance.

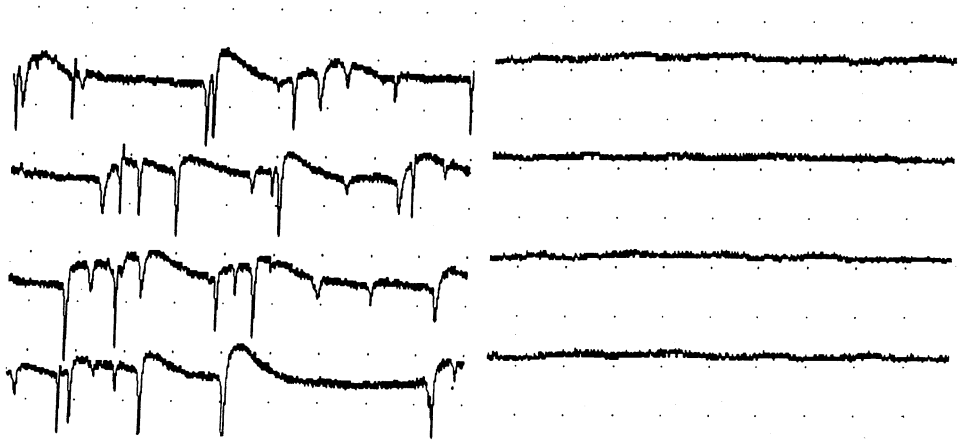

Fig. 1. EMG recording from the right deltoid muscle of a patient with CIP (left) and a normal control (right), showing abundant positive sharp waves occurring spontaneously in the diseased muscle. Calibration is as follows: time base 20 ms/division, amplitude 50 μV/division.

3. Results

From October 1994 to July 1995 1511 adult patients were admitted to our ICU. A total of 44 patients (2.9%) stayed longer than 7 days in our intensive care unit.

Of these, 7 patients (incidence: 0.46%) developed CIP as documented by the presence of grade 2–3 denervations, i.e. abundant florid denervations of at least four muscles. Six of the patients had reduced CMAP amplitudes, while sensory nerve action potential (SNAP) amplitudes were normal. Fig. 1 shows an original registration from a patient with yCIP compared to a normal control.

The median time to develop CIP was 14 days. Four patients after coronary artery bypass grafting, 1 patient with an additional aortic valve replacement, 1 patient after surgical repair of the descending aorta and 1 patient after orthotropic heart transplantation developed grade 3 denervations. Denervation activity developed in a gradual manner and resolved in those who survived the critical condition before weaning could be accomplished. In those who died denervation activity was present until the last examination before death. The results of the electromyographic examinations are shown in Table 1.

3.1. Clinical courses of the patients

3.1.1. Patient 1

This was a 66-year-old male patient suffering from endstage coronary heart disease with vanishing peripheral arteries. A coronary artery bypass grafting was performed. Following hemodynamic instability due to a perioperative ischemia he required high doses of catecholamines for circulatory support immediately after the operation. On the tenth postoperative day the diagnosis of sepsis due to pulmonary infection was made, hemodiafiltration was established on day 13, on day 23 CIP was diagnosed on the basis of abundant denervation potentials in any muscle examined. He died due to multiple organ failure 53 days after the bypass grafting. Ventilation support was continuous throughout the stay in the ICU.

3.1.2. Patient 2

A 73-year-old male patient suffering from severe coronary heart disease. After coronary artery bypass grafting he was extubated on the first postoperative day. A rethoracotomy had to be performed due to bleeding on the second postoperative day. On day 9 he developed SIRS, and sepsis was diagnosed on day 11 due to pulmonary infection requiring higher amounts of catecholamines from day 12. Due to acute renal insufficiency renal replacement therapy was established on day 15. The diagnosis of CIP was made on day 25, when grade 3 denervations were present in all muscles examined. He developed a multiple organ dysfunction syndrome affecting kidney, liver, lung and heart. After the second thoracotomy he was continuously ventilated until death due to multiple organ failure on day 143 after the bypass grafting.

