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The pathophysiology of propofol infusion syndrome: a simple name for a complex syndrome

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Abstract Propofol infusion syndrome (PRIS) is a rare and often fatal syndrome described in critically ill children undergoing long-term propofol infusion at high doses. Recently several cases have been reported in adults, too. The main features of the syndrome consist of cardiac failure, rhabdomyolysis, severe metabolic acidosis and renal failure. To date 21 paediatric cases and 14 adult cases have been described. These latter were mostly patients with acute neurological illnesses or acute inflammatory diseases complicated by severe infections or even sepsis, and receiving catecholamines and/or steroids in addition to propofol. Central nervous system activation with production of catecholamines and glucocorticoids, and systemic inflammation with cytokine production are *priming factors* for cardiac and peripheral muscle dysfunction. High-dose propofol, but also supportive treatments with catecholamines and corticosteroids, act

as *triggering factors*. At the subcellular level, propofol impairs free fatty acid utilisation and mitochondrial activity. Imbalance between energy demand and utilisation is a key pathogenetic mechanism, which may lead to cardiac and peripheral muscle necrosis.

Propofol infusion syndrome is multifactorial, and propofol, particularly when combined with catecholamines and/or steroids, acts as a triggering factor. The syndrome can be lethal and we suggest caution when using prolonged (>48 h) propofol sedation at doses higher than 5 mg/kg per h, particularly in patients with acute neurological or inflammatory illnesses. In these cases, alternative sedative agents should be considered. If unsuitable, strict monitoring of signs of myocytolysis is advisable.

Keywords Propofol · Catecholamines · Corticosteroids · Cardiac failure · Rhabdomyolysis · Brain injury

Introduction

Propofol infusion syndrome (PRIS) is a rare and often fatal syndrome originally described in critically ill children undergoing long-term (>48 h) propofol infusion at high doses (>4 mg/kg per h) [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14]. Severe metabolic acidosis, rhabdomyolysis, renal failure and fatal cardiac failure are the features.

In adults, propofol has proven to be safe and efficacious in several clinical randomised trials of short- and

long-term (>48 h) sedation [15, 16, 17, 18, 19, 20, 21, 22, 23]. Propofol has therefore become a widely used agent to sedate critically ill adult patients. However, from 1998 on, 14 cases of PRIS have also been described in adults [5, 24, 25, 26, 27, 28, 29] (Table 1). All but five patients were critically ill neurological patients and 12 received catecholamines. Three patients had signs of infection and one had sepsis; for the rest of the patients information regarding concomitant infections was not reported and probably went unrecognised, as com-

Table 1 Summary of propofol infusion syndrome cases in adults

Reference	Gender, age Diagnosis	Propofol infusion		Clinical features	Laboratory results	Catecholamine infusion	Severe infection/sepsis	Steroids in ICU	Outcome
		Dose (mg/kg/h)	Duration (h)						
Marinella 1996 [24]	F, 30 Severe asthma	NA	12		Lactic acidosis	No	No	Yes (+previous steroid therapy)	Survived
Hanna 1998 [5]	M, 17 Refractory epilepsy	8.8–17.5	44	Anuria hypotension bradycardia	Lipaeamic serum metabolic acidosis myoglobinuria elevated CK	Yes	Fever 38.5°C	No	Died
Stelow 2000 [25]	*F, 47 Refractory asthma	12	36	Dark urine hypotension VT anuria hypertermia	Elevated CK elevated cTnl metabolic acidosis hyper K+ renal failure	Yes	Chest infiltrate	Yes (+previous steroid therapy)	Died
Perrier 2000 [26]	M, 41 Refractory asthma	13.3	144	Dark urine oliguria reduced EF	Elevated CK cTnl myoglobinuria	No	Possible chest infiltrate	Yes (+previous steroid therapy)	Survived
	F, 18 Severe multiple trauma (with severe head trauma)	5.8–7.6	98	AF, LBBB hypotension PEA	Elevated CK metabolic acidosis lipaeamic serum hyper K+ myoglobinuria	Yes	b. Gram negative in tracheal cultures Fever 39°C	No	Died
Cremer 2001 [27]	Head injury	7.3	91	VT	Hyper K+ rhabdomyolysis	Yes	NA	NA	Died
	Head injury	5.7	101	ST, SVT	Metabolic acidosis hyper K+ rhabdomyolysis	Yes	NA	NA	Died
	Head injury	6.6	82	AF, VT	Metabolic acidosis hyper K+ lipaeamic serum	Yes	NA	NA	Died
	Head injury	5.5	88	ST, VR	Metabolic acidosis rhabdomyolysis	Yes	NA	NA	Died
	Head injury	7.4	106	SVT, VT	Metabolic acidosis rhabdomyolysis	Yes	NA	NA	Died
	Head injury	5.8	65	SVT, NR, VT	Metabolic acidosis hyper K+ lipaeamic serum	Yes	NA	NA	Died

