Published in final edited form as:

Heart Rhythm. 2006 February ; 3(2): 131–137.

Electrocardiographic changes predicting sudden death in propofol-related infusion syndrome

Kevin Vernoooy, MD^a, Tammo Delhaas, MD, PhD^a, Olaf L. Cremer, MD^b, José M. Di Diego, MD^c, Antonio Oliva, MD^c, Carl Timmermans, MD, PhD^a, Paul G. Volders, MD, PhD^a, Frits W. Prinzen, PhD^a, Harry J.G.M. Crijns, MD, PhD^a, Charles Antzelevitch, PhD^c, Cornelis J. Kalkman, MD, PhD^b, Luz-Maria Rodriguez, MD, PhD^a, and Ramon Brugada, MD^d

*a*From the Cardiovascular Research Institute Maastricht, Maastricht, The Netherlands

*b*Department of Perioperative Care, Anaesthesiology and Pain Treatment, University Medical Centre Utrecht, Utrecht, The Netherlands

*c*Masonic Medical Research Laboratory, Utica, New York

*d*Montreal Heart Institute, Montreal, Quebec, Canada

Abstract

BACKGROUND The occurrence of metabolic acidosis, rhabdomyolysis, hyperkalemia, and sudden cardiac death after long-term, high-dose propofol infusion has been referred to as propofol infusion syndrome (PRIS).

OBJECTIVES The purpose of this study was to explore the ECG abnormalities observed in a patient with PRIS in order to identify possible pathophysiologic mechanisms of the syndrome.

METHODS ECG changes in the index case were characterized by down-sloping ST-segment elevation in precordial leads V₁ to V₃ (Brugada-like ECG pattern). We subsequently assessed the relationship between this ECG pattern and the propofol infusion rate, the development of arrhythmias, and the occurrence of sudden death in a previously described cohort of 67 head-injured patients, seven of whom had been identified as having PRIS.

RESULTS Six of the PRIS patients developed the ECG pattern of ST-segment elevation in leads V₁ to V₃ and died within hours of irrecoverable electrical storm. This ECG pattern was the first aberration recorded hours before the death of these patients. ECGs that were available for 30 of 60 unaffected patients exhibited a normal pattern. None of the 60 patients developed ventricular arrhythmias.

CONCLUSION Our findings indicate that development of an acquired Brugada-like ECG pattern in severely head-injured patients is a sign of cardiac electrical instability that predicts imminent cardiac death. Future studies will determine whether such an ECG pattern also predicts imminent cardiac arrhythmia in other patient populations.

Keywords

Electrocardiography; Sudden death; Propofol-related infusion syndrome; Ventricular arrhythmia

Address reprint requests and correspondence: Dr. Ramon Brugada, University of Montreal, Research Center, Montreal Heart Institute, 5000 Rue Belanger, Montreal, QC H1T 1C8, Canada. E-mail address: ramon@brugada.org or ramon.brugada@icm-mhi.org. .

This study was supported by The Netherlands Organization for Health Research and Development to Dr. Vernoooy; RESCAR to Dr. Vernoooy; Grant 2000T036 from the Netherlands Heart Foundation to Dr. Delhaas; Grants HL47678 and HL66169 from the National Heart, and Lung Institute to Drs. Antzelevitch and Brugada; grants from the American Heart Association to Drs. Antzelevitch and Brugada; and NYS and Florida Grand Lodges F.&A.M and the Ramon Brugada Sr. Foundation to Dr. Brugada.

Introduction

Traumatic brain injury is the leading cause of death among young adults in the industrialized world. Following injury, propofol is commonly used in the intensive care unit to facilitate mechanical ventilation and decrease cerebral metabolic demand. Several randomized clinical trials have suggested that propofol is a safe and effective intravenous agent for the induction and maintenance of general anesthesia.^{1,2}

Despite its commendable record, there have been scattered reports of an association of propofol use with sudden death. Since the 1992 description of unexplained death in five children,³ several cases of sudden death in critically ill patients undergoing long-term propofol infusion have been reported.⁴⁻⁶ A new clinical entity, termed *propofol infusion syndrome* (PRIS), describes the occurrence of a critical illness, cardiac failure, and rhabdomyolysis in the presence of high-dose infusion of propofol and catecholamines or steroids.⁷