3.1.3. Patient 3

A 69-year-old male patient suffering from coronary heart disease and aortic stenosis. Subsequent to coronary bypass grafting and aortic valve replacement he demonstrated impaired left ventricular performance, probably due to imperfect myocardial protection, needing a higher amount of catecholamine support immediately after the operation. Initially, the application of catecholamines improved the left ventricular performance and he was weaned off the ventilator on day 4. Due to an acute respiratory insufficiency accompanied by an acute renal insufficiency requiring renal replacement therapy, he was intubated again on day 5. Bacterial translocation from the gut caused sepsis diagnosed

Table 1
Electrodiagnostic findings of 7 patients with CIP

Nerve	Conduction velocity (m/s)	CMAP amplitude (mV)	SNAP amplitude (μV)
Median, motor	49.2 ± 1.8 (>48.0)	1.8 ± 0.5 (>5.0)	—
Median, sensory	47.9 ± 2.5 (>49.0)	—	12.4 ± 1.7 (>12.0)
Ulnar, motor	53.4 ± 4.0 (>47.0)	1.9 ± 0.7 (>5.2)	—
Ulnar, sensory	45.2 ± 3.3 (>50.5)	—	13.8 ± 2.1 (>10.5)

Results are mean $\pm$ S.E. Normal values are given in brackets.
CMAP, compound muscle active potential; SNAP, sensory nerve action potential.

on day 6. The diagnosis of CIP was ascertained on day 7 after the open heart surgery due to grade 3 denervations. The patient died 18 days thereafter due to multiple organ failure.

3.1.4. Patient 4

Subsequent to an acute dissection of the descending aorta surgical repair was performed. Additionally, this 71-year-old female patient was suffering from chronic obstructive pulmonary disease. On day 8 she developed sepsis due to an acute sinusitis frontalis and maxillaris. In the course of the severe sepsis she needed elevated amounts of catecholamines from day 9 and due to an acute renal insufficiency the establishing of the chronic venovenous hemodiafiltration from day 10. Despite the satisfactory status of her arterial blood gases we failed to wean her from the ventilator. CIP was diagnosed on day 14 on the basis of florid denervations on the EMG (grade 3). She was discharged 43 days after the surgical procedure with minimal residual disease (grade 1 denervations, day 39). She died in the later course (day 139) of causes not related to her primary and neurological diseases.

3.1.5. Patient 5

After coronary artery bypass grafting this 64 year old male patient required mechanical ventilation due to severe chronic obstructive pulmonary disease. Despite the satisfactory status of his arterial blood gases on day 10 the patient failed to be weaned off the ventilator and CIP was diagnosed on day 16 after the operation on the basis of florid grade 3 denervation in all muscles examined. He was ventilated until day 80 and was discharged home on day 93 with residual disease. Six months after the operation he still showed minimal disease (grade 1 denervations) and is actually in good condition without any electromyographic features of CIP.

3.1.6. Patient 6

A 74-year-old male patient suffering from coronary heart disease. The coronary bypass graft was performed with an uneventful postoperative course. Twenty-three days thereafter he developed severe sepsis due to an acute mediastinitis and a second thoracotomy with debridement had to be performed. He was admitted again to our ICU with acute respiratory and acute renal insufficiency and the elevated amounts of catecholamines were administered immediately after the rethoracotmy. CIP was diagnosed on day 6 (grade 3 denervations in all muscles examined) after the second thoracotomy and the patient died due to multiple organ failure 23 days thereafter.