Table 1 (continued)

Reference	Gender, age Diagnosis	Propofol infusion		Clinical features	Laboratory results	Catecholamine infusion	Severe infection/sepsis	Steroids in ICU	Outcome
		Dose (mg/kg/h)	Duration (h)						
	Head injury	6.9	177	ST, VR	Metabolic acidosis hyper K ⁺ lipaemic serum	Yes	NA	NA	Died
Kelly 2001 [28]	M, NA Head trauma	7.5	55	Cardiac and renal failure	Metabolic acidosis		NA	NA	Died
Friedman 2002 [29]	M, 23 Refractory epilepsy	12	106	VT with wide complex cardiac failure	Metabolic acidosis hyper K ⁺	Yes	NA	NA	Died

*Postmortem examination performed

NA not available, RBBB right bundle branch block, LBBB left bundle branch block, AF atrial fibrillation, VF ventricular fibrillation, VR idioventricular rhythm, NR nodal rhythm, PEA pulseless electrical activity, EF cardiac ejection fraction, M male, ST sinus tachycardia, SVT supraventricular tachycardia, VT ventricular tachycardia, F female, CK creatine kinase, cTnI cardiac troponin I

monly seen in neurological literature [30]. Steroids probably played a role in three patients developing rhabdomyolysis. Acute central nervous system (CNS) diseases, systemic inflammatory response syndrome (SIRS), multiple-organ dysfunction syndrome (MODS), catecholamines, steroids and propofol all have the potential to cause cardiac and muscle injury. Since these factors can be concomitant, the independent role of propofol is difficult to establish.

The purpose of this review is to synthesise the available evidence regarding the pathogenesis of PRIS in adults. In the conclusions, we define some categories of patients for whom alternative sedative agents to propofol are worth considering.

Cardiac and peripheral muscle injury: the role of propofol

Large plasmatic increases of creatine kinase (CK) and troponin I, and myoglobinuria have been documented both in children [1, 3, 5] and adults [5, 25, 26, 27] receiving propofol, and they have been interpreted as proof of a direct necrotising effect of propofol on peripheral and cardiac muscles (Table 1). Histological studies showed signs of severe myocytolysis in the skeletal muscle and myocardium of affected patients [1, 3, 5, 25, 27].