Sudden death related to PRIS is presumed to be of cardiac origin because patients with PRIS develop malignant cardiac arrhythmias. However, despite this observation and increasing knowledge of the influences of propofol on the cardiovascular system, no causal relation between PRIS and sudden cardiac death has been established. Following a recent index case of PRIS in our hospital, this study identifies an easily recognizable ECG pattern that predicts imminent risk for sudden death in patients with PRIS and explores using a wedge model the basic mechanisms underlying arrhythmogenesis.

Methods

Clinical methods

A 15-year-old boy was transported to a regional hospital in The Netherlands after he had sustained a severe head injury. Propofol was started for sedation, and dopamine, norepinephrine, and mannitol were administered to maintain cerebral perfusion pressure. Six days after admission, the patient was transferred to the University Hospital Maastricht because he had developed rhabdomyolysis (myoglobinuria, creatine kinase 92,300 U/L), renal insufficiency (creatinine 265 μ mol/L), and ECG changes consistent with ST-segment elevation in the right precordial leads (Figure 1A). To identify whether our index patient suffered from an inherited form of ST-segment elevation linked to *SCN5A*,⁸ DNA was screened for mutations in the exons and intron-exon boundaries of this gene. The result of a flecainide challenge test was negative.

The patient showed remarkable similarities to those previously reported as being part of PRIS.^{4-6,9,10} We reanalyzed the clinical data reported by Cremer et al⁴ on 67 additional patients who were admitted to the neurosurgical intensive care unit of the University Medical Center Utrecht, The Netherlands, between 1996 and 1999 and had received long-term propofol infusion. Patients were alive, sedated, and mechanically ventilated in the intensive care unit 24 hours after they had sustained severe head injury. From among these 67 patients, seven cases of apparent PRIS were identified.

All 12-lead ECGs were reviewed. ECGs were available for the seven identified PRIS patients and for 30 of the remaining 60 non-PRIS patients. Medical records of all 67 patients were reviewed for propofol infusion rates, development of hyperkalemia, metabolic acidosis, and fever. Our index patient and the seven PRIS patients were analyzed for development of cardiac arrhythmias. From among the patients who developed the typical ECG pattern of ST-segment elevation in the right precordial leads, laboratory values and body temperature were analyzed at the time the ECG changes were recorded.

Wedge model

To assess whether the ECG pattern and arrhythmic manifestations during propofol infusion result from its direct actions on the ventricular myocardium, we evaluated the effects of the anesthetic in five arterially perfused right ventricular wedge preparations. The detailed methods used for isolation, perfusion, and recording of transmembrane activity have been previously reported.¹¹⁻¹⁴ In brief, trans-mural wedge preparations with dimensions of approximately 20-25 mm × 10-12 mm × 8-10 mm (transmural width) were dissected from the right ventricle of male dog hearts. The preparations were placed in a small tissue bath and arterially perfused with Tyrode's solution at 35°C to 36°C. The preparations were continuously endocardially stimulated at a basic cycle length of 2,000 ms. After a stabilization period of approximately 1 to 2 hours, transmural ECG and transmembrane action potentials were recorded simultaneously from epicardial (Epi) and midmyocardial (M) regions.

The effect of propofol phosphate (a gift from Dr. Sheldon Hendler, Vyrex Corporation) was assessed 45 to 60 minutes after addition of the drug to the perfusate at a concentration of 30 µg/mL (stock solution: 10 mg/mL of distilled water containing 50 µM MgCl₂ and 1 U/mL alkaline phosphatase [Sigma-Aldrich St Louis, MO]). To investigate the effect of high-dose propofol concentration, we used a concentration six to eight times higher than the concentration used for clinical practice.¹⁵ From pharmacokinetic studies,¹⁶ it is known that propofol infusion at a rate of 1.8 mg/kg/hr leads to a concentration of 1.0 µg/mL. A "normal" concentration, even for brain-injured patients, is 1.2 µg/mL, so 30 µg/mL is approximately 25 times more than the concentration used for clinical practice. The infusion rate for our patients was 7.6 mg/kg/hr. For these patients, 30 µg/mL is approximately six to eight times the concentration they had (assuming a linear relationship between infusion rate and concentration reached). In preliminary experiments, the electrophysiologic effects of propofol on the wedge preparation were tested at increasing propofol concentrations up to 100 µg/mL. Further studies in the presence of hyperkalemia (up to 8 mmol/L) and acidosis (down to pH 6.0) were performed to assess a possible concomitant effect of the metabolic abnormalities with propofol.