3.1.7. Patient 7

A 61-year-old male patient suffering from dilative cardiomyopathy. Subsequent to orthotopic heart transplantation elevated pulmonary vascular resistance mandated the application of inhalative nitric oxide. On day 12 the diagnosis of sepsis due to bacterial translocation from the gut was ascertained. Two days before acute renal insufficiency required the establishing of renal replacement therapy. In the course of the sepsis higher amounts of catecholamines were administered from day 14. CIP was diagnosed on day 18 after the transplant on the basis of grade 3 denervations. Like all the patients after heart transplantation he was discharged to our Department of Cardiology on day 58 after the transplant with minimal residual disease (grade 1 denervations). He died in the later course because of an acute pulmonary embolism.

Table 2 summarizes the traits characterizing the patients who developed CIP throughout the postoperative course.

The control group consisted of 37 patients staying longer than seven days in our ICU at the same time as the CIP patients, without electrodiagnostic evidence of CIP. Twenty patients after coronary artery bypass grafts, 5 patients with an additional aortic valve replacement, 1 patient with an additional mitral valve replacement, 7 patients after aortic valve replacement, 2 patients after mitral valve replacement and 2 patients after aortic and mitral valve replacement. The most common reason for an extended stay in the ICU was the appearance of respiratory failure requiring prolonged ventilation support beyond 3 days (9/37) or the need for an ongoing elevated oxygen supply after extubation for several days, (9/37). Pulmonary infection occurred in 8 patients and was the cause for the prolonged stay in our ICU. Of these, 3 patients developed sepsis and multiple organ failure in the later course.

Table 2
Characterization of the patients developing CIP

Patient ID	Diagnosis	Additional diseases	Surgical procedure	Time (min)	NYHA catagory	LVEDP (mmHg)	Onset of CIP (days)
1	Coronary artery disease	None	CABG	94	IV	14	23
2	Coronary artery disease	COPD; preterminal renal insufficiency	CABG	95	III	14	25
3	Coronary artery disease; aortic valve stenosis	None	CABG; AVR	130	III	14	7
4	Acute aortic dissection type B	COPD; peripheral arterial occlussive disease	Repair of the descending aorta	206	IV	—	14
5	Coronary artery disease	COPD	CABG	155	III	14	16
6	Coronary artery disease, mediastinitis	None	CABG	98	III	36	6
7	Dilative cardiomyopathy	Preterminal renal insufficiency	Htx	105	IV	32	18

CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; AVR, aortic valve replacement; Htx, heart transplantation.

11/37 Patients showed hemodynamic instability, 6 patients had an acute perioperative myocardial infarction and 5/11 patients had a preexisting reduced left ventricular performance.

The mean age of the CIP group and the control group was 68.2 ± 3.9 and 73.9 ± 4.6 years, respectively. The difference was not statistically significant. The mean duration of stay in our ICU and the time of ventilation support is shown in Table 3. Compared to the control group, patients with CIP had a significant longer stay in our ICU and a significant longer time on ventilation support ($P < 0.01$).

3.2. Clinical outcome

4/7 (57.1%) patients in the CIP group died due to multiple organ failure, in contrast to 3/37 (8.1%) patients in the control group, 22, 86, 14 days thereafter, again due to multiple organ failure. The mortality of the patients in the CIP group was statistically significantly higher. Two patients of the 3 survivors died in the later course from causes not related to their primary illness. After six months the remaining one patient was showing minimal residual disease with some weakness in the control EMG. Actually he is in very good condition without any signs of CIP according the control EMG.

3.3. Sepsis

Six patients who developed CIP demonstrated the clinical features of sepsis. In 1 case due to an acute mediastinitis, in another case due to sinusitis frontalis et maxillaris, in 2 cases due to pulmonary infection and in 2 cases due to bacterial translocation from the gut. All these patients required chronic venovenous hemodiafiltration due to acute renal insufficiency. All patients who developed sepsis showed severe hemodynamic instability which required elevated amounts of catecholamines.