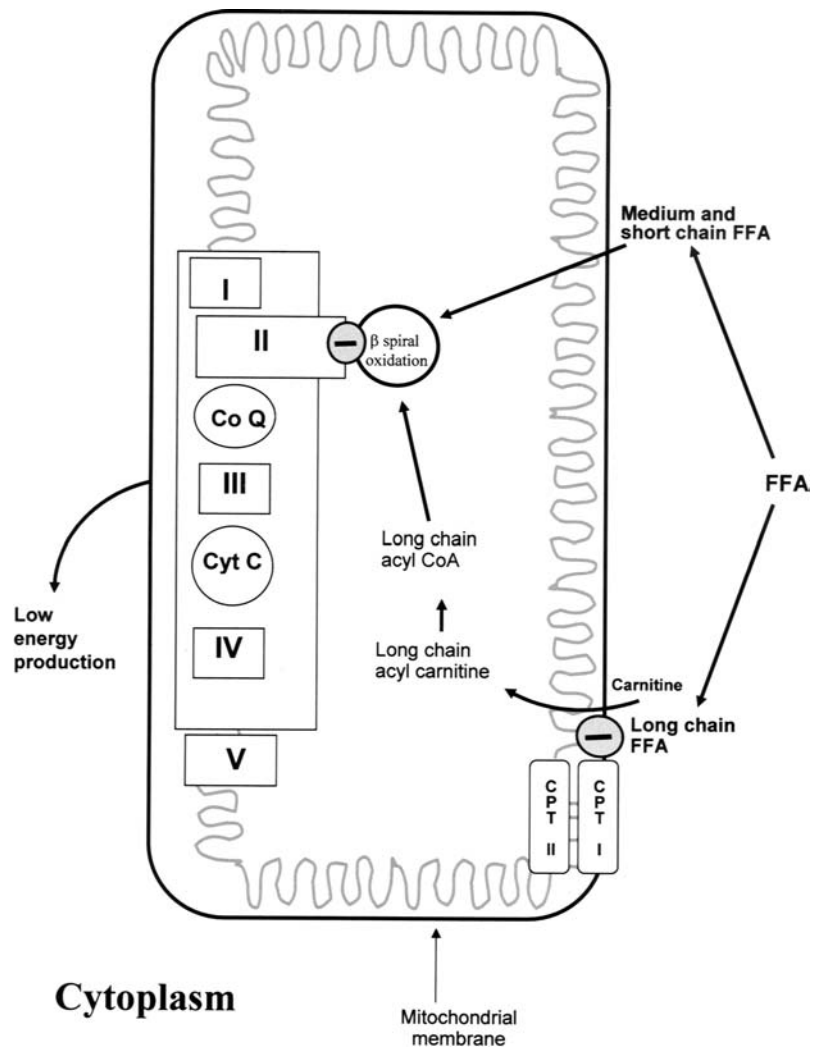
Following is a description of the subcellular mechanisms through which propofol may alter cardiac contractility, and energy production and utilisation in peripheral and cardiac muscle (Fig. 1).

Direct inhibitory effects of propofol in vitro and in vivo

In animal models, propofol uncouples oxidative phosphorylation and energy production in the mitochondria [31], impairs oxygen utilisation and inhibits electron flow along the mitochondrial electron transport chain [32], decreases the ventricular performance [32], antagonises β -adrenoceptor binding [33] and acts directly on calcium-channel proteins resulting in diminished cardiac contractility [34]. These mechanisms may all be involved in the lack of response to catecholamines and the need for escalating inotropic support observed in critically ill patients.

In humans, muscle cytochrome oxidase deficiency was demonstrated in a child who received prolonged high-dose propofol infusion [4]. No genetic defect of cytochrome oxidase accounted for this deficiency, which was interpreted as secondary to propofol infusion. Decreased complex IV activity and a low cytochrome oxidase ratio of 0.004 (normal range 0.014–0.034) were found in a muscle biopsy from another child with clinical features of PRIS [11], suggesting a mitochondrial respiratory-chain enzyme deficiency.

Fig. 1 Propofol increases the activity of malonyl coenzyme A (not shown), which in turn inhibits (\ominus) the carnitine palmitoyl transferase I (CPT I), so that long-chain FFA cannot enter the mitochondrion. Propofol also uncouples (\ominus) β -spiral oxidation and respiratory chain at complex II; therefore, neither medium- nor short-chain FFA, that freely cross the mitochondrion membranes, can be utilised. Low energy production can lead to cardiac and peripheral muscle necrosis if energy demand is high (CoA coenzyme A, CoQ coenzyme Q, Cyt C cytochrome C, I, II, III, IV, V complexes of the respiratory chain)



Propofol-mediated impaired fatty acid oxidation

Free fatty acids (FFA) derive from catecholamine-mediated lipolysis of adipose tissues and are the most important fuel for myocardium and skeletal muscle under fasting conditions or in critical conditions. Intra-mitochondrial β -spiral oxidation is the key process generating electrons which are transferred to the respiratory chain. Any obstacle to FFA utilisation determines various grades of myocytolysis [35].