Statistical analysis

Data are presented as mean ± SD. Appropriate statistical testing of equality of proportion between the seven PRIS and 60 non-PRIS patients is not possible because the values from the PRIS patients were obtained at the moment the ECG changes were recorded, whereas values from the non-PRIS represent maximal values during admission.

Results

Clinical data

An ECG pattern of coved-type ST-segment elevation in the right precordial leads V₁ to V₃ was observed in six of the seven PRIS patients (Figure 2), and in none of the 30 unaffected patients for whom a 12-lead ECG recording was available. All patients with the ECG pattern developed ventricular arrhythmias that subsequently degenerated into irrecoverable ventricular fibrillation and death. At the time of recorded ECG pattern, the propofol infusion rate in the six PRIS patients was 7.9 ± 1.2 mg/kg/hr. All six patients died of ventricular arrhythmias within 10 ± 12 hours after identification of the ECG changes.

The only PRIS patient (no. 2) who did not exhibit the typical ECG changes did not develop ventricular arrhythmias. However, he developed a very fast supraventricular tachycardia with poor ventricular contractility that resulted in severe hypotension. Ventricular pacing was unsuccessful, and the patient died.

In the non-PRIS group, 11 deaths occurred from causes other than cardiac arrhythmias (neurologic in nine and multiorgan failure in two).

In patients for whom more than one ECG was available, the ST-segment elevation was the first ECG abnormality present (Figure 3). In the following hours, the patients progressively developed prolonged QT interval, idioventricular rhythm, and ventricular tachycardia/fibrillation. In the other three patients with ST elevation for whom only one ECG was available, the ECG already was abnormal with ST-segment elevation and prolonged QT, probably in a more advanced stage of electrical instability. This finding indicates that the development of ST-segment elevation in the precordial leads is the first warning sign of electrical instability and imminent sudden cardiac death.

In our index patient who developed the clinical signs of PRIS, propofol was stopped as soon as the ECG pattern was observed (Figure 1A). He did not develop any arrhythmias. The ST-segment elevations in leads V₁ to V₃ normalized over the following hours, and the patient survived (Figure 1B). In addition to the typical ECG pattern, he showed inverted T waves (Figure 1A) that persisted after withdrawal of propofol (Figure 1B). Genetic analysis of this patient revealed no mutations in the *SCN5A* gene.

Table 1 lists the distinctions between patients who developed PRIS and those who did not. The mean propofol infusion rate was 6.5 ± 0.8 mg/kg/hr in the seven patients who developed PRIS compared with 4.8 ± 1.5 mg/kg/hr in the 60 patients who did not. Laboratory findings showed that the Brugada-like ECG pattern was accompanied by a metabolic acidosis in two patients and elevated potassium levels in three patients. Four patients, including our index patient, had fever at the time the abnormal ECG was recorded.

Experimental data

Canine right ventricular wedge preparations were perfused with Tyrode's solution containing 30 µg/ml propofol. In one experiment, the concentration was increased up to 100 µg/mL. ST-segment elevation was not observed at any concentration of the drug, and no significant change in repolarization (action potential duration and QT interval) was detected (data not shown). Propofol-induced ST-segment elevation was not observed even in the presence of hyperkalemia and acidosis.

