ANESTHESIOLOGY

Electrocardiographic Effects of Propofol *versus* Etomidate in Patients with Brugada Syndrome

Panagiotis Flamée, M.D., Varnavas Varnavas, M.D., Ph.D., Wendy Dewals, M.D., Hugo Carvalho, M.D., Wilfried Cools, Ph.D., Jigme Tshering Bhutia, M.D., Stefan Beckers, M.D., Vincent Umbrain, M.D., Ph.D., Christian Verborgh, M.D., Ph.D., Patrice Forget, M.D., Ph.D., Gian-Battista Chierchia, M.D., Ph.D., Pedro Brugada, M.D., Ph.D., Jan Poelaert, M.D., Ph.D., Carlo de Asmundis, M.D., Ph.D.

ANESTHESIOLOGY 2020; 132:440–51

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Brugada syndrome is an inherited cardiac ion channel disorder that places patients at increased risk of cardiac arrhythmias including those resulting in sudden cardiac death.
- While there is concern that propofol use may trigger life-threatening ventricular arrhythmias in patients with Brugada syndrome, this has not been assessed using prospective randomized, controlled trials.

What This Article Tells Us That Is New

- This study was a prospective randomized double-blind trial that compared groups receiving propofol (n = 43) *versus* etomidate (n = 37) for induction of general anesthesia. No significant difference in electrocardiographic changes was observed between these two groups.

ABSTRACT

Background: Brugada Syndrome is an inherited arrhythmogenic disease, characterized by the typical coved type ST-segment elevation in the right precordial leads from V_1 through V_3. The BrugadaDrugs.org Advisory Board recommends avoiding administration of propofol in patients with Brugada Syndrome. Since prospective studies are lacking, it was the purpose of this study to assess the electrocardiographic effects of propofol and etomidate on the ST- and QRS-segments. In this trial, it was hypothesized that administration of propofol or etomidate in bolus for induction of anesthesia, in patients with Brugada Syndrome, do not clinically affect the ST- and QRS-segments and do not induce arrhythmias.

Methods: In this prospective, double-blinded trial, 98 patients with established Brugada syndrome were randomized to receive propofol (2 to 3 mg/kg^{-1}) or etomidate (0.2 to 0.3 mg/kg^{-1}) for induction of anesthesia. The primary endpoints were the changes of the ST- and QRS-segment, and the occurrence of new arrhythmias upon induction of anesthesia.

Results: The analysis included 80 patients: 43 were administered propofol and 37 etomidate. None of the patients had a ST elevation greater than or equal to 0.2 mV, one in each group had a ST elevation of 0.15 mV. An ST depression up to –0.15mV was observed eleven times with propofol and five with etomidate. A QRS-prolongation of 25% upon induction was seen in one patient with propofol and three with etomidate. This trial failed to establish any evidence to suggest that changes in either group differed, with most percentiles being zero (median [25th, 75th], 0 [0, 0] *vs.* 0 [0, 0]). Finally, no new arrhythmias occurred perioperatively in both groups.

Conclusions: In this trial, there does not appear to be a significant difference in electrocardiographic changes in patients with Brugada syndrome when propofol *versus* etomidate were administered for induction of anesthesia. This study did not investigate electrocardiographic changes related to propofol used as an infusion for maintenance of anesthesia, so future studies would be warranted before conclusions about safety of propofol infusions in patients with Brugada syndrome can be determined.

(ANESTHESIOLOGY 2020; 132:440–51)

Brugada syndrome is a distinct clinical entity that was first described in 1992 by Brugada and Brugada.[1] It is an inherited arrhythmogenic disease, characterized by the typical coved type ST-segment elevation in the right precordial leads from V_1 through V_3. It is associated with life threatening ventricular arrhythmias, syncope and sudden cardiac death. This channelopathy is based on mutations in myocardium ionic channel genes and is associated with increased propensity to develop malignant ventricular arrhythmia.[2,3] Based on its sodium channel blocking properties, propofol has been alleged to induce ventricular arrhythmias in patients with Brugada syndrome.

To date, there are no prospective studies demonstrating a causative relation with such arrhythmic events. Nevertheless, the advisory board of BrugadaDrugs.org suggests on the official website to avoid propofol administration in patients with established or suspected Brugada syndrome (https://www.brugadadrugs.org/avoid/; accessed March 1, 2012). The current strength of recommendation is class IIa (there is conflicting evidence and/or divergence of opinion about the drug, but the weight of evidence/opinion is in favor of a potentially arrhythmic effect in Brugada syndrome

This article is accompanied by an editorial on p. 411. Part of this work has been presented at Euroanaesthesia 2018 in Copenhagen, Denmark, on July 4, 2018.

Submitted for publication October 24, 2018. Accepted for publication September 26, 2019. Published online first on November 13, 2019. From the Department of Anesthesiology and Perioperative Medicine (P.F., H.C., J.T.B., S.B., V.U., C.V., P.F., J.P.) and the Heart Rhythm Management Center, Center of Heart and Vascular Disease (V.V., W.D., G-B.,C., P.B., C.d.A.), University Hospital Brussels; and the Interfaculty Center Data processing & Statistics (W.C.), Free University Brussels, Laarbeeklaan, Brussels, Belgium.

 Anesthesiology 2020; 132:440–51. DOI: 10.1097/ALN.0000000000003030

patients). Administration of propofol remains thus a matter of debate, whether it can trigger malignant arrhythmias in patients with Brugada syndrome.

The current study aimed to compare the electrocardiographic effects of propofol *versus* etomidate on the ST- and QRS-segments upon induction of anesthesia in patients with Brugada syndrome. Moreover, occurrence of new arrhythmias during induction of anesthesia and at the postanesthesia care unit was assessed.

Materials and Methods

Design

This study was registered with European Clinical Trials on March 29, 2012 (identifier: NCT 2012-000584-25). Ethical approval for the study protocol (Registration No.: 2012/027) was provided by the Ethical Committee (Institutional Review Board) of the University Hospital of Brussels, Brussels, Belgium (Dr. P. Devroey, M.D., Ph.D.) on February 16, 2012. With Institutional Review Board approval and written informed consent from each participating patient, a double-blind randomized trial was conducted to analyze the electrocardiographic effects of propofol and etomidate in patients with established Brugada syndrome.

Population

Patients with established Brugada syndrome, scheduled for elective surgery, were enrolled by the principal investigator or a member of the study investigators in the University Hospital of Brussels between March 2012 and March 2018. Patients were diagnosed with Brugada syndrome according to the modified task force criteria. When a type 1 electrocardiogram was registered with greater than or equal to 2-mm ST elevation in one or more right precordial or inferolateral leads, either spontaneously or during a sodium-channel blocker challenge, patients were diagnosed with Brugada syndrome.[4–6] All patients older than 1 yr who had an American Society of Anesthesiologists Physical Status classification II to III with established Brugada syndrome were included. There was no exclusion criterion for type of surgery. Patients were only excluded when one of the following criteria were met: a specific allergy or sensitivity for propofol or one of its emulsion components (Propolipid 1%; Fresenius Kabi, Austria GmbH), a specific allergy for Etomidate-Lipuro (B Braun, Germany), fever, ionic imbalances, and any other condition that rendered the patient unfit to undergo elective surgery.