A link between FFA metabolism and myocytolysis in PRIS was found in a case of a 2-year-old boy with raised plasma concentrations of malonyl carnitine (3.3 mol/l, normal value <0.2 mmol/l) and C5-acylcarnitine (8.4 mol/l, normal value <0.8 mmol/l), which returned to normal after recovery [12]. These metabolic findings indicated that altered long-chain FFA entry into the mitochondrion (caused by inhibition of carnitine palmitoyl transferase 1) and uncoupling of β -spiral oxidation and respiratory chain at complex II were the critical events (Fig. 1). Therefore, on the

one hand, long-chain FFA could not enter the mitochondrion while, on the other, medium- and short-chain FFA, that freely cross the mitochondrion membranes and do not require enzyme-mediated transfer, could not be utilised.

Imbalance between energy demand and supply is a key pathogenetic mechanism which may lead to cardiac and peripheral muscle necrosis. Furthermore, a propofol-induced blockade of mitochondrial fatty acid oxidation will, in the end, determine accumulation of unutilised FFA that possess pro-arrhythmogenic properties [36], thus contributing to the clinical syndrome.

Cardiac and peripheral muscle injury: the role of catecholamines

As previously noted, many patients with PRIS actually received catecholamines. These latter may act both indirectly, by increasing propofol requirements, and directly, by damaging the myocyte (Fig. 2).