Discussion

An ECG pattern characterized by coved-type ST-segment elevation in the right precordial leads is observed in several diseases and may be induced by medications and external factors.¹⁷ The ECG pattern observed as the first sign of electrical instability in the majority of our cohort of PRIS patients is similar to a pattern that has received a great deal of attention over the past decade, that of an inherited sudden cardiac death syndrome known as the Brugada syndrome.¹⁸ Brugada syndrome affects young individuals with no previous history of cardiac disease. It is characterized by the presence of ST-segment elevation in leads V₁ to V₃, a structurally normal heart, and the occurrence of malignant arrhythmias. ST-segment elevation in the Brugada syndrome is thought to result from a rebalancing of the ion channel currents active at the end of phase 1 of the epicardial ventricular action potential.¹⁹ The right ventricular outflow tract is predisposed to development of these ECG changes because of the presence of a more prominent transient outward potassium current in right vs left ventricular epicardial²⁰ and midmyocardial²¹ cells. This situation can lead to loss of the action potential dome in epicardium but not in endocardium, resulting in the development of a marked transmural dispersion of repolarization and refractoriness, which is responsible for ST-segment elevation as well as creation of a vulnerable window during which an extrasystole generated by the same substrate can induce ventricular tachycardia.

The ST-segment elevation and electrical instability of the myocardium can result from an outward shift in the balance of currents active at the end of phase 1 of the action potential. Vagotonic agents, I_{K-ATP} activators, and hyperkalemia can facilitate this process by augmenting outward currents,²² whereas sodium channel blockers, cocaine, antidepressants, ischemia, acidosis, and antihistaminics such as terfenadine can accomplish this by reducing inward currents.²² Loss of function or mutations in the *SCN5A* gene, responsible for the Brugada syndrome, shift the balance of current by reducing sodium channel current density and/or changing ion channel kinetics. A febrile state also has been shown to facilitate ST-segment elevation in the Brugada syndrome because of its ability to reduce sodium channel current.²³ A reduction in inward currents causes ST elevation more readily in the right ventricle because of the prominence of the transient outward current (I_{to}) in this part of the heart, accounting for its manifestation in the right pre-cordial leads recorded from patients with Brugada syndrome.²⁰

Propofol is one of the most common anesthetics used in present-day medicine. Its relatively short half-life makes it highly desirable for use in short-duration surgeries and for quick recoveries. The anesthetic usually is free of significant side effects. However, high doses of propofol given for several days to patients with severe head injury can be associated with sudden death.¹⁰ The term *propofol infusion syndrome* has been proposed to describe this ill-fated outcome. The development of an ECG pattern of ST-segment elevation in leads V_1 to V_3 in our cohort of patients with PRIS preceding the development of sudden cardiac death suggests that the mechanism underlying the arrhythmogenesis in PRIS is similar to that responsible for ventricular arrhythmias in the Brugada syndrome. Six of seven patients who died suddenly developed the ECG pattern just before precipitation of the malignant arrhythmias. These data are consistent with a 2001 case report in which a patient with PRIS developed the ECG pattern before dying of ventricular arrhythmias.⁵ The ECG pattern was not recognized at the time.

The role of propofol in the development of arrhythmias is unclear. The fact that the anesthetic was withdrawn as soon as the ECG pattern was observed in the only patient who survived points to a possible role of the anesthetic in arrhythmogenesis. Various experimental studies have shown several effects of propofol on the myocardium. Propofol uncouples oxidative phosphorylation and energy production,²⁴ impairs mitochondrial respiration,²⁵ increases acetylcholine receptor activity,²⁶ attenuates beta-adrenergic signal transduction,²⁷ and inhibits cardiac L-type calcium current resulting in reduced myocardial contractility.²⁸

However, our studies involving the wedge preparation indicate that propofol-induced ST-segment elevation is not the result of a direct effect of the drug during short-term exposure to high concentrations of propofol. It is possible that a metabolite, the presence of electrolyte abnormalities, acidosis, fever, or the combination with other medications contributes to development of the ECG pattern and arrhythmias. Severe metabolic acidosis, observed in two of the sudden death victims, inhibits sodium and calcium inward currents.²⁹⁻³² The presence of a febrile state in four patients could likewise reduce inward sodium channel current by speeding up inactivation of the channel.²³ Hyperkalemia in three patients was effective in augmenting outward currents. Thus, it is possible that high-dose propofol has an indirect effect, shifting the balance of current in the outward direction and facilitating the development of ST-segment elevation and the substrate for reentrant arrhythmias. Factors such as previous cardiac history or myocardial ischemia likely did not play a role in these cases because of the young age of the patients (mean 27 years). It is also unlikely that all eight PRIS patients had a primary genetic defect causing the phenotype.