In the control group only 4 patients developed sepsis. Two patients had pulmonary infection, 1 patient bacterial translocation from the gut. One patient had sepsis with an unknown infectious focus. This patient survived and was discharged in a good physical condition. Two out of these 4 patients developed acute renal insufficiency with the need for chronic venovenous hemodiafiltration. All patients with sepsis in the control group required higher catecholamine support in order to achieve a sufficient hemodynamic performance. Compared to the control group the proportion of patients suffering from sepsis was significant higher in the CIP group ($P < 0.01$).

3.4. Application of corticosteroids

All patients who developed SIRS received hydrocortisone according to Briegel et al. [6]. The application was continued even when the diagnosis of sepsis was ascertained. Therefore, all patients who developed sepsis were treated with hydrocortisone within three days after the diagnosis was made. One patient developed sepsis in the postoperative course after heart transplantation. In addition to prednisone as a part of the immune suppressive regimen, this patient also received hydrocortisone therapy as described above. Therefore the proportion of patients who received corticosteroids were statistically higher in the CIP group than in the control group ($P < 0.01$).

3.5. Application of aminoglycosides

Only one patient in the CIP group and 2 patients in the control group received netilmicine sulfate. All the patients had severe pulmonary infection caused by *Klebsiella pneumoniae*. The proportion of patients in both groups who required this antibiotic drug was not significantly different.

Table 3
Analysis of the traits appearing in the patients in the CIP and control groups

Items	CIP group ($n = 7$)	Control group ($n = 37$)	P value
ICU stay (days)	62 ± 32	14 ± 8	<0.01
Ventilatory support (days)	50 ± 28	7 ± 13	<0.01
NYHA II (%)	0	108	n.s.
NYHA III (%)	57.2	48.6	n.s.
NYHA IV (%)	42.8	40.5	n.s.
LVEDP (mmHg)	20.6 ± 8.8	15.6 ± 8.4	n.s.
Bypass time (min)	126 ± 32	125 ± 39	n.s.
Sepsis (%)	85.7	10.8	<0.05
Corticosteroids, % (mg/kg body weight)	100 (16.4 ± 5.6)	10.8 (20.3 ± 4.0)	<0.01
Chronic venovenous hemodiafiltration (%)	71.4	5.4	<0.01
Catecholamine-support Status I (%)	14.3	64.9	<0.05
Aminoglycosides, % (mg/kg body weight)	14.3 (23.1)	5.4 (16.4 ± 3.0)	n.s.
Nondepolarising neuromuscular blocking agents, % (mg/kg body weight)	85.7 (0.37 ± 0.3)	29.7 (0.52 ± 0.6)	n.s.

3.6. Application of nondepolarising neuromuscular blocking agents

Six out of 7 patients in the CIP group and 11/37 patients of the control group received the bolus application of vecuroniumbromid or pancuroniumbromid in order to facilitate ventilation. The proportion of patients in both groups receiving nondepolarising muscle relaxants was not statistically significant.

3.7. Chronic venovenous hemodiafiltration

In the CIP group chronic venovenous hemodiafiltration had to be established in 6 patients because of acute renal failure, which appeared in the course of sepsis. Besides respiratory insufficiency renal failure was the earliest clinical sign of multiple organ dysfunction syndrome in all cases. In the control group 2 patients required chronic venovenous hemodiafiltration. All patients with sepsis in the CIP group and 2 patients with sepsis in the control group developed acute renal insufficiency. The proportion of patients requiring chronic venovenous hemodiafiltration was statistically significantly higher in the group of patients showing CIP ($P < 0.01$).

3.8. Catecholamine status

Six out of 7 patients in the CIP group required higher doses of catecholamines, especially more than 0.1 μg/kg body weight epinephrine and norepinephrine (catecholamine status II). In all of these patients the reason for this circulatory support was major hemodynamic instability due to sepsis or impaired left ventricular performance. Twenty-four patients of the control group were ranked in catecholamine status I, and 13 patients in catecholamine status II. The need for higher catecholamine application was due to sepsis (4/13) or impaired left ventricular function (9/13). The differences between the two groups in ranking to the different status were statistically significant ($P < 0.05$).