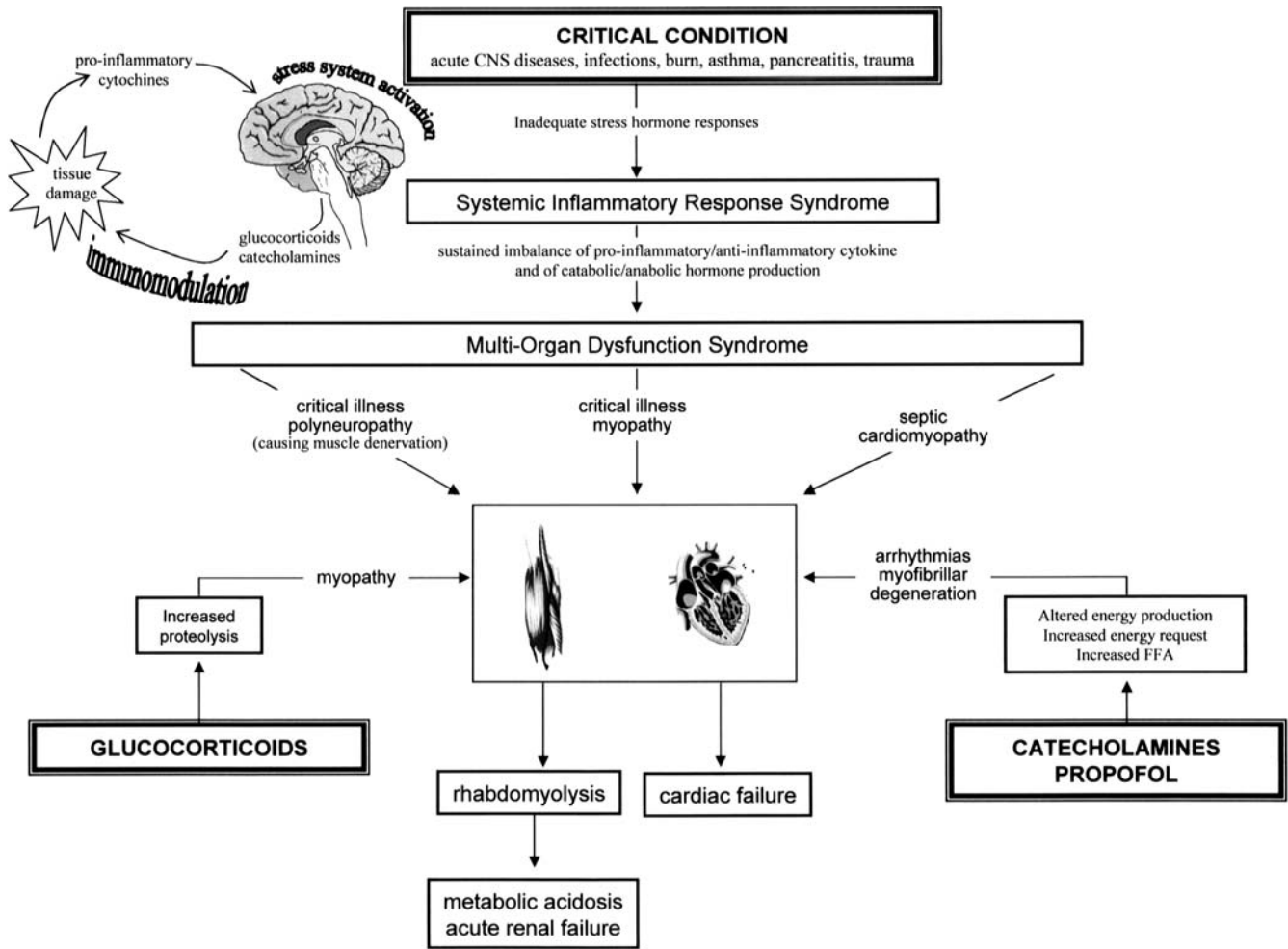


Fig. 2 Propofol infusion syndrome: a critical illness cardiac failure and rhabdomyolysis associated with high-dose propofol, catecholamines or steroids. Critical illness, the *priming factor*, is the essential prerequisite for the PRIS to develop; high-dose propofol, catecholamines and/or steroids are the *triggering factors*. Pro-inflammatory cytokines produced at the site of tissue damage activate the stress system, causing glucocorticoid and catecholamine secretion. Stress response usually has an anti-inflammatory and immunosuppressive effect. If this is inadequate, susceptibility to inflammatory diseases is enhanced. The persistent pro-inflammatory state with hypercatabolism causes progressive organ dysfunction, including cardiac and skeletal muscle dysfunction. With the body so primed, high doses of drugs like propofol, glucocorticoids and catecholamines may trigger the syndrome of cardiac failure and rhabdomyolysis, followed by metabolic acidosis and acute renal failure (*FFA* plasmatic free fatty acids)

The catecholamine-propofol vicious circle

A possible explanation of high propofol requirements observed in certain clinical situations is provided by an interesting experimental study of concomitant propofol and catecholamine infusion [37]. Catecholamines significantly increased cardiac output. Concurrently, mean propofol arterial concentration was linearly reduced from

baseline. While catecholamines and cardiac output peaked, propofol blood concentration decreased to the lowest levels and was associated with a *reversal of anaesthesia*. Such results were attributed to increased first-pass dilution and clearance of propofol secondary to the increased cardiac output [37]. Propofol antagonism of β -adrenoceptor binding may be a further explanation [33].

Catecholamine surge in acute neurological conditions is well recognised (see CNS stimulation) and could be responsible for decreasing the anaesthetic effect of propofol. Since the management of these patients requires adequate sedation, the clinicians are so induced to intensify propofol infusion rates further. The negative inotropic effect of propofol, resulting in increased catecholamine requirements, could create a vicious circle, in which propofol and catecholamines drive each other in a progressive myocardial depressive effect.