Although the pathophysiologic mechanism remains unclear, the data from our cohort of patients indicate that the development of ST-segment elevation in the right precordial leads is the first warning sign of electrical instability and is a predictor of imminent sudden death.

Study limitations

Patients with PRIS are severely ill. Fever and multiorgan damage cause important metabolic and electrolyte disturbances. Use of vasopressors, inotropes, and high-dose sedation complicates the understanding of arrhythmogenesis. Mimicking all these parameters in experimental models is extremely difficult. Furthermore, the wedge preparation is reliable for 6 to 8 hours, whereas the patients developed PRIS after 48 hours of propofol infusion.

The preliminary data in one patient indicate that stopping propofol might be helpful. This finding requires validation in more patients in whom the ECG pattern of ST-segment elevation in the precordial leads and PRIS are identified. The extent to which this finding applies to other anesthetics and whether the dire outcome applies principally to patients with severe head injury receiving high-dose propofol are not known.

Conclusion

Our data indicate that development of the ECG pattern of ST-segment elevation in leads V₁ to V₃ is the first indicator of electrical instability and high risk for imminent sudden death. The data are based on a cohort of individuals with PRIS. Whether this finding applies to other patient cohorts is unclear, but the association of sudden death and the acquired ECG pattern has been observed in other disease states.¹⁸

Our data suggest that ECG monitoring in patients receiving high-dose propofol can avert sudden cardiac death by alerting the physician to impending cardiac rhythm disturbances following the appearance of marked ST-segment elevation in the right precordial leads.

References

1. Aitkenhead AR. Propofol and intensive care. *Lancet* 1989;2:1281. [PubMed: 2573797]
2. Ronan KP, Gallagher TJ, George B, Hamby B. Comparison of propofol and midazolam for sedation in intensive care unit patients. *Crit Care Med* 1995;23:286–293. [PubMed: 7867354]
3. Parke TJ, Stevens JE, Rice AS, Greenaway CL, Bray RJ, Smith PJ, Waldmann CS, Verghese C. Metabolic acidosis and fatal myocardial failure after propofol infusion in children: five case reports. *BMJ* 1992;305:613–616. [PubMed: 1393073]
4. Cremer OL, Moons KG, Bouman EA, Kruijswijk JE, de Smet AM, Kalkman CJ. Long-term propofol infusion and cardiac failure in adult head-injured patients. *Lancet* 2001;357:117–118. [PubMed: 11197401]
5. Cannon ML, Glazier SS, Bauman LA. Metabolic acidosis, rhabdomyolysis, and cardiovascular collapse after prolonged propofol infusion. *J Neurosurg* 2001;95:1053–1056. [PubMed: 11765823]
6. Ernest D, French C. Propofol infusion syndrome—report of an adult fatality. *Anaesth Intensive Care* 2003;31:316–319. [PubMed: 12879680]
7. Vasile B, Rasulo F, Candiani A, Latronico N. The pathophysiology of propofol infusion syndrome: a simple name for a complex syndrome. *Intensive Care Med* 2003;29:1417–1425. [PubMed: 12904852]
8. Chen Q, Kirsch GE, Zhang D, Brugada R, Brugada J, Brugada P, Potenza D, Moya A, Borggrefe M, Breithardt G, Ortiz-Lopez R, Wang Z, Antzelevitch C, O'Brien RE, Schulze-Bahr E, Keating MT, Towbin JA, Wang Q. Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. *Nature* 1998;392:293–296. [PubMed: 9521325]
9. Hanna JP, Ramundo ML. Rhabdomyolysis and hypoxia associated with prolonged propofol infusion in children. *Neurology* 1998;50:301–303. [PubMed: 9443502]