According to the NYHA classification, left ventricular end diastolic pressure and duration of cardiopulmonary bypass there were no significant differences between the two groups.

4. Discussion

Since the original description of CIP in 1986 [3] widespread interest in intensive care units all over the world has become evident. CIP was established as a new neurological entity. Though clinically similar to the well known Guillain–Barre syndrome, often diagnosed in the critical care setting before the concept of CIP was established, Bolton et al. [3] could show that those two types of polyneuropathy are separate entities that can be distinguished by the predisposing illness, electrophysiological features and cerebrospinal fluid samples. Despite an increasing number of studies about the clinical spectrum and possible causes of this disorder, CIP has been largely unrecognized in cardiac surgery intensive care units. Alhan et al. [1] were the first who drew attention to a case of CIP which complicated the surgical repair of an acute aortic dissection. Wagner et al. [19] gave a description of 20 patients suffering from CIP after open heart surgery. They reported about 11 patients after heart transplantation, 2 patients after left ventricular assist device implantation, 1 patient after surgical repair of the ascending aorta, 4 patients after coronary artery bypass grafting and 1 patient with an additional aortic valve replacement. Similar to our group of patients the distribution of surgical procedures performed on patients developing CIP was not homogenous. In addition, no significant difference according to the duration of cardiopulmonary bypass was found, therefore it appears to us that the development of CIP probably is not associated with a specific cardiac

surgical procedure nor prolonged perfusion times. Additionally, as we could not find any significant differences from the preoperative status, we assume that the determination of the NYHA classification and the hemodynamic performance of the patient prior to the operation does not allow the prediction of the development of CIP throughout the postoperative course.

The earliest symptom of CIP is the difficulty in weaning the patient off the ventilator. It is followed by the appearance of distal weakness and reduced deep-tendon reflexes. In severe forms complete quadriplegia and respiratory paralysis occurs with relative sparing of the cranial musculature [4]. Tendon reflexes are usually reduced or absent, though in patients with intracranial disease, they may even be exaggerated [11]. The diagnosis is mainly based on electromyographic studies showing the predominant involvement of motor fibres [10,12]. Despite the fact that the reasons for the development of CIP remain unclear, this disorder has frequently been found in patients suffering from sepsis and multiple organ failure. As sepsis affects the nervous system, CIP is associated with a typical series of events including encephalopathy, respiratory failure and neuropathy [4]. Moreover, sepsis affects various organs leading to a state that has been termed multiple organ dysfunction syndrome. The cause of various organ dysfunctions seems to be an alteration of the oxidative metabolism at the cellular level produced by hypoxia secondary to hypoperfusion. As a result a rapid decline of ATP takes place, which in turn causes accumulation of ADP and AMP [8]. Lopez et al. [15] had assumed that this mechanism of tissue damage in patients with severe infections could be the same as that occurring at the peripheral nerve level.

In accordance with other studies, most of our patients (6/7) developing CIP were suffering from sepsis throughout the postoperative course after open heart surgery, thus sepsis probably is the major risk factor contributing to the onset of CIP. But as we compared the clinical courses of all patients developing sepsis in order to get a further idea about the underlying pathogenesis we could not find any major differences. As one patient without sepsis developed CIP, and as four patients with sepsis did not show the clinical signs of CIP, sepsis may not be the only decisive risk factor for the development of CIP.

Recently additional mechanisms for the development of CIP have been discussed. Several authors have indicated that the administration of corticosteroids [2], aminoglycosides [3] and neuromuscular blocking agents [7,18] may contribute to the occurrence of this disturbing neurological disorder. However, both retrospective and prospective studies failed to implicate these factors in the pathogenesis of CIP [4]. In our study group all patients developing SIRS or sepsis received hydrocortisone. The proportion of patients which received nondepolarising agents was not significantly higher in the group of patients developing CIP compared to the control group. Therefore it appears to us to be unlikely that the application of nondepolarising agents alone contributes to the onset of critical illness polyneuropathy.