Direct myocytolytic effects of catecholamines

Systemic administration of catecholamines is associated with electrocardiographic signs of ischaemia and with pe-

cular anatomic-pathological findings described as myofibrillar degeneration (MD; or contraction band necrosis or coagulative myocytolysis) identical to that seen in patients with pheochromocytoma [38, 39]. This characteristic form of cardiac damage can be produced not only by catecholamine infusion, but also by various stress models (burns, surgery, trauma, pancreatitis, sepsis, asthma) plus or minus steroids, leading to the definition of this condition as human stress cardiomyopathy [40]. CNS stimulation and reperfusion are other well known causes [41]. These apparently disparate aetiologies are tied together by a common thread, the essential feature of which is sympathetic overactivity with secondary endogenous catecholamine toxicity.

MD is a definite response of myocardial tissue to several injuries, distinct from myocardial infarction [42]. Muscle fibres become functionally useless in an excessively contracted state with prominent contraction bands clearly distinguishable from myocardial infarction, where the myocytes die in a relaxed state without contraction bands. Furthermore, in MD, histological changes can be seen early, probably within minutes, with monocyte activation and calcifications as prominent features. In ischaemic necrosis, histological changes are seen late, calcification is rare and infiltration is mainly by polymorphonuclear cells [43]. The pathogenesis involves large amounts of norepinephrine released into the myocardium and, by opening of the calcium channel, cellular influx of Ca^{2+} and efflux of K^+ . Under the influence of Ca^{2+} , actin and myosin filaments interact and do not relax unless the calcium channel closes. If high levels of catecholamines are continuously discharged or administered, calcium channels fail to close, thus leading to cell death in an excessively contracted state. MD is predominantly subendocardial, which explains the early involvement of the cardiac conducting system and the risk of arrhythmias.

MD is typically described in patients with an asthma attack, a life-threatening stress complicated by the use of exogenous corticosteroids and catecholamines [44]. Burns are another typical stress situation [45]. In patients who died as a consequence of assault-induced stress, the histological documentation of MD poses special legal questions (homicide?). Finally, the beneficial effects of β -blockers in children with severe burns demonstrate that catecholamine surge is a clinically relevant target [46]. The true incidence of MD in critically ill patients remains unknown because diagnosis is autoptic or, more rarely, biptic.

Peripheral muscle injury: the role of steroids

Steroids are commonly cited as a cause of muscle damage. However, while the evidence for chronic steroid use is overwhelming, it is much less so for short-term steroid

use. Even when the authors ascribed the myopathy to steroids, accurate analysis of the data revealed that other factors were the cause [30]. Steroid administration is associated with ICU-acquired paresis [47], however disease severity is a major contributing factor [48]. Therefore, steroids have a triggering role in acute muscle damage. Proteolysis due to activation of the ubiquitin-proteasome system [49] is a central pathogenetic mechanism, leading to disarrangement of contractile myofilaments, which are proteins.

Cardiac and peripheral muscle injury: the role of systemic inflammatory response syndrome and multiple-organ dysfunction syndrome

The most common cause of death in patients with critical illness is MODS [50]. SIRS is associated with the development of MODS and may result from either an exaggerated pro-inflammatory cytokine response or an inadequate anti-inflammatory cytokine response [51]. Commonly affected organs include the lungs, liver and kidneys, however cardiac and skeletal muscle are not spared (Fig. 2).

Cardiac cell injury in sepsis and septic shock has recently been demonstrated to be a common event, which correlates with cardiac dysfunction [52]. Global myocardial ischaemia has been excluded as an important pathophysiological mechanism by a number of clinical studies showing that total coronary blood flow is not reduced [53, 54].

In recent years, a critical illness polyneuropathy [55] and a critical illness myopathy [56], whose spectrum extends from pure functional impairment to massive necrotising myopathy [57], have been recognised. The muscle is hit twice in critically ill patients: directly because of the myopathy, and indirectly because of the muscle denervation caused by the polyneuropathy (Fig. 2).