The allocation sequence was concealed from the researchers enrolling and assessing participants through third-party allocation. A research assistant created a computer-generated simple randomization list, with Microsoft Excel (version 14.7.7). A research nurse or a research assistant assessed the patients during preoperative visits for eligibility and obtained the informed consent for enrollment. A dedicated research nurse not involved in enrolling patients and obtaining informed consents revealed the next randomization assignment to the anesthesiologist responsible for the surgical case and anesthesia before induction.

Evidently, the anesthesiologists were not blinded for the induction agent. The cardiologists, who performed the analysis of the electrocardiograms were not present during anesthesia induction and the electrocardiogram acquisition, were therefore considered blinded. Moreover, all electrocardiographic measurements occurred after complete data collection, before unblinding the groups.

Modified 12-Lead Electrocardiogram

Electrocardiographic registrations were performed in presence of the principal investigator in the majority of the cases, or one of the participating researchers, ensuring consistency in data collection. Modified 12-lead electrocardiograms, identical to ones acquired during pharmacologic provocation tests with ajmaline, were obtained in this trial due to their higher sensitivity for ST-segment changes.[5,7–9] The setup consisted of two 12-lead electrocardiograms, one with leads at the third and one at the fourth intercostal space.

In each patient, a total of four modified 12-lead electrocardiograms were acquired. A set of two electrocardiograms was obtained in baseline conditions (before anesthesia induction) and another set of two electrocardiograms upon induction. All electrocardiograms were acquired using electrodes that were kept in position. The first set of electrocardiograms was acquired before induction of anesthesia, with patients in supine position and a stable heart rate. The second set of electrocardiograms was acquired 3 min after sufentanil and the hypnotic agent were injected in bolus through a good running intravenous line and when loss of consciousness was clinically confirmed through loss of eyelash reflex and well-tolerated mask ventilation. The investigators considered 3 min after injection of the hypnotic agent with subsequent clinical confirmation of loss of consciousness as a clinically relevant timepoint for the second set of electrocardiographic recordings. Although drug plasma concentrations were not assessed in this study, it was assumed that the hypnotic plasma concentration at the second timepoint (when the second set of electrocardiograms was taken) would still be high and would still exert its action on the myocardial receptors. The measurements derived from those two timepoints were then compared.

Additionally, patients were screened for the onset of new supraventricular (bradycardia, premature atrial contractions, atrial tachycardia, and atrial fibrillation) and ventricular arrhythmias (premature ventricular contractions and ventricular tachycardia).

A MAC 1600 Electrocardiographic Analysis System (GE Healthcare, USA) was used for electrocardiographic recording (25 mm/s, 0.5 to 50 Hz, 10 mm/mV).

Induction of Anesthesia

Anesthesia was induced as standard of care prescribes for elective surgical procedures. Preoxygenation with increased inspiratory air–oxygen gas mixture was maintained for at least 3 min before intravenous injection of the anesthetic agents. Patients received a sufentanil bolus (0.1 to 0.3 mcg/kg^{-1}) and immediately after a bolus of one of the hypnotics (propofol or etomidate), depending on the randomization sequence. The induction dose of propofol was 2 to 3 mg/kg^{-1}, whereas the dose of etomidate was 0.2 to 0.3 mg/kg^{-1}. In case the initial induction bolus of the hypnotic was judged to be insufficient (patient movement, not well-tolerated mask ventilation), an additional bolus was injected, without exceeding the maximal predetermined dose-range. The total administrated dose was logged. Lidocaine, pure or in mixture with propofol or etomidate, was excluded during the whole surgical procedure; as a sodium channel blocker it is listed as a drug preferably to be avoided in patients with Brugada syndrome (https://www.brugadadrugs.org/pref_avoid/). In case an endotracheal tube was deemed necessary, a muscle relaxant was administered. Anesthesia was maintained with the volatile anesthetic gas sevoflurane, targeting a minimal alveolar concentration[10] value of 1.0, in an oxygen–air mixture, aiming for an oxygen saturation of more than 97%. Normocapnic levels were attained through end-tidal carbon dioxide measurements and controlled mechanical ventilation. Furthermore, perioperative standard monitoring consisted of a five-lead electrocardiogram, pulse oximetry, and invasive or noninvasive blood pressure, at the discretion of the anesthesiologist. At the end of the surgery and after emergence from anesthesia, patients were transferred to the postanesthesia care unit for intensive monitoring until postanesthesia discharge criteria were met. Occurrence of new arrhythmias during their stay was registered.

Electrocardiographic Measurements

Two independent cardiologists (absent during the surgical interventions of the present study, and therefore blinded for the induction agent) individually assessed the registered electrocardiograms at the end of the trial. In case of inconclusive assessments between the first two cardiologists, a third experienced cardiologist was involved to reach a conclusion.

The primary endpoints of this clinical trial were the change of the ST- and QRS-segments and the occurrence of new arrhythmias upon induction of anesthesia. Simultaneously, additional measurements were performed, such as the Jp-segment (ST-segment at J-point) and the QT-interval (the longest QT-interval across leads) that was measured and corrected according to the Bazett (QTc_B) and Fridericia formula (QTc_{Fr}).[10,11] The JT-interval was also measured as the longest JT-interval and corrected according to the Bazett formula (JTc_B).

Moreover, estimation of transmural dispersion of repolarization, represented by $T_{(peak-end)}$ and $T_{(peak-end)}$ /QT, as indexes of ventricular arrhythmogenesis were calculated. The $T_{(peak-end)}$-interval was defined as the interval from the peak of the T-wave to the intersection of the tangent to the downslope of the T-wave and the isoelectric line in lead V_5 or to the nadir between the T- and U-waves (by presence of a U-wave).[12,13]

Sample Size Calculation

The authors hypothesized that with a mean ST elevation of 0 mm in the group of patients receiving etomidate, a mean ST elevation of 0.5 mm in the group of patients receiving propofol, and an SD of 0.5 mm, two equal groups of 37 subjects should be recruited, with a statistical power of 99% ($\beta = 0.01$) and a type I error or $\alpha = 0.05$ when performing a two-sided test of the difference between two independent groups. Avoiding the normality assumption and making use of the asymptotic relative efficiency, this number of observations would increase to 88. This conservative power was chosen to decrease the risk of a type II error, which may challenge the interest of the results in terms of safety of the tested intervention. Dropouts were anticipated; therefore, enrollment of patients was extended until a total of 98 was achieved. Note that sample size calculations became obsolete as data characteristics forced us to abandon strict statistical testing.

Statistical Analysis

The data showed an abundance of zero values and/or zero changes. Combined with the relatively small sample sizes, and the suggested differences in the distributions, no parametric model was fully suitable, and even non-parametric models largely failed. A mood test was considered, but it seemed hardly viable when often more than half of the values were zero. A permutation test was used in an attempt to present a tentative inference with a focus on the seventy-fifth percentile, to evaluate whether the measured differences in scores—before and after induction of anesthesia—would be different for the two groups of propofol and etomidate. On the other hand, the authors believe that the data, presented in a descriptive way with graphical visualizations, are very illustrative. Therefore, instead of focusing on statistical testing, visualizations were provided to demonstrate what is truly of clinical interest. Note that the *a priori* plan to compare averages was altered in response to peer review, in favor of a stronger focus on the descriptive analyzes and a tentative comparison between the groups using permutation tests.