In the discussion of possible risk factors for the development of CIP, a chief concern still is whether antibiotics, like metronidazole and aminoglycosides, might cause the polyneuropathy. Antibiotics are the most obvious source of an exogenous toxin, and Witt et al. [20] showed that a defect in neuromuscular transmission is a well documented complication of these agents. However, in their study they failed to implicate any particular antibiotic agent. In our ICU metronidazole is only applied if a second surgical procedure for the gut was performed. None of the patients in the CIP group and the control group received metronidazole throughout their stay in our ward. Only one patient with CIP received netilmicine. According to our results it appears that CIP developed, as in many other cases [4], independently of the application of those two antibiotics.

One of the first reports on CIP claimed hypotensive shock as the cause of widespread but reversible damage to spinal motor neurones [15,17]. Most of the patients in our ICU who did require high dosages of catecholamines were in hypotensive shock due to low cardiac output. It is well known that high doses of, for example, norepinephrine leads to microcirculatory disturbances resulting in an alteration of peripheral nerve function [20]. Thus, it is reasonable to assume that all patients suffering from CIP in our study had microcirculatory disturbances, either due to sepsis or due to the large amount of catecholamines. Only further investigations will determine if microhemodynamic disturbances may be, in part, responsible for the development of CIP and examine the fact that there is a group of patients who received large amounts of catecholamines throughout their stay in the ICU and did not develop CIP.

The appearance of acute renal insufficiency was one of the first manifestations of organ failure appearing in our patients suffering from sepsis. The proportion of patients requiring chronic venovenous hemodiafiltration was statistically significantly higher in patients of the CIP group (85.7%) than in the control group (5.4%) and was associated with the appearance of sepsis. Six out of 7 patients required chronic renal replacement therapy. In each case it was initiated prior to the appearance of CIP. It has been suggested that hemodiafiltration is a modality for the removal of immunmodulatory mediators responsible for the systemic inflammatory response [9] and, thereby, reduces sepsis. Therefore, one can expect that chronic venovenous hemodiafiltration may be able to attenuate the clinical course of sepsis and therefore improve the clinical outcome of these patients. However, in our experience

the hemodiafiltration failed to improve the patient's clinical performance and it would be interesting to discuss if chronic venovenous hemodiafiltration itself may contribute to the onset of CIP.

In conclusion, CIP is a newly described disturbing complication appearing in patients after cardiac surgery. According to our retrospectively performed study and despite the low incidence of CIP, it appears that besides sepsis, interventions like chronic hemodiafiltration and the application of corticosteroids as therapy for SIRS and sepsis are associated with CIP. However, whether this implies a causal relationship or simply reflects the advanced state of the disease remains unsolved. It also remains unclear whether patients developed CIP due to severe states of sepsis or had sepsis due to mechanical ventilation prolonged by CIP. Anyway, guiding the patient securely through episodes of sepsis and/or low cardiac output finally leads to a complete restoration of peripheral motor function without residual neurological deficit in those who survived. A prospective study is needed to further evaluate the significance of various risk factors or to find out the specific cause of CIP after open heart surgery.

References

[1] Alhan HC, Cakalagaoglu C, Hanci M, et al. Critical illness polyneuropathy complicating cardiac operation. Ann Thorac Surg 1996;61:1237–9.

[2] Bolton CF. Neuromuscular complications of sepsis. Intensive Care Med 1993;19:S58–63.

[3] Bolton CF, Laverty DA, Brown JD, Witt NJ, Hahn AF, Sibbald WJ. Critically ill polyneuropathy: electrophysiological studies and differentiation from Guillain–Barre syndrome. J Neurol Neurosurg Psychiatry 1986;49:563–73.

[4] Bolton CF. Sepsis and the inflammatory response syndrome: neuromuscular manifestations. Crit Care Med 1996;24:1408–16.

[5] Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest 1992;101:1644–55.