10. Stelow EB, Johari VP, Smith SA, Crosson JT, Apple FS. Propofol-associated rhabdomyolysis with cardiac involvement in adults: chemical and anatomic findings. *Clin Chem* 2000;46:577–581. [PubMed: 10759487]
11. Yan GX, Antzelevitch C. Cellular basis for the normal T wave and the electrocardiographic manifestations of the long-QT syndrome. *Circulation* 1998;98:1928–1936. [PubMed: 9799215]
12. Shimizu W, Antzelevitch C. Cellular basis for the ECG features of the LQT1 form of the long-QT syndrome: effects of beta-adrenergic agonists and antagonists and sodium channel blockers on transmural dispersion of repolarization and torsade de pointes. *Circulation* 1998;98:2314–2322. [PubMed: 9826320]
13. Shimizu W, Antzelevitch C. Sodium channel block with mexiletine is effective in reducing dispersion of repolarization and preventing torsade des pointes in LQT2 and LQT3 models of the long-QT syndrome. *Circulation* 1997;96:2038–2047. [PubMed: 9323097]
14. Emori T, Antzelevitch C. Cellular basis for complex T waves and arrhythmic activity following combined I(Kr) and I(Ks) block. *J Cardiovasc Electrophysiol* 2001;12:1369–1378. [PubMed: 11797994]
15. Swinhoe CF, Peacock JE, Glen JB, Reilly CS. Evaluation of the predictive performance of a "Diprifusor" TCI system. *Anaesthesia* 1998;53:61–67. [PubMed: 9640119]
16. McMurray TJ, Johnston JR, Milligan KR, Grant IS, Mackenzie SJ, Servin F, Janvier G, Glen JB. Propofol sedation using Diprifusor target-controlled infusion in adult intensive care unit patients. *Anaesthesia* 2004;59:636–641. [PubMed: 15200536]
17. Wilde AA, Antzelevitch C, Borggrefe M, Brugada J, Brugada R, Brugada P, Corrado D, Hauer RN, Kass RS, Nademanee K, Priori SG, Towbin JA. Proposed diagnostic criteria for the Brugada syndrome: consensus report. *Circulation* 2002;106:2514–2519. [PubMed: 12417552]
18. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. *J Am Coll Cardiol* 1992;20:1391–1396. [PubMed: 1309182]
19. Antzelevitch C. The Brugada syndrome: ionic basis and arrhythmia mechanisms. *J Cardiovasc Electrophysiol* 2001;12:268–272. [PubMed: 11232628]
20. Di Diego JM, Sun ZQ, Antzelevitch C. I(to) and action potential notch are smaller in left vs. right canine ventricular epicardium. *Am J Physiol* 1996;271:H548–H561. [PubMed: 8770096]
21. Volders PG, Sipido KR, Carmeliet E, Spatjens RL, Wellens HJ, Vos MA. Repolarizing K⁺ currents I_{TO1} and I_{Ks} are larger in right than left canine ventricular midmyocardium. *Circulation* 1999;99:206–210. [PubMed: 9892584]
22. Antzelevitch C, Brugada P, Brugada J, Brugada R, Towbin JA, Nademanee K. Brugada syndrome: 1992-2002: a historical perspective. *J Am Coll Cardiol* 2003;41:1665–1671. [PubMed: 12767644]
23. Dumaine R, Towbin JA, Brugada P, Vatta M, Nesterenko DV, Nesterenko VV, Brugada J, Brugada R, Antzelevitch C. Ionic mechanisms responsible for the electrocardiographic phenotype of the Brugada syndrome are temperature dependent. *Circ Res* 1999;85:803–809. [PubMed: 10532948]
24. Branca D, Roberti MS, Lorenzin P, Vincenti E, Scutari G. Influence of the anesthetic 2,6-diisopropylphenol on the oxidative phosphorylation of isolated rat liver mitochondria. *Biochem Pharmacol* 1991;42:87–90. [PubMed: 2069600]
25. Schenkman KA, Yan S. Propofol impairment of mitochondrial respiration in isolated perfused guinea pig hearts determined by reflectance spectroscopy. *Crit Care Med* 2000;28:172–177. [PubMed: 10667518]
26. Yamamoto S, Kawana S, Miyamoto A, Ohshika H, Namiki A. Propofol-induced depression of cultured rat ventricular myocytes is related to the M2-acetylcholine receptor-NO-cGMP signaling pathway. *Anesthesiology* 1999;91:1712–1719. [PubMed: 10598614]
27. Kurokawa H, Murray PA, Damron DS. Propofol attenuates beta-adrenoreceptor-mediated signal transduction via a protein kinase C-dependent pathway in cardiomyocytes. *Anesthesiology* 2002;96:688–698. [PubMed: 11873046]
28. Zhou W, Fontenot HJ, Liu S, Kennedy RH. Modulation of cardiac calcium channels by propofol. *Anesthesiology* 1997;86:670–675. [PubMed: 9066334]