Results

A total of 98 patients with established Brugada syndrome, scheduled for elective surgery under general anesthesia, were enrolled in this clinical trial over a 6-yr period. The

trial was conducted in accordance to the original trial protocol. The flowchart in figure 1 displays the path of the participants during the study. After assessment for eligibility, 98 patients were enrolled and randomized in two groups and received either propofol or etomidate. Upon allocation, 18 patients were lost during follow-up due to irreversible hardware failure of the hard disk drive that was used to store the acquired electrocardiograms (6 patients had received propofol and 12 etomidate). Since those electrocardiograms were irretrievable, no electrocardiographic analysis was possible. Consequently, a total of 80 patients were analyzed (43 patients received propofol and 37 etomidate). Demographic and clinical characteristics of the 80 analyzed patients are reported in table 1, revealing two homogenous and comparable groups. The mean age of the studied population was 45 ± 18 yr old (ranging from 13 to 92 yr). Forty-three (54%) patients were male. Baseline electrocardiograms before anesthesia showed that only four patients who received propofol *versus* one who received etomidate, had a spontaneous type 1 electrocardiographic pattern. The ajmaline challenge test was positive for 34 (92%) patients who received propofol *versus* 33 (89%) who received etomidate. The remaining patients underwent a drug challenge test in another center.

Of all 80 patients, none had an ST-segment increase by greater than or equal to 0.2 mV upon induction of anesthesia. As clearly displayed in figure 2, only 2 of all 80 patients had a ST elevation of maximum 0.15 mV in one of the four precordial leads (one patient received propofol and one etomidate). The majority of the patients had either no or a slight ST elevation (maximum of 0.10 mV). Note that none of the permutation tests offered much evidence to suggest that the ST-changes for both propofol and etomidate would differ. This was expected due to the large number of zero-changes with median and quartiles almost equal to zero ($P > 0.999$). This was clearly displayed with the box plots (containing the median, the first and third quartiles) which are compressed into one single line in all four leads except for ΔST-C_4V_2. In table 2 patients are ranked according to the size of the highest ST-segment change in all four precordial registrations. For cumulative visualization purposes, the corresponding ST-segment change categories were plotted in

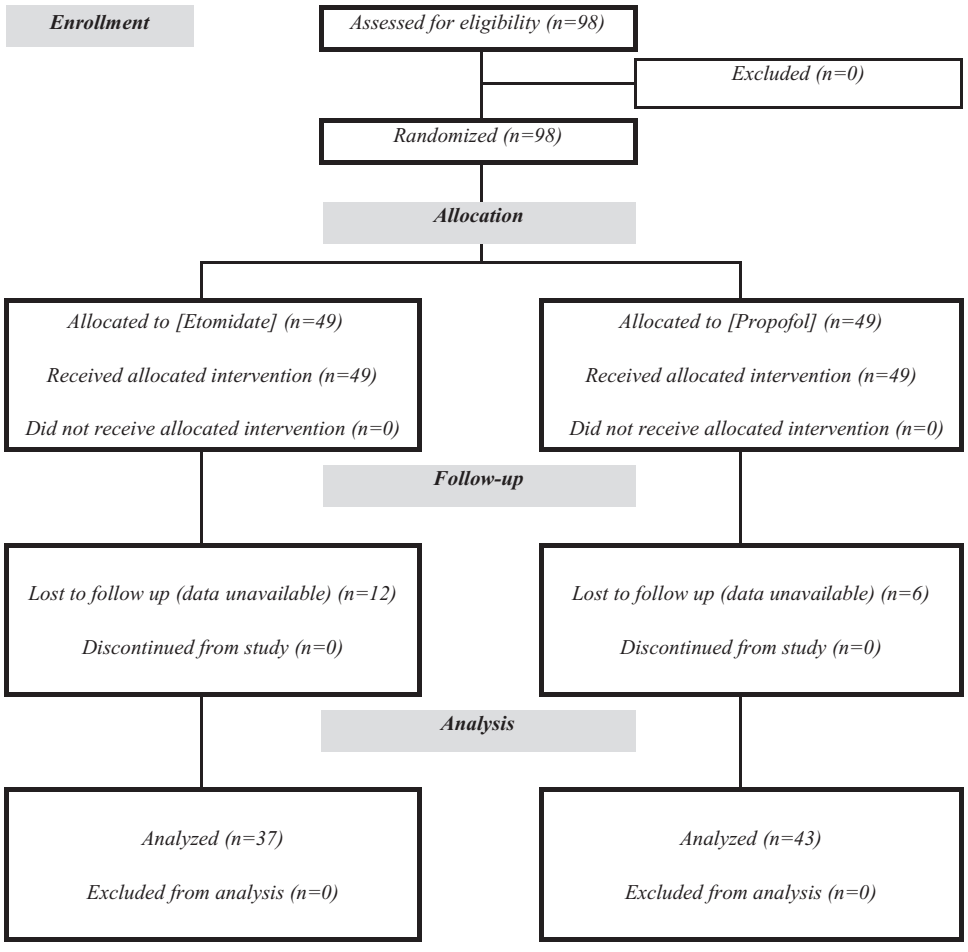

Fig. 1. Flow chart of screened and enrolled patients, throughout the trial.

Table 1. Demographic and Clinical Patient Characteristics

	Propofol (n = 43)	Etomidate (n = 37)
Age, yr	45 ± 18	45 ± 17
Male	27 (63%)	16 (43%)
Weight, kg	77 ± 22	77 ± 18
Height, cm	173 ± 11	172 ± 8
Body mass index, kg/cm^2	25,7 ± 5,7	25,9 ± 5,5
American Society of Anesthesiologists physical status classification II/III, n	32/11	28/9
Automated implantable defibrillator possession	33 (89%)	26 (70%)
Positive ajmaline test	34 (92%)	33 (89%)
Spontaneous type 1 electrocardiogram	4 (9 %)	1 (3%)
Syncope	16 (43%)	11(30%)
Sodium channel α subunit 5 mutation*	5 (29%)	5 (29%)

Data are presented as mean ± SD or numbers with percentage when applicable.

* Not all patients did consent for genetic screening, or results were not available or retrievable (%is referring to total available data [34 patients]).

figure 3A. Interestingly, the authors observed that in several patients the ΔST-segment was negative, indicating a reduction of the ST-segment upon induction of anesthesia. More specifically, both a decrease in the highest ST-segment as in the ST- at J-point were observed. In fact, 11 (25%) patients who received propofol *versus* 5 (13%) who received etomidate had a ST depression between −0.05 to −0.15 mV in at least in one precordial lead (table 2).