[6] Briegel J, Kellermann W, Forst H, et al. Phospholipase A_2 Study Group. Low-dose hydrocortisone infusion attenuates the systemic inflammatory response syndrome. Clin Invest 1994;72:782–7.

[7] Giostra E, Magistris MR, Pizzolato G, Cox J, Chevrolet J-C. Neuromuscular disorder in intensive care unit patients treated with pancuronium bromide. Chest 1994;106:210–20.

[8] Grum CM, Simon RH, Dantzker DR, Fox IH. Evidence for adenosine triphosphate degradation in critically-ill patients. Chest 1985;88:763–7.

[9] Hoffmann JN, Hartl WH, Deppisch R, Faist E, Jochum M, Inthorn D. Hemofiltration in human sepsis: evidence for elimination of immunmodulatory substances. Kidney Int 1995;48:1563–70.

[10] Hund EF. Neuromuscular complications in the ICU: the spectrum of critical illness-related conditions causing muscular weakness and weaning failure. J Neurol Sci 1996;136:10–6.

[11] Hund EF, Fogel W, Krieger D, DeGeorgia M, Hacke W. Critical illness polyneuropathy: clinical findings and outcomes of a frequent cause of neuromuscular weaning failure. Crit Care Med 1996;24:1328–33.

[12] Hund EF, Genzwürker H, Böhrer H, Jakob H, Thiele R, Hacke W. Predominant involvement of motor fibres in patients with critical illness polyneuropathy. Br J Anaesth 1997;78:274–8.

[13] Kimura J. Nerve conduction studies and electromyography and neurophysiologic recording. In: Dyck PJ, Thomas PK, editors. Peripheral Neuropathy, vol. 1. 2nd ed. Philadelphia: Saunders, 1993:597–644.

[14] Leijten FSS, de Weerd AW. Criticall illness polyneuropathy. A review of the literature, definition and pathophysiology. Clin Neurol Neurosurg 1994;96:10–9.

[15] Lopez Messa JB, Garcia A. Acute polyneuropathy in critically ill patients. Intensive Care Med 1990;16:159–62.

[16] McLeod JG. Investigation of peripheral neuropathy. J Neurol Neurosurg Psychiatry 1995;58:274–83.

[17] Rivner MH, Kim S, Greenberg M, Swift TR. Reversible generalized paresis following hypotension: a new neurological entity. Neurology 1983;33(2):164–5.

[18] Segredo V, Caldwell JE, Matthay MA, Sharma ML, Gruenke LD, Miller RD. Persistent paralysis in critically ill patients after long-term administration of vecuronium. New Engl J Med 1992;327:524–8.

[19] Wagner F, Ziegler U, Behse F, Hummel M, Hetzer R. Inzidenz, klinik, verlauf und langzeitergebnisse der critical illness polyneuropathy (CIP) nach kardiochirurgischen eingriffen. Thorac Cardiovasc Surg 1996;44(1):110.

[20] Witt NJ, Zochodne DW, Bolton CF, et al. Peripheral nerve function in sepsis and multiple organ failure. Chest 1991;99:176–84.

Appendix A. Conference discussions

Mr Treasure (*London, UK*): I think this is fascinating and it begs some very fundamental questions. You have 7 cases, that is nearly 0.5% in your unit. It is either truly a new condition, in which case you must perform some sort of cluster analysis to try and help us understand why this should have occurred; or on the other hand, it is a new diagnostic frame. Have you found something in common about a group of cases that the rest of us see but call by different names? Which do you think it is? Do you think it is a new cluster of 7 cases or that you have found diagnostic unity where others have not?

Dr Thiele: I think it is both. In cardiac surgery only two reports were presented about the CIP, one case report about a patient who developed CIP after the surgical repair of an acute aortic dissection. In 1996 the Berlin group gave a description of 20 patients who developed CIP after cardiac surgery. As we know from other faculties CIP is a new entity with a rising incidence, and as we have an increasing number of critically ill patients CIP 'affects' cardiac surgery ICUs. Now we have the opportunity to determine the onset of CIP with electromyographic studies as a new diagnostic tool.