29. Watanabe I, Johnson TA, Buchanan J, Engle CL, Gettes LS. Effect of graded coronary flow reduction on ionic, electrical, and mechanical indexes of ischemia in the pig. *Circulation* 1987;76:1127–1134. [PubMed: 3664997]
30. Gilliam FR III, Rivas PA, Wendt DJ, Starmer CF, Grant AO. Extra-cellular pH modulates block of both sodium and calcium channels by nicardipine. *Am J Physiol* 1990;259:H1178–H1184. [PubMed: 2171365]
31. Fan Z, Furukawa T, Sawanobori T, Makielski JC, Hiraoka M. Cytoplasmic acidosis induces multiple conductance states in ATP-sensitive potassium channels of cardiac myocytes. *J Membr Biol* 1993;136:169–179. [PubMed: 8107073]
32. Coraboeuf E, Deroubaix E, Coulombe A. Acidosis-induced abnormal repolarization and repetitive activity in isolated dog Purkinje fibers. *J Physiol (Paris)* 1980;76:97–106. [PubMed: 6772764]

Figure 1.

A: ECG of our index patient at the time of diagnosis of propofol infusion syndrome. Note ST-segment elevation in right precordial lead V₂, consistent with a typical Brugada-like ECG pattern. **B:** ECG of index patient 12 hours after withdrawal of propofol. Note that, despite the still abnormal ST segments, inverted T waves, and prolonged QT interval, the ST segment in lead V₂ is dramatically decreased compared with the previous ECG (panel A).

Figure 2.

Twelve-lead ECGs of the seven patients with propofol infusion syndrome in the neurosurgical intensive care unit. With the exception of patient 2, all patients show a coved-type ST-segment elevation in the right precordial leads.

Figure 3.

Serial ECGs of three of the patients with propofol infusion syndrome. ST-segment elevation in precordial leads V_1 to V_3 precedes any other ECG abnormality. After development of ST-segment elevation over the following hours, the ECG degenerates into wide-complex tachycardia, idioventricular rhythm, and ventricular fibrillation.

Table 1
Clinical characteristics of the index patient (A), PRIS patients, and non-PRIS patients

Patient characteristic	Index patient (A)	PRIS patients							Non-PRIS patients
		1	2	3	4	5	6	7	
Age (yr):gender (M/F)	15:M	17:F	44:M	17:M	20:F	24:M	40:M	31:F	33±11
Brugada-like ECG pattern	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	0/30
Ventricular tachyarrhythmia	No	Yes	No	Yes	Yes	Yes	Yes	Yes	0/30
Mean propofol dose (mg/kg/hr)	4.5	7.3	5.7	6.6	5.5	7.4	5.8	6.9	4.8±1.5
Hyperkalemia (>5.5 mmol/L)	No	Yes	No	No	No	No	Yes	Yes	6/60
Metabolic acidosis (base excess ≤8 mmol/L)	No	No	No	No	Yes	No	No	Yes	3/60
Fever (> 38.5°C)	Yes	Yes	Yes	No	No	No	Yes	No	35/60
Death	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11/60

Values from the patients with propofol infusion syndrome (PRIS) were obtained at the moment the ECG changes were recorded, whereas values from the non-PRIS patients represent maximal values during admission. Statistical analysis compares the 60 non-PRIS patients with the seven PRIS patients.