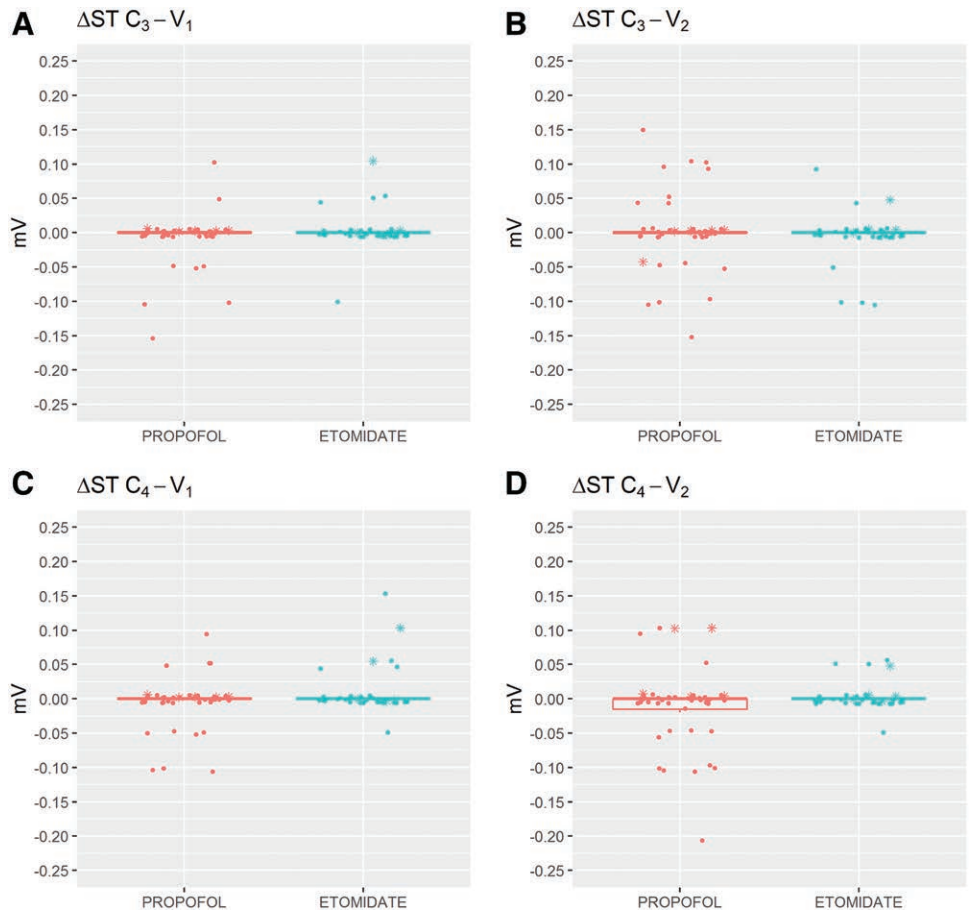

Fig. 2. Scatter plots with imposed median and first and third quartiles of ΔST-segment at the C_3V_1, C_3V_2, C_4V_1, and C_4V_2 leads. Note that the box plots containing the median, the first and third quartiles are compressed into one single line in all four leads except for C_4V_2. C_3V_1, third intercostal V_1 lead; C_3V_2, third intercostal V_2 lead; C_4V_1, fourth intercostal V_1 lead; C_4V_2, fourth intercostal V_2 lead.

Table 2. Distribution of Highest ST-Segment Change in All Precordial Leads

Highest ΔST (mV)	Propofol (n = 43)	Etomidate (n = 37)	Total (n = 80)
0.20 mV	0 (0%)	0 (0%)	0 (0%)
0.15 mV	1 (2.3%)	1 (2.7%)	2 (2.5%)
0.10 mV	10 (23.2%)	3 (8.1%)	13 (16.2%)
0.05 mV	6 (13.9%)	6 (16.2%)	12 (15.0%)
0.00 mV	15 (34.8%)	22 (59.4%)	37 (46.3%)
−0.05 mV	6 (14.0%)	1 (2.7%)	7 (8.8%)
−0.10 mV	3 (7.0%)	4 (10.8%)	7 (8.8%)
−0.15 mV	2 (4.6%)	0 (0%)	2 (2.5%)
−0.20 mV	0 (0%)	0 (0%)	0 (0%)

Data are presented as numbers (populational percentage within parenthesis).

Moreover, the majority of the patients had unchanged QRS-segments, while none of them exhibited a QRS prolongation greater than 30% in comparison to baseline values. One patient who had propofol and two who had etomidate administered had a QRS-augmentation of 25%. A QRS shortening was observed in eight patients who received propofol *versus* four who received etomidate. Similar to the permutation test for the ST-changes, the permutation test for the QRS-changes did not offer any evidence to suggest that the changes induced by propofol and etomidate would differ. This was also expected due to the large number of zero-changes. Figure 4 demonstrates those findings with the box plot (containing the median, the first and third quartiles) compressed into one single line.

Regarding the additionally recorded electrocardiographic measurements QT-, QTc_B, QTc_{Fr}, and JTc_B segments, all remained stable after induction of anesthesia in both groups (fig. 4 and 5). Similarly, the $T_{(peak-end)}$ and the $T_{(peak-end)}$/QT ratio, as indexes of arrhythmogenesis, did not change in a clinically relevant manner (fig. 5). Considering the variation of Jp-segment (ST-segment at J-point), regarded as a more sensitive parameter of repolarization disorders, no elevation higher than 0.1 mV was observed in the entire study population.[14] The highest registered ΔJp was 0.1 mV in seven patients who received propofol *versus* three who received etomidate. Note that the box plots containing the median, the first and third quartiles are also compressed into one single line in all four leads except for ΔJp_{32} (fig. 6).

Finally, no new ventricular or supraventricular arrhythmias were registered upon induction of anesthesia or at the postanesthesia care unit.

Discussion

This randomized trial was designed to assess effects of induction dose boluses of propofol *versus* etomidate in Brugada syndrome patients. Electrocardiographic changes for maintenance of anesthesia with continuous propofol infusion were not assessed. The results of the current study suggest that propofol is devoid of an arrhythmogenic profile during induction of anesthesia in patients with Brugada Syndrome based on the following observations: (1) an induction bolus of propofol did not induce a clinically relevant change in the ST- and QRS-segment; (2) the transmural dispersion of repolarization as index of arrhythmogenesis, estimated by $T_{(peak-end)}$ and the $T_{(peak-end)}$/QT-ratio, remained stable, as did the JTc_B-, QTc_B-, and QTc_{Fr}-intervals; and (3) absence of the occurrence of new ventricular or supraventricular arrhythmias from induction until discharge from the postanesthesia care unit. All electrocardiographic and clinical findings were comparable for propofol and etomidate.

Since the first description of the Brugada syndrome in 1992, there has been considerable progress in our knowledge on this entity. Mainly due to retrospective studies and case reports linking propofol to malignant arrhythmias in patients with Brugada syndrome, concerns about the administration of propofol in patients with this channelopathy have been raised.[15,16] The BrugadaDrugs.org advisory board advises to avoid the use of propofol in patients with established or suspected Brugada syndrome, or to use them only after extensive consideration.[17] On the other hand, several authors have already reported a safe administration of propofol for diagnostic and surgical procedures in patients with Brugada syndrome.[18–21] Thus, it is hard to establish a causative relation between propofol and malignant arrhythmias from the aforementioned reports. The theoretical pathophysiologic mechanism through which propofol (which has sodium-channel blocking properties) would interfere with the already altered function of cardiac sodium channels in patients with Brugada syndrome, would probably make more sense in patients with a mutation on the sodium voltage-gated channel alpha subunit 5 gene (SCN5A). Since this mutation only accounts for 11 to 18% of the patients with Brugada syndrome, it could be challenging to prove a causative relation.[22,23] To the best of our knowledge, the evidence for such a causative relation is nonexistent. In the current study only 10 patients had a positive SCN5A mutation; 5 patients received propofol and 5 received etomidate. A subpopulation analysis was not performed due to the small size of this subgroup.