Mr Treasure: Do they develop it? Are these patients who come out from cardiac surgery, wake up and move all four limbs, and then at some later stage develop this peripheral nerve problem.

Dr Thiele: Yes and no, the first symptom after cardiac surgery is the difficulty to wean the patient off the ventilator. We think that it develops, but we can not determine exactly the onset of this disorder.

Mr Treasure: There are signs before weaning off a ventilator. You know whether a patient is conscious and can move all four limbs before you try and wean them.

Dr Thiele: It differs from all the other neurological disorders known until now. The diagnosis of this disorder is based on electromyographic studies and they show specific traits or specific features for this disorder. Again, mainly, it is reduced compound muscle action potential, it is a reduced sensory nerve action potential with normal or near normal nerve conduction velocities with a spontaneous denervation of the patient.

Mr Treasure: And to pin you down then, when does it happen? At what point in the process of cardiopulmonary bypass, coming off bypass, coming to the ITU, failing to wean, do you believe that this starts or occurs?

Dr Thiele: We do not know when it starts. We know that there are no risk factors in the preoperative performance of the patients; we checked it. There is no association with the time of bypass; we checked it, too. And the reason or the mechanism for the onset of this disorder is, to my knowledge, up to now unknown.

There are some others who focus on the disturbances of microcirculation. Some authors mention that it only develops in the case of multiple organ dysfunction syndrome. But there was one report and one case in our intensive care unit of patients developing severe CIP without any possible risk factors. For example, a patient was admitted to our ICU and developed CIP and was showing no infection, no multiorgan dysfunction, requiring no catecholamine support. The only symptom of this patient was that we were not able to wean him off the ventilator, but after a period of eight weeks he was in good condition.

Dr Wesselink (*Nieuwegein*, *Netherlands*): I fully agree with Mr Treasure that this CIP, we diagnosed that in the last years in our intensive care unit as well, exists not only in cardiac bypass patients but also in critically ill patients. It is easily measurable but you cannot explain it very well. There is no doubt that it happens to patients who are very ill and somewhere during their illness their nerves get damaged. I don't know exactly how or why. It's not specifically from bypasses, it is something that happens, but there is a moment in their course of disease that the peripheral nerves get ill and then you have this syndrome. The fact that our neurologist measures more EMGs in the ICU contributes to the fact that we diagnose this syndrome now.

Mr Treasure: I am very grateful to you for explaining it, because I have studied all the neurological aspects of cardiac surgery for the last 15 years, including the phrenic nerve, so called peripheral neuropathies, brachial plexus lesions, and stroke, and I am struggling to see which of the many patients I have observed fit into this pattern. Now it is beginning to become clear that these are patients who develop this in the course of a multisystem failure rather than it being a cardiac surgical phenomenon. That is very helpful.

Dr Wesselink: It is one of the organs that gets ill in multiorgan failure. That is the way I see it.

Dr Mestres (*Barcelona*, *Spain*): I was fascinated after reading this paper. You mentioned something in your response which I would like to go back to. It seems to me that the word 'diverse' applies, i.e. preoperative diagnosis, patients from different groups, like valve replacements, transplantation and so on. According to your data it seems to me that many of those patients will die in sepsis, that is shown in the clinical pattern of multiorgan failure. So once again, because to me it is very important, did you identify, other than these operation related factors, any other preoperative factors like, say, renal dysfunction or things like this that you could link to the postoperative outcome in this particular group of patients?

Dr Thiele: No, we are not able to predict the onset of CIP. There are some more mechanisms discussed for the onset, for example, nutritional disorders in postoperative care and some changes in hemodynamic performances, but there are, up to now, no absolute predictive factors which lead us to the expectation that the patient will develop CIP.