Pathogenesis includes tumour necrosis factor production, which in turn is an important autocrine contributor to myocardial dysfunction and cardiomyocyte death [58], as well as to peripheral muscles proteolysis [49, 59]. Proteolysis in rat muscle, especially the degradation of myofibrillar proteins, increases within hours after the injection of endotoxin or live bacteria or after puncture of the cecum to cause peritonitis and sepsis [49].

The role of central nervous system stimulation

Bilateral and persistent hypothalamic stimulation, as well as stimulation of the limbic cortex and mesencephalic reticular region, regularly produce MD indistinguishable from that produced by catecholamines and stress [60]. Recent experiments in rats showed a cardio-specific region in the insular cortex whose stimulation

produces lethal cardiac arrhythmias and MD [61]. The cellular mechanism determining rhythm and conduction disturbances, as well as myocardial necrosis with increased serum levels of CK-MB and various degrees of ventricular dysfunction, is probably due to the large volumes of norepinephrine released into the myocardium by the sympathetic nerve terminals [60]. Many neurological conditions, including subarachnoid haemorrhage, severe head trauma, status epilepticus, encephalitis, meningitis and stroke, are complicated by sudden death or non-fatal cardiovascular disturbances [62].

To appreciate the complex interrelationship between CNS stimulation, drugs and inflammation, two concepts need to be emphasised. First, catecholamines and steroids, two classes of drugs which are involved in PRIS, are also the two major end-products of the stress system (Fig. 2). Second, catecholamines and steroids exert profound effects on immunity and inflammation. While this is well known for glucocorticoids and the hypothalamic–pituitary–adrenal axis, it is not for catecholamines and the sympathetic nervous system. Research in the last 20 years indicates that norepinephrine released by nerve terminals into lymphoid organs and circulating catecholamines such as epinephrine affect lymphocyte traffic, circulation and proliferation, and modulate cytokine production and the functional activity of different lymphoid cells [63]. The available data suggest a net immunosuppressive effect of catecholamines in major injury and sepsis [63]. Therefore, patients with acute neurological illnesses accompanied by excessive stress response activation have impaired immune responses and increased susceptibility to severe infection: in this condition cardiac and peripheral muscle damage can be boosted by the increased levels of endogenous steroids and catecholamines, as well as by complications arising from severe infection (Fig. 2).

Conclusions

The term PRIS is misleading. In fact, an adequate description of this syndrome requires considering both *the priming factor*—critical illness— and *the triggering factors*—use of high-dose propofol, catecholamines and steroids. Furthermore, there is overlapping between the priming and triggering factors, since glucocorticoids and catecholamines are the primary end-product of the stress response which characterises the critical illness. Therefore, a more descriptive term of *critical illness cardiac failure and rhabdomyolysis associated with high-dose propofol, catecholamines or steroids* seems more appropriate. It would be a good reminder that the patients described are always critically ill with catastrophic events on admission and multiple organ dysfunctions during the clinical course, rather than patients simply receiving high-dose drugs [30].

Patients with severe head injury receiving high-dose propofol (≥ 5 mg/kg per h) have double the risk of developing the syndrome compared to those receiving smaller doses [27]. For this reason, high-dose propofol for prolonged periods (>48 h) is not recommended in these patients [64]. Other categories of critically ill neurological patients, such as those with subarachnoid haemorrhage, status epilepticus, meningitis, encephalitis and stroke, as well as patients with severe burns, trauma, severe infections, pancreatitis and acute exacerbation of asthma, might show a similar risk due to shared pathophysiological mechanisms. It is therefore prudent to avoid prolonged infusion of high-dose propofol in these patients, too. Lorazepam (0.01–0.1 mg/kg per h) or midazolam (0.04–0.2 mg/kg per h) are effective alternatives [64]. If various combinations of propofol, catecholamines and steroids are clinically dictated, careful monitoring of the plasmatic levels of troponin I, CK and myoglobin is warranted.

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