Propofol (2,6-di-isopropylphenol) is probably the most commonly used intravenous anesthetic agent to induce anesthesia, having a well-known broad utility and safety profile. Besides indispensable in the surgical setting, it has been massively used for procedural sedations and diagnostic procedures, and has an undoubtedly important role in the intensive care unit.[24] A known hypersensitivity to propofol, albeit very rare, is the only absolute contraindication for administration. Its estimated incidence lies between 1:3,500 and 1:20,000 patients.[25]

A previously performed retrospective analysis in our center focusing on a homogenous cohort of high-risk Brugada syndrome patients with an automated implantable cardiac

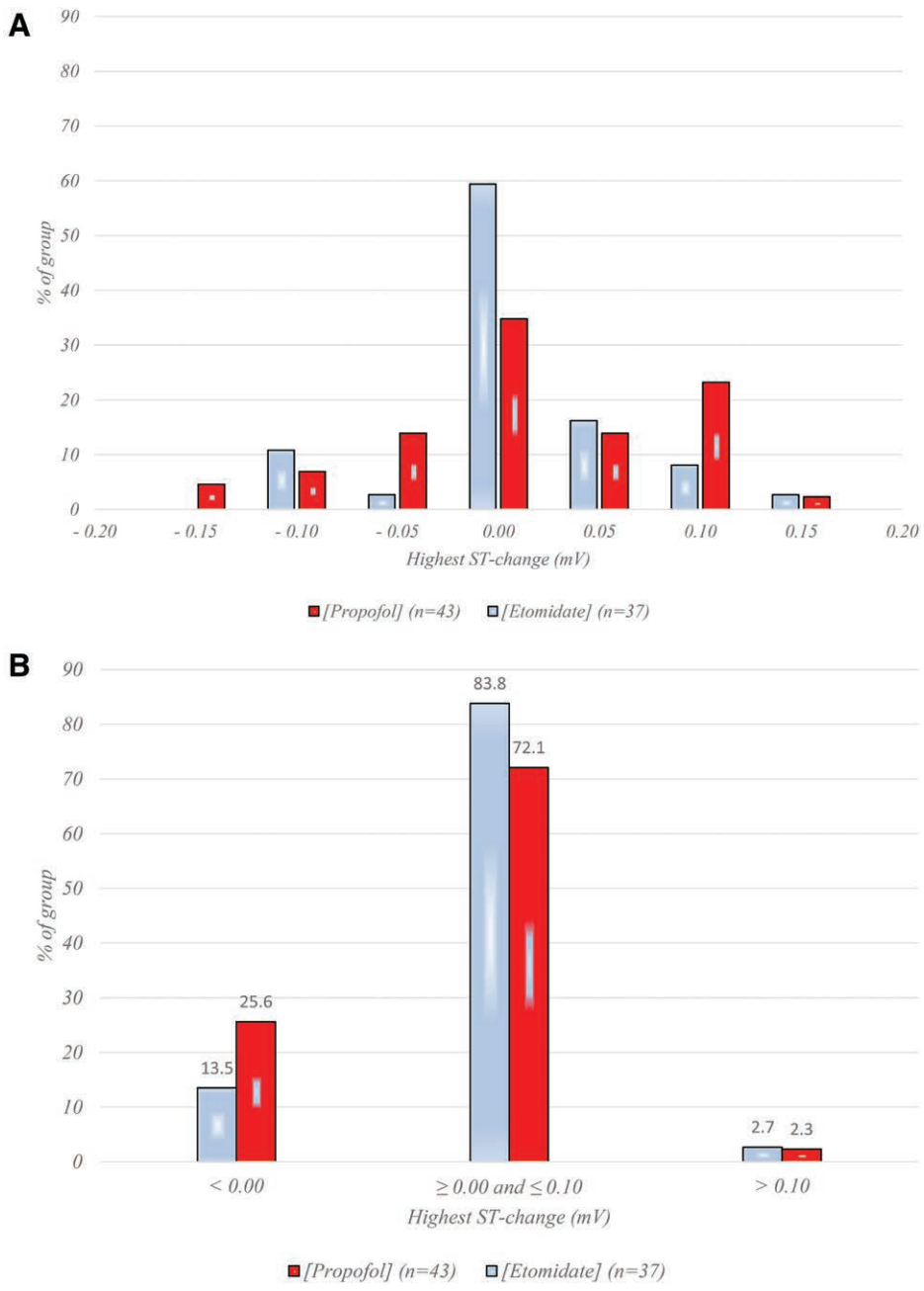

Fig. 3. Distribution of highest ST-change in all precordial leads. Part *A* is a visualization of ranking based on size of ST-change (as in table 2). Part *B* reveals an arbitrary ranking of the patients based on the highest ST-change in at least one precordial lead. Group 1: ΔST is greater than 0.10 mV; Group 2: ΔST is greater than or equal to 0.0 mV and less than or equal to 0.10 mV; Group 3: ΔST is less than 0.0 mV.

defibrillator who were undergoing general anesthesia with propofol already revealed no arrhythmia induction perioperatively.[18] With this prospective study we confirmed those findings, overcoming the limitations of the previous one.

Furthermore, some of the observations of the present study are in line with those of a recently published prospective clinical trial studying the effect of general anesthesia in high-risk Brugada Syndrome patients undergoing epicardial ablation. Concordantly, figures 2 and 6 illustrate a slight decrease in the highest ST- and Jp-segments in some patients (between −0.05 to −0.1 mV, with one outlier showing a depression of −0.2 mV). It was unanticipated to find that 16 (20.0%) of all patients had a ST depression upon induction of anesthesia (11 patients had propofol [25.6% of the propofol group] *vs.* 5 who had etomidate [13.5% of the etomidate group]; fig. 3, A and B).

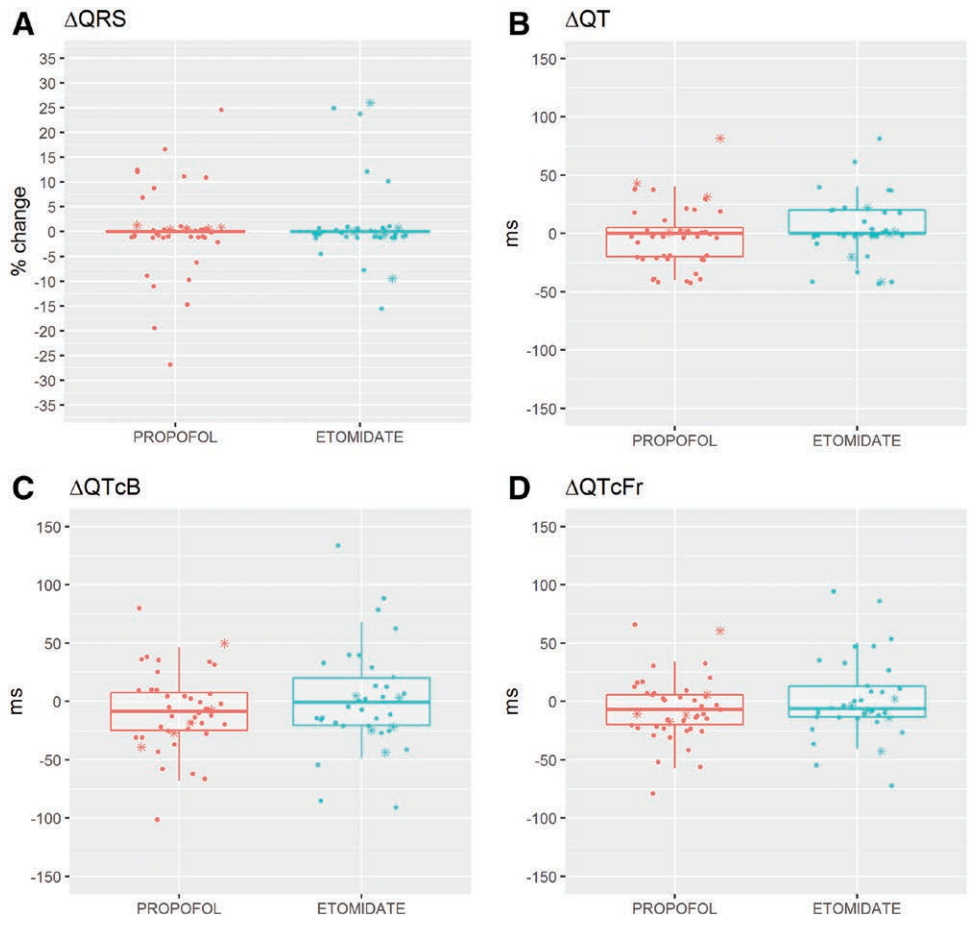

Fig. 4. Scatter plots with imposed median and first and third quartiles of the ΔQRS-, ΔQT-, ΔQTc_B-, and ΔQTc_{Fr}-segments. Note that the box plots containing the median, the first and third quartiles are compressed into one single line at the ΔQRS chart. ΔQTc_B, ΔQT corrected (Bazett); ΔQTc_{Fr}, ΔQT corrected (Fridericia).

The research group of Ciconte *et al.* similarly reported a statistically significant ST-segment reduction immediately after propofol induction, which persisted for 20 min, albeit anesthesia maintenance was achieved with the volatile anesthetic sevoflurane.[26] According to the well-known pharmacokinetic profile of propofol, one would expect the effect to have worn off by that time. Nevertheless, the authors revealed comparably reduced values. In the current study, the majority of the patients had no ST elevations at all or no clinically-relevant ST elevations, while some of the patients unexpectedly demonstrated a ST depression. These observations could suggest that propofol, etomidate, and sevoflurane could all directly or indirectly influence the ST-segment through a suppressed orthosympathetic adrenergic state.

A literature analysis reveals that some authors have reported antiarrhythmic effects of propofol.[27] Concordantly, our department has reported a case in which propofol exhibited antiarrhythmic properties in a patient with Brugada syndrome who developed incessant ventricular fibrillation during an ajmaline challenge. Upon administration, the young female patient instantly regained sinus rhythm and spontaneous circulation. Subsequently, she was sedated by means of continuous propofol infusion at the intensive care unit for several days without occurrence of malignant arrhythmias.[28]

A decrease of the ST-segment upon induction of anesthesia in some patients, albeit not significant (in both groups), is probably the most unanticipated finding in this trial, which coheres with those from the trial of Ciconte *et al.* The majority of our patients had no ST elevation. This might imply that the diagnosis of Brugada syndrome could be masked when patients are challenged with intravenous ajmaline under general anesthesia. In our university center, it is protocol to proactively contact and screen the family of the proband. When it concerns young patients, they are offered the choice to undergo the ajmaline challenge under sedation if they are too anxious. In most of those cases, this

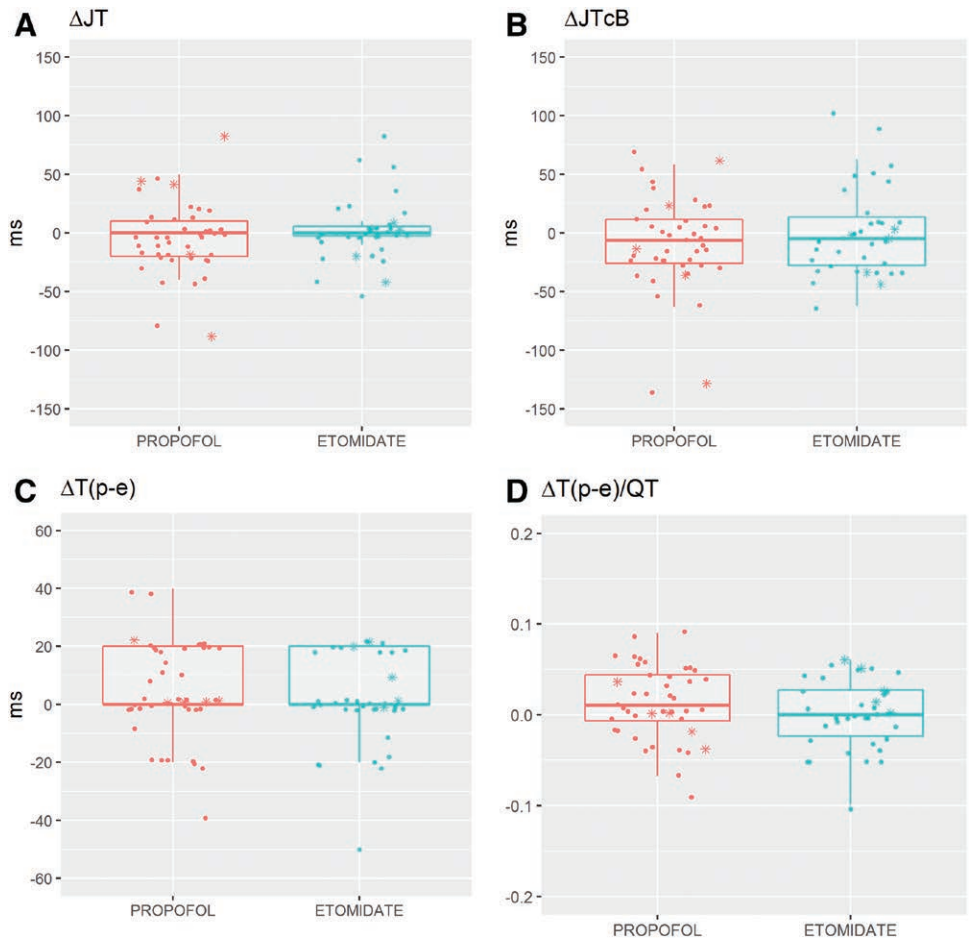

Fig. 5. Scatter plots with imposed median and first and third quartiles of the ΔJT-, ΔJTc_B-, $\Delta T_{(peak\text{-}end)}$-, and $\Delta T_{(peak\text{-}end)}$/QT-segments. JTcB, JTc_B corrected (Bazett).

is performed under sedation with propofol. Anesthesia for children under approximately 20 kg, without an intravenous line, is exclusively achieved by mask induction with the volatile anesthetic sevoflurane. Consequently, in both anesthetic techniques, and as observed in both aforementioned studies, the ST-segment could be affected, possibly interfering with the changes that are expected to be induced during the ajmaline provocation test. Unintentional tampering with the provocation test could therefore further complicate the challenging diagnostic path in patients suspected with Brugada syndrome.

Besides being conducted in a single center, the current study has some additional limitations. First, the authors would like to report that during the study's early collection phase it was decided to acquire additional measurements (ST-segment at J-point, QTc_B- and QTc_{Fr}-segment), and to determine the transmural dispersion of repolarization and the $T_{(peak\text{-}end)}$/QT-ratio as indexes of arrhythmogenesis. Although all measurements (primary endpoint and additional measurements) occurred before unblinding and data analysis, and even though this did not alter the drive or methodology of patient recruitment and data acquisition, the authors failed to register the aforementioned variables as secondary endpoints on the European Clinical Trials Database. Therefore, they are only described as additional measurements.

The data presented severe challenges for its analysis, especially because of the strong skewness, abundance of zero values and differences in variance. While a permutation test avoids relying on several of the assumptions that are clearly not adhered to, such models are much less flexible. The implied superiority testing did not show any significant difference, but also fails to argue for equality as an equivalence test would.

Considering the data collection, the authors regard the differential loss of electrocardiographic data in the study arms—due to a hard disk failure of the stored electrocardiograms—also as a limitation. Eighteen electrocardiograms were not accessible for measurements (6 patients had received propofol and 12 had received etomidate; fig. 1). Therefore, patient enrollment was extended.

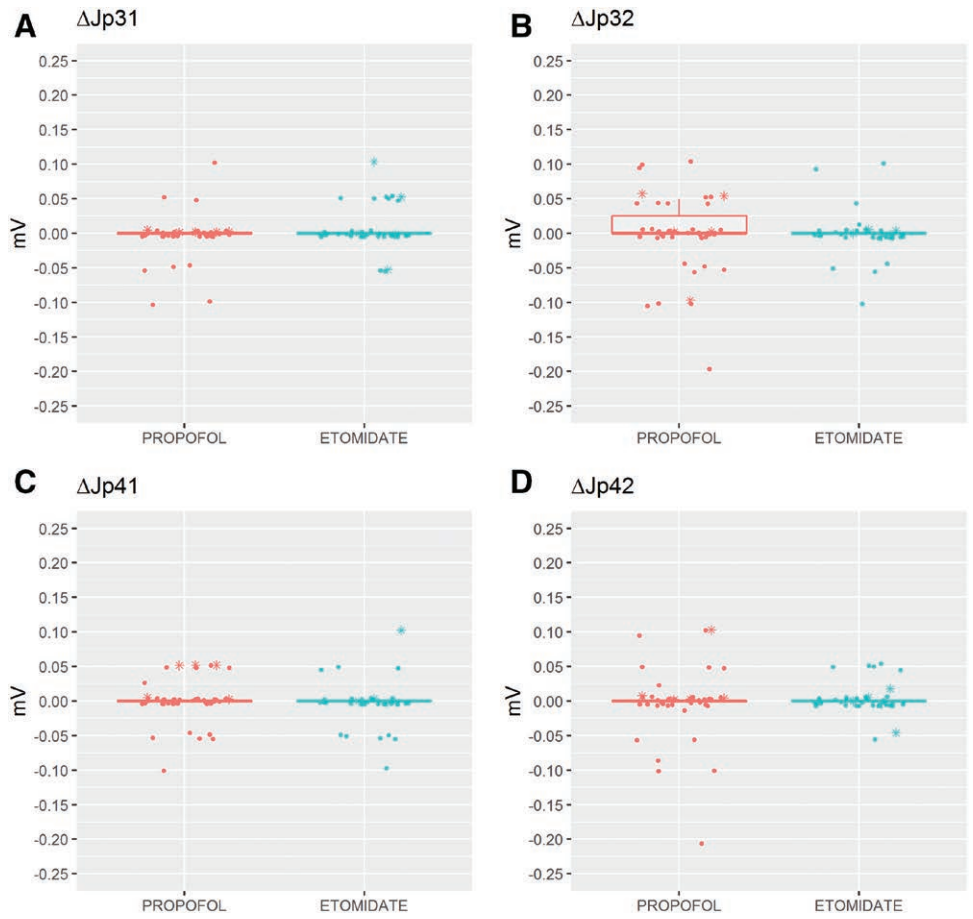

Fig. 6. Scatter plots with imposed median and first and third quartiles of ΔJp- at the C_3V_1, C_3V_2, C_4V_1, and C_4V_2 leads. Note that the box plots containing the median, the first and third quartiles are compressed into one single line in all four leads, except for C_3V_2. Jp-, ST at J-point; C_3V_1, third intercostal V_1 lead; C_3V_2, third intercostal V_2 lead; C_4V_1, fourth intercostal V_1 lead; C_4V_2, fourth intercostal V_2 lead.

Another limitation related to the noninvasive nature of this clinical study is that the authors were unable to correlate real-time plasma concentrations to the acquisition time of the electrocardiograms. Propofol plasma concentrations were expected to render some pharmacokinetic/dynamic variability at the moment of electrocardiogram acquisition. Nevertheless, the investigators considered that the timepoint of 3 min after injection of the hypnotic agent—with subsequent clinical confirmation of loss of consciousness of the patient—was a clinically relevant timepoint for the second set of electrocardiographic recordings. This sampling time frame assumed that plasma concentrations were still high, and that the hypnotic agent still exerted its action on the myocardial receptors. Obviously, this limitation is inherent to the challenge of assessing anesthetic depth as surrogate of plasma concentrations and could therefore have an influence on the electrocardiographic measurements. On the other hand, clinical evaluation of the patients and registration of the occurrence of new arrhythmias were not expected to be affected by such proceedings.

Additionally, it was assumed that the possible administration of a fluid bolus or a small dose of a vasoactive drug (ephedrine or phenylephrine)—often administered to counteract the reduction of the systemic vascular resistance—would not have a notable effect during the induction phase of anesthesia under investigation. Vasoactive drug administration was not prospectively collected and was therefore considered as a limitation.

Finally, it is important to bear in mind that propofol infusion syndrome (an uncommon, but well-described complication) can occur in any patient receiving high rates of propofol for a prolonged period.[29,30] Although several predisposing factors, such as critical or inflammatory illness or exogenous catecholamines and glucocorticoids, have been described as triggers of propofol infusion syndrome, there is still an ongoing debate about the exact underlying pathophysiologic mechanism.[31,32] Interestingly, the ST-coved type elevation that has been described in propofol infusion syndrome is very similar to the electrocardiographic pattern in Brugada syndrome. This could be simply a common

electrocardiographic finding. Up to date, there is no proven causative relation between these two entities.

In summary, the effect of propofol in bolus, for induction of anesthesia, in 43 patients with established Brugada syndrome was assessed and compared to 37 patients receiving etomidate. Maintenance of anesthesia was achieved with inhalational agents, the effect of which was beyond the scope of this study. The authors reinforce the statement of the advisory board of BrugadaDrugs.org, that vigilance is still required in patients receiving prolonged propofol infusions, as similarly required for all patients, when anesthesia is maintained with propofol. On the other hand, there was no electrocardiographic or clinical evidence to support the potential proarrhythmic risk of propofol as an anesthetic induction agent. The results of this study thus, suggest that an induction dose of propofol (2 to 3 mg/kg^{-1}) is safe for patients with Brugada syndrome. In the current trial, occurrence of electrocardiographic changes during continuous propofol infusion for sedation or maintenance of general anesthesia in patients with Brugada syndrome was not assessed. Future studies are warranted before conclusions about safety of propofol infusions in Brugada syndrome can be determined.

Research Support

Support was provided solely from institutional and departmental sources.

Competing Interests

The authors declare no competing interests.

Reproducible Science

Full protocol and raw data available at: panagiotis.flamee@me.com. Raw data available at: panagiotis.flamee@me.com.

Correspondence

Address correspondence to Dr. Flamée: Department of Anesthesiology and Perioperative Medicine, Vrije Universiteit Brussel, Universitair Ziekenhuis Brussel, Laarbeeklaan 101, 1090 Brussels, Belgium. E-mail: Panagiotis.Flamee@uzbrussel.be.

References

1. 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; 20:1391–6
2. Berne P, Brugada J: Brugada syndrome 2012. Circ J 2012; 76:1563–71
3. Lippi G, Montagnana M, Meschi T, Comelli I, Cervellin G: Genetic and clinical aspects of Brugada syndrome: An update. Adv Clin Chem 2012; 56:197–208
4. Wilde AA, Antzelevitch C, Borggrefe M, Brugada J, Brugada R, Brugada P, Corrado D, Hauer RN, Kass RS, Nademanee K, Priori SG, Towbin JA; Study Group on the Molecular Basis of Arrhythmias of the European Society of Cardiology: Proposed diagnostic criteria for the Brugada syndrome: Consensus report. Circulation 2002; 106:2514–9
5. Antzelevitch C, Brugada P, Borggrefe M, Brugada J, Brugada R, Corrado D, Gussak I, LeMarec H, Nademanee K, Perez Riera AR, Shimizu W, Schulze-Bahr E, Tan H, Wilde A: Brugada syndrome: Report of the second consensus conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. Circulation 2005; 111:659–70
6. Sieira J, Brugada P: The definition of the Brugada syndrome. Eur Heart J 2017; 38:3029–34
7. Shimizu W, Matsuo K, Takagi M, Tanabe Y, Aiba T, Taguchi A, Suyama K, Kurita T, Aihara N, Kamakura S: Body surface distribution and response to drugs of ST segment elevation in Brugada syndrome: Clinical implication of eighty-seven-lead body surface potential mapping and its application to twelve-lead electrocardiograms. J Cardiovasc Electrophysiol 2000; 11:396–404
8. Nakazawa K, Sakurai T, Takagi A, Kishi R, Osada K, Miyazu O, Watanabe Y, Miyake F: Clinical significance of electrocardiography recordings from a higher intercostal space for detection of the Brugada sign. Circ J 2004; 68:1018–22
9. Makarawate P, Chaosuwannakit N, Ruamcharoen Y, Panthongviriyakul A, Pongchaiyakul C, Tharaksa P, Sripo T, Sawanyawisuth K: Prevalence and associated factors of early repolarization pattern in healthy young northeastern Thai men: A correlation study with Brugada electrocardiography. J Arrhythm 2015; 31:215–20
10. Luo S, Michler K, Johnston P, Macfarlane PW: A comparison of commonly used QT correction formulae: The effect of heart rate on the QTc of normal ECGs. J Electrocardiol 2004; 37 Suppl:81–90
11. Bazett HC: The time relations of the blood-pressure changes after excision of the adrenal glands, with some observations on blood volume changes. J Physiol 1920; 53:320–39
12. Panikkath R, Reinier K, Uy-Evanado A, Teodorescu C, Hattenhauer J, Mariani R, Gunson K, Jui J, Chugh SS: Prolonged Tpeak-to-tend interval on the resting ECG is associated with increased risk of sudden cardiac death. Circ Arrhythm Electrophysiol 2011; 4:441–7

13. Antzelevitch C, Yan GX, Shimizu W: Transmural dispersion of repolarization and arrhythmogenicity: The Brugada syndrome *versus* the long QT syndrome. J Electrocardiol 1999; 32 Suppl:158–65
14. Surawicz B, Macfarlane PW: Inappropriate and confusing electrocardiographic terms: J-wave syndromes and early repolarization. J Am Coll Cardiol 2011; 57:1584–6
15. Junttila MJ, Gonzalez M, Lizotte E, Benito B, Vernooy K, Sarkozy A, Huikuri HV, Brugada P, Brugada J, Brugada R: Induced Brugada-type electrocardiogram, a sign for imminent malignant arrhythmias. Circulation 2008; 117:1890–3
16. Vernooy K, Delhaas T, Cremer OL, Di Diego JM, Oliva A, Timmermans C, Volders PG, Prinzen FW, Crijns HJ, Antzelevitch C, Kalkman CJ, Rodriguez LM, Brugada R: Electrocardiographic changes predicting sudden death in propofol-related infusion syndrome. Heart Rhythm 2006; 3:131–7
17. Postema PG, Wolpert C, Amin AS, Probst V, Borggrefe M, Roden DM, Priori SG, Tan HL, Hiraoka M, Brugada J, Wilde AA: Drugs and Brugada syndrome patients: Review of the literature, recommendations, and an up-to-date website (www.brugadadrugs.org). Heart Rhythm 2009; 6:1335–41
18. Flamée P, De Asmundis C, Bhutia JT, Conte G, Beckers S, Umbrain V, Verborgh C, Chierchia GB, Van Malderen S, Casado-Arroyo R, Sarkozy A, Brugada P, Poelaert J: Safe single-dose administration of propofol in patients with established Brugada syndrome: A retrospective database analysis. Pacing Clin Electrophysiol 2013; 36:1516–21
19. Santambrogio LG, Mencherini S, Fuardo M, Caramella F, Braschi A: The surgical patient with Brugada syndrome: A four-case clinical experience. Anesth Analg 2005; 100:1263–6, table of contents
20. Fujiwara: Ventricular tachycardia in a patient with Brugada syndrome during general anesthesia combined with thoracic paravertebral block. Anesth Analg 2006; 102: 1585–98
21. Brunetti ND, De Gennaro L, Pellegrino PL, Ieva R, Di Nardo F, Cuculo A, Campanale G, Di Biase M: Intra day ECG variation after general anesthesia in Brugada syndrome. J Interv Card Electrophysiol 2008; 21:219–22
22. Kapplinger JD, Tester DJ, Alders M, Benito B, Berthet M, Brugada J, Brugada P, Fressart V, Guerchicoff A, Harris-Kerr C, Kamakura S, Kyndt F, Koopmann TT, Miyamoto Y, Pfeiffer R, Pollevick GD, Probst V, Zumhagen S, Vatta M, Towbin JA, Shimizu W, Schulze-Bahr E, Antzelevitch C, Salisbury BA, Guicheney P, Wilde AA, Brugada R, Schott JJ, Ackerman MJ: An international compendium of mutations in the SCN5A-encoded cardiac sodium channel in patients referred for Brugada syndrome genetic testing. Heart Rhythm 2010; 7:33–46
23. Sarquella-Brugada G, Campuzano O, Arbelo E, Brugada J, Brugada R: Brugada syndrome: Clinical and genetic findings. Genet Med 2016; 18:3–12
24. Smith I, White PF, Nathanson M, Gouldson R: Propofol. An update on its clinical use. Anesthesiology 1994; 81:1005–43
25. Hepner DL, Castells MC: Anaphylaxis during the perioperative period. Anesth Analg 2003; 97:1381–95
26. Ciconte G, Santinelli V, Brugada J, Vicedomini G, Conti M, Monasky MM, Borrelli V, Castracane W, Aloisio T, Giannelli L, Di Dedda U, Pozzi P, Ranucci M, Pappone C: General anesthesia attenuates Brugada syndrome phenotype expression: Clinical implications from a prospective clinical trial. JACC Clin Electrophysiol 2018; 4:518–30
27. Burjorjee JE, Milne B: Propofol for electrical storm; A case report of cardioversion and suppression of ventricular tachycardia by propofol. Can J Anaesth 2002; 49:973–7
28. Flamee P, Dewals W, Poelaert J: Uneventful prolonged propofol infusion in a patient with Brugada syndrome. Anaesth Intensive Care 2017; 45:124–5
29. 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; 305:613–6
30. Bray RJ: Propofol infusion syndrome in children. Paediatr Anaesth 1998; 8:491–9
31. Kam PC, Cardone D: Propofol infusion syndrome. Anaesthesia 2007; 62:690–701
32. 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; 29:1417–25