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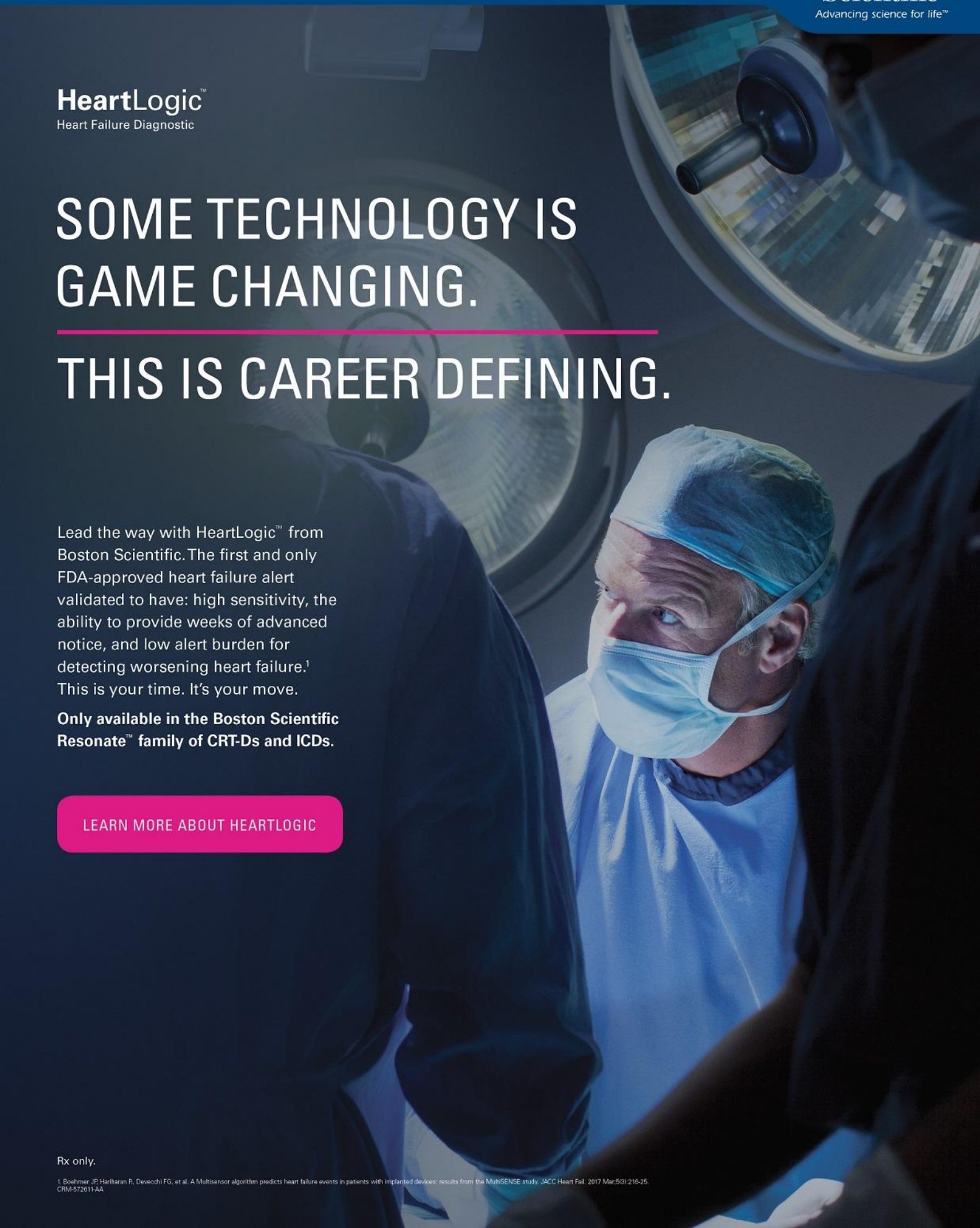

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Randomized Study of Propofol Effect On Electrophysiological Properties of the Atrioventricular Node in Patients with Nodal Reentrant Tachycardia

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Background: *Atrioventricular nodal reentrant tachycardia (AVNRT) is probably the most common form of paroxysmal supraventricular tachycardia. Percutaneous catheter ablation is a technique to interrupt cardiac conduction pathways selectively. The anesthetist is challenged to provide a safe anesthetic which takes into account the electrophysiologist's requirements for minimal cardiac conduction interference. Propofol is an ideal drug. However, previous studies have shown that the infusion of propofol has sometimes been associated with bradyarrhythmias or conversion of arrhythmias to sinusal rhythm. The purpose of this report is to verify the interferences of propofol in the electrophysiological properties of the atrioventricular (AV) node conduction system in patients with AVNRT.*

Methods: *Patients were randomly assigned to receive either a placebo or propofol at sedative doses. An electrophysiological study was performed consisting of measuring the anterograde (AERPFP) and retrograde effective refractory period of the fast (RERPFP) and the anterograde effective refractory period of the slow (AERPSP) AV nodal pathway. Reciprocating tachycardia was induced and the cycle length (CL) and atrial-His (AH), His-ventricular (HV), and ventriculoatrial (VA) intervals were measured.*

Results: *Propofol did not cause alteration ($P > 0.05$) in the AERPFP or RERPFP and the AERPSP AV nodal pathway. The AH, HV, and VA intervals were not affected. Sustained reciprocating tachycardia could be induced in the all patients. All slow pathways were successfully identified and ablated.*

Conclusion: *Propofol has no effect on the electrophysiological properties of the AV node conduction system. It is thus a suitable anesthetic agent for use in patients undergoing ablative procedures. (PACE 2006; 29: 1375–1382)*

propofol*, *sedation*, *anesthesia*, *radiofrequency ablation*, *tachyarrhythmias*, *AV node reentry

Introduction

Among paroxysmal supraventricular tachycardias (PSVT), the most common in adults is atrioventricular nodal reentry tachycardia (AVNRT), and radiofrequency (RF) catheter ablation is a therapeutic modality extensively used in its treatment.[1–6]

Sedation may be indicated during this procedure to suppress sympathetic nervous system (SNS) responses, promote analgesia, amnesia, immobilization, and well-being of patients.[7]

Propofol is an intravenous anesthetic agent that is widely used due to its favorable pharmacokinetic properties, such as rapid awakening, absence of cumulative effects, and easy titration.[8,9] However, it promotes a reduction in arterial pressure (AP) and peripheral vascular resistance (PVR), and these alterations, in general, are not followed by a compensatory increase in the heart rate (HR).[10,11]

This absence of HR compensation, reported bradyarrhythmias,[12] and suppression of tachyarrhythmias[13,14] during the use of propofol suggest the possibility of baroreceptor block or depression of the cardiac conduction system caused by this drug.[14,15] These facts have caused controversy over possible direct effects of propofol on the cardiac conduction system. Wu et al.,[16] demonstrated in a study carried out in animals the direct effects of propofol on the atrioventricular (AV) conduction and His-Purkinje systems. These authors found that propofol prolonged AV conduction (atrial-His [AH] interval) and suggest that this drug may directly modify AV conduction

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and potentially interfere with the induction of supraventricular tachyarrhythmias (SVTs) during electrophysiological study (EPS). Lai et al.[17] presented a series of 150 patients with 152 tachyarrhythmias, in which most (148/152) of SVTs remained inducible after anesthesia with propofol. However, in this group, in 4 out of 7 (57%) pediatric patients with ectopic atrial tachycardia, this stopped after the infusion of propofol and could not be induced, even after infusion of isoproterenol.

On the other hand, the studies by Sharpe et al.,[18] who evaluated the electrophysiological variables of the AV node in adults suffering from Wolff–Parkinson-White (WPW) syndrome and those by Lavoie et al.,[19] who studied the function of the AV and sinoatrial node in children, did not demonstrate a direct effect of propofol on these electrophysiological properties.

The clinical observation of possible alterations in the effective refractory periods of the fast and slow AV nodal pathways during sedation with propofol, as well as the suspicion that this drug may prevent PSVT induction by programmed electrical stimulation, during electrophysiological study (EPS), motivated this clinical assay.

The aim of this study was to assess possible effects of propofol on the electrophysiological properties of the fast and slow AV nodal pathway, as well as on the inducibility of arrhythmia in patients with AVNRT.

Materials and Methods

Approval from the Institution's Committee on Clinical Investigation and informed consent from the patients were obtained before initiating this study.

The study consisted of a randomized, double-blinded, crossover trial, as demonstrated in Figure 1. Twelve consecutive patients, candidates to RF ablation for AVNRT were studied. In order to be able to participate in the trial, they had to be aged between 15 and 60 years and present typical (slow-fast) AVNRT confirmed during electrophysiological (EP) analysis.

Patients were excluded if they had a history of allergy to propofol, egg, or any other drug in the trial; previous psychiatric pathology; previous liver or kidney disease; severe cardiopathy; hypertensive and/or ischemic myocardiopathy; valvulopathy; congenital cardiopathy; obesity (BMI $>$ 35), or if they were on an antirhythmic drug for a period shorter than five half-lives, for its washout. No patient using amiodarone was included in the study.

The selected patients were subjected to a clinical examination performed by a cardiologist and an anesthetist of the staff. They underwent rest electrocardiography and transthoracic echocardiography tests prior to the procedure, and showed a normal cardiac condition. The patients were advised to fast for 6 hours and received 10 mg diazepam orally as premedication 1 hour before the procedure.

When arriving at the Electrophysiology Laboratory the patients were monitored using equipment for cardioversion-defibrillation (Cardioserv, Marquett Hellige Medical Systems; Friburg, Germany), pulse oximetry (Ohmeda Biox 3700 Pulse Oximeter, Louisville, KY, USA), and non-invasive AP. The EF polygraph used was the CardioLab 4.0, Prucka Engineering Inc. Houston, TX, USA, and a Medtronic stimulator-programmer (Model 5328, Minneapolis, MN, USA) was used for electrostimulation.

The intravenous access was made with a 20 G catheter in a thick vein in the antecubital space. A nasal catheter was introduced with an oxygen flow at 2 L/min or the oxygen flow necessary for maintaining oxygen saturation above 90%.

Initially, midazolam was administered at judicious doses of 1 mg every 2–3 minutes, with a mean dose of 0.06–0.1 mg kg^{-1} and fentanyl 1 μg kg^{-1}, aiming at a sedation level (SED) eight of a sedation score, as shown in Table 1. All patients were studied in the recumbent position while spontaneously breathing. No patient was intubated during the study after propofol administration.

Table I shows a variation of the Aldrete score developed for postanesthetic recovery and adapted for conscious sedation, which has been used by the North American Society for Pacing and Electrophysiology (NASPE) based on the 1998 Expert Consensus Statement (Part 1).[20] It was chosen for this study because it was specifically developed for EPS and ablation procedures.

The introduction of percutaneous catheters for EPS was done under local anesthesia, with infiltration of 1% lidocaine and fluoroscopic management. Three Cordis Webster catheter electrodes (6–8 Fr) (Diamond Bar, CA, USA) were introduced intravenously, placed at the high right atrium, at the right ventricle apex, and adjacently to the bundle of His, at the septal level of the tricuspid valve, to record the His bundle electrogram.

Initially, EPS was carried out for confirmation of AVNRT with previous electrocardiographic diagnosis. Inclusion in the trial occurred after confirming the presence of the fast and slow pathways, that is, the presence of intranodal dissociation and typical AVNRT induction, without needing to use isoproterenol or atropine. At that point, the patients were randomized to participate in the series A or B. For randomization, sealed opaque envelopes were used, which were enclosed in a larger envelope and through a draw assigned to one of

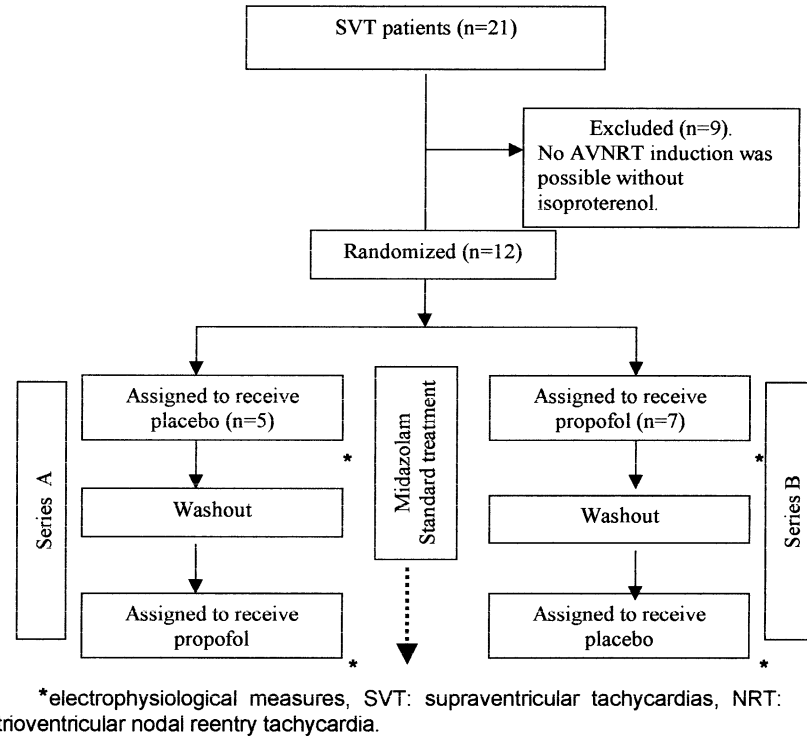


Figure 1. *Patient selection.*

the two series. Only the anesthetist knew the draw results.

The study was double-blinded. The serum flasks and infusion devices used were opaque, preventing the identification of drugs, and a surgical field isolated the anesthetic equipment and the patient from the staff that analyzed the electrophysiological parameters. For intravenous administration of drugs, a syringe infusion pump (Nikkiso Co. Ltd. Model PSK-01, Shibuyaru, Tokyo, Japan) was used.

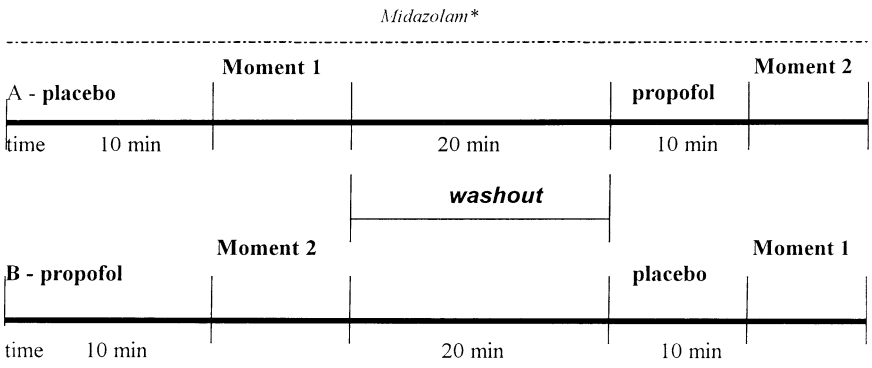
The patients that participated in series A initially were given placebo (5% dextrose in water) by intravenous infusion (IV). After the electrophysiological analysis was performed and the drug washout period was over, they received IV

TABLE I.

Sedation Scale and Its Corresponding Levels

Level	Consciousness	Responds Intentionally Verbal Stimulus	Physical Stimulus	Airways	Breathing	Total Score SED
Light sedation	Near normal	2	2	2	2	8
IV Sedation						
(a) Drowsy		1–2	2	2	2	7–8
(b) Asleep		0–1	1	2	1–2*	4–6
(c) Sound asleep		0	1	1–2†	1	3–4
Deep sedation	Very depressed	0	0	0–1	0-1	0–2
General anesthesia	Non-responsive	0	0	0(-1)	0-(-1)	0-(1–2)

Adapted from Bubien RS, Fisher JD, Gentzel JA, et al. NASPE Expert Consensus Statement-Position Statements: Feb, 1998.
SED: sedation level. Scores: 2: present; 1: limited; 0: absent.
*Nasal oxygen administration may be needed to maintain saturation >90%, which must be routine, especially for SED score <7.
†Ventilatory support may be needed.



*Midazolam: steady-state drug. Moments 1 and 2: time intervals in which the analyses of electrophysiological parameters and NRT induction were performed.Moment 1 corresponds to the electrophysiological study during the use of placebo and Moment 2 during the use of propofol; min: minutes.

Figure 2. *Drug administration times and data analysis and washout intervals.*

propofol. The patients in series B initially were given propofol and then placebo, as shown in Figure 2. Thus, each case was its own control.

In series A, after the infusion of placebo for 10 minutes, an EPS protocol was applied. In this period, sedation was promoted with the administration of midazolam (steady-state drug) at titrated doses of 1 mg every 2–3 minutes, aiming at SED level 7 in the sedation scale (Table I). After analysis 1, a 20-minute period was waited for washout. A new electrophysiological analysis was performed 10 minutes after the bolus administration of propofol (300 ug kg^{-1}), followed by an infusion of 50–60 $\mu g\ kg^{-1}\ min^{-1}$, when plasma equilibrium was achieved. The sedation level with this infusion was SED 7 (Table I). The physical stimulus used was a soft touch on the patient's shoulder with the hand.

In series B, the first measure of electrophysiological parameters was taken already under propofol infusion, using the same doses as in series A. After the analysis was done, the infusion was stopped for 20 minutes, allowing the washout. A new measurement was performed after placebo infusion for 10 minutes. In this period, midazolam was administered at the same doses mentioned above, aiming at SED 7 level.

The standard EPS protocol, with measurement of electrophysiological properties, was applied to all patients. This protocol consisted of the performance of atrial or ventricular extra-stimuli after eight stimulations in the high right atrium or right ventricle apex with basic cycles of 500 and 600 ms. The refractory period of the fast and slow pathway was assessed with a gradual reduction by 10 ms at every new extra-stimulus. Refractory periods were obtained three times at each cycle, the mean value being adopted.

The conduction intervals and refractory periods of interest are described in Table II, as well as their definitions.

The main goal was to verify the occurrence of changes in the anterograde and retrograde effective refractory periods of the slow and fast AV nodal pathway, in a patient with AVNRT, promoted by propofol at sedative doses compared with a placebo.

TABLE II.

Conduction Intervals and Periods Measured (ms) and Their Definitions

Term	Definition of Conduction Intervals
PA	= onset of P wave-atrium = intra-atrial conduction time, from onset of P wave to atrial depolarization
AH	= Atrial-His interval = AV nodal conduction time, measured from atrium to His bundle deflection
HV	= His-ventricular interval = time of conduction across the His-Purkinje system measured from His deflection to onset of ventricular depolarization
CL	= cycle length
Refractory periods measured at 500/600 ms cycles:	
AERPFP	= Anterograde effective refractory period of fast pathway
AERPSP	= Anterograde effective refractory period of slow pathway
RERPFP	= Retrograde effective refractory period of fast pathway
RERPSP	= Retrograde effective refractory period of slow pathway

Statistical Analysis

To detect a difference of 25 ms or more between the effective refractory periods of the fast and slow pathway, considering a significance level at 0.05 and 80% statistical power, it was established that 12 patients had to be randomized. The electrophysiological variables achieved before and after the administration of propofol were compared using the Student's *t*-test. The continuous variables were shown as mean ± standard deviation (SD).

For quantitative variables with more than three associations, an analysis of variance (ANOVA) test was applied. For qualitative variables, McNemar's χ^2 test was used.

The significance level was set at $P < 0.05$. For the databank, the Excel 2003 software was used, and statistical calculations were made using the SPSS 10.0.1 software (Chicago, IL, USA) for Windows.

Results

Twelve patients who presented typical AVNRT diagnosis were studied. The demographic data are demonstrated in Table III. Most showed a physical condition compatible with the American Society of Anesthesiologists (ASA) I and II classification.

Table IV shows the hemodynamic parameters at the three moments analyzed. Systolic (SAP) and diastolic (DAP) arterial pressures did not have any significant change at analyses 1 and 2, but there was a statistically significant decline ($P = 0.05$) at analyses 1 and 2 for SAP and DAP, when compared with the baseline value. This decline was by 15% in relation to the baseline. The HR did not change at the three moments, that is, no compensatory tachycardia to the reduction in AP occurred. For oxygen saturation, there was no statistically significant difference among the three moments. Regarding sedation level, there was a statistically significant difference between the baseline and moments 1 and 2; however, between these latter moments no difference was found.

The intra-atrial and atrioventricular conduction intervals, measured at the two moments and checked through an analysis of onset of P wave atrium (PA), AH, and His-ventricular interval (HV) intervals, are shown in Table V and did not show a statistically significant difference, except for cycle length (CL), which was lower in the propofol group ($P = 0.002$).

The anterograde and retrograde effective refractory periods of the fast pathway and the anterograde period of the slow pathway, measured during propofol infusion and compared with the placebo, did not have a statistically significant difference, when measured at 500 or 600 ms baseline stimulation cycles. These figures are shown in Table VI. In Figure 3, we illustrated two examples of these periods. Regarding the retrograde effective refractory period of the slow pathway, we were unable to measure it in most patients, hence, it was not analyzed.

AVNRT induction was possible for all patients, with no need for the use of facilitating drugs (isoproterenol or atropine).

The mean propofol dose used during the study was 60 $\mu g\ kg^{-1}\ min^{-1}$. This dose, associated with fentanyl and midazolam at the doses mentioned, did not cause a decline in oxygen saturation in any patient, nor did it lead to obstruction of upper airways or apnea. Thus, an instrumentation of airways was not necessary, in addition to the oxygen catheter, with the association of these drugs and doses.

Regarding the side effects evaluated no patient experienced pain during propofol injection. Also, no hypotension was observed in any case; therefore, the use of a vasopressor was not necessary. There was no bradycardia, nor reports of nausea or vomiting, shivering or uncoordinate motions, as well as drug allergy. All patients woke up within a few minutes after drug infusion was interrupted, and reported being satisfied with the procedure, without unpleasant memories or painful episodes.

Ablation was carried out successfully in all patients under study. During ablation, propofol doses were changed to 80–90 $\mu g\ kg^{-1}\ min^{-1}$ and a second fentanyl dose was administered 5 minutes prior to this procedure.

At the completion of the procedure, the patients were referred to the recovery room, where they stayed for at least 6 hours, and their vital

TABLE III.

Patient Demographic Data

Parameters	Total
Patients	12
Sex (M/F)	02 (16.7%) / 10 (83.3%)
Age	40.75 ± 12.45
Weight	66.7 ± 8.51 kg
Height	164 ± 6.92 cm
BMI	24.8 ± 3.15
ASA	
I	03 (25%)
II	07 (58.3%)
III	02 (16.7%)
LV ejection	70.33% ± 5.56

Values are means ± SD. BMI = body mass index, ASA: physical status according to ASA classification, LV: left ventricle.

TABLE IV.

Hemodynamic Parameters Measured

Parameters	Baseline	Moment 1 (Placebo)	Moment 2 (Propofol)	P
HR (bpm)	75.25 ± 11.98[a]	75.41 ± 11.85[a]	76.66 ± 7.37[a]	0.625
SAP (mmHg)	125.83 ± 15.05[a]	106.66 ± 6.51[b]	106.66 ± 7.78[b]	1
DAP (mmHg)	77.5 ± 6.21[a]	69.16 ± 2.88[b]	69.16 ± 5.14[b]	1
O2 sat.(%)	97.66 ± 1.61[a]	98.41 ± 1.5[a]	98.58 ± 1.24[a]	0.615
Sedation	7.83 ± 0.38[a]	6.66 ± 0.49[b]	6.5 ± 0.52[b]	0.166

Values are means ± SD. Moment 1: analysis conducted during placebo infusion. Moment 2: analysis during propofol infusion. The presence of different index letters "a" or "b" indicates a statistically significant difference ($P < 0.05$) versus baseline.
Baseline: moment before infusion of drugs. HR = heart rate; bpm = beats per minute; SAP = systolic arterial pressure; DAP = diastolic arterial pressure; 02 Sat: peripheral oxygen saturation. P: descriptive level of t test calculated between moments 1 and 2.

signs were monitored: continuous electrocardiogram (ECG), pulse oxymetry, and AP measured by oscillometry. The signs remained stable in all cases. The patients were discharged in the next morning, uneventfully.

Discussion

There was no statistically significant difference for hemodynamic variables (SAP, DAP, HR) between the analyses with propofol and placebo, when midazolam was used as steady-state drug to promote equal levels of sedation.

Our findings are also similar to those in Romano et al.,[21] who did not demonstrate depressive effects on the AV node conduction system caused by propofol and did not find bradyarrhythmias during the use of this drug either.

Studies analyzing the influence of propofol on baroreceptor sensitivity[22] did not demonstrate depression in their activity from the use of the drug. Therefore, hemodynamic changes can be accounted for by the central sympathicolytic and/or vagotonic effects elicited by propofol. This view is supported by Deutschman et al.,[23] who found that propofol anesthesia decreases the parasympathetic tonus to a lesser degree than the sympathetic tonus, resulting in parasympathetic dominance, which may explain the bradyarrhythmias that occur with its use.

Our findings about the possible influence of propofol on the AV nodal conduction system were similar to those in Sharpe et al.[18] and Lavoie et al.,[19] since propofol did not cause a significant change in the electrophysiological variables of the AV node. However, Sharpe et al.[18] studied patients with WPW syndrome, unlike our study, evaluating the effective refractory periods of the slow and fast pathway in AVNRT patients. Lavoie et al.[19] studied

TABLE V.

Propofol Anesthesia Effect at Sedative Doses

Measures	Moment 1 (ms) (Placebo)	Moment 2 (ms) (Propofol)	P
PA	31.58 ± 9	31.5 ± 9.24	0.674
AH	74.33 ± 13.23	72.58 ± 10.74	0.340
HV	40.83 ± 5.95	40.58 ± 5.66	0.191
CL	834.58 ± 126.19	821.5 ± 123.54	0.002*

Values are means ± SD.
PA = onset of P wave-Atrium; AH = Atrial-His interval; HV = His-Ventricular interval; CL = cycle length; ms = milliseconds.

TABLE VI.

Propofol Effect on Refractory Periods of the Fast and Slow Pathways

Measures	Moment 1 (ms) (Placebo)	Moment 2 (ms) (Propofol)	P
AERPFP (600 cycles)	405.45 ±110.12	395.45 ± 86.18	0.324
AERPFP (500 cyles)	403.75 ± 103.77	402.5 ± 31.83	0.893
AERPSP (600 cycles)	305 ± 53.68	310 ± 52.22	0.339
AERPSP (500 cycles)	308.88 ± 62.33	314.44 ± 47.19	0.613
RERPFP (600 cycles)	311.11 ± 119.94	296.66 ± 88.88	0.485
RERPFP (500 cycles)	324.28 ± 158.83	295.71 ± 105.64	0.431

Values are means ± SD.
AERPFP = anterograde effective refractory period of the fast pathway; AERPSP = anterograde effective refractory period of the slow pathway; RERPFP = retrograde effective refractory period of the fast pathway; ms = milliseconds.

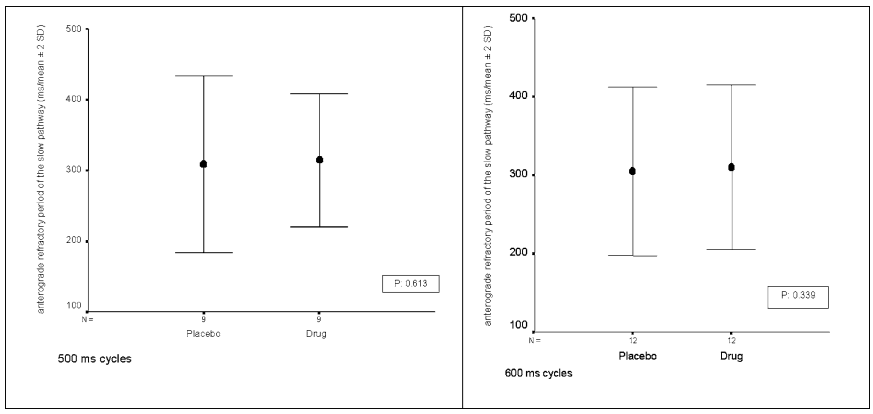


Figure 3. *Representation of anterograde refractory period of the slow pathway measured at 500 or 600 ms baseline stimulation cycles.*

20 children, of who 17 had accessory pathways, 1 had junctional reciprocating tachycardia, and 2 had classic "slow-fast" AVNRT.

The methodology used also differed. In the study by Sharpe et al.,[18] electrophysiological measures were taken under the effect of higher propofol doses (2 mg kg^{-1}, followed by 120 μg kg^{-1} min^{-1}), and compared with an analysis under effect of total intravenous anesthesia with midazolam/alfentanil/vecuronium. This might have been a limitation in this study, since vecuronium is known to cause bradycardia, particularly if administered with other vagotonic drugs, such as the opioids.

Similarly, Lavoie et al.[19] studied 10 children anesthetized with propofol, compared with another 10 subjected to general anesthesia, which was composed of thionembutal/fentanyl/pancuronium/nitrous oxide, which maintained a basic anesthetic state. Pancuronium is a vagolytic drug with postganglionary terminal action and may increase the HR, in addition to releasing norepinephrine through the terminal sympathetic nervous system (SNS), and can thus interfere with the EPS.

In these two studies, by Sharpe et al.[18] and Lavoie et al.,[19] deep anesthetic planes were maintained, which according to the authors may have a limiting factor. Unlike these studies, the present trial was carried out with propofol at doses necessary for maintaining a "conscious sedation," closer thus to the usual clinical practice of these procedures. For the other drugs used in the study, midazolam and fentanyl proved not to interfere with the cardiac conduction system.[24]

Moreover, none of the patients were taking any other antirhythmic drugs; those who were taking an antirhythmic drug with too long terminal half life were either excluded or requested to quit it for a period longer than five half-lives, so that the drug could be properly washed out.

Also, the selected sample comprised only patients with AVNRT diagnosis, which was not evaluated in a previous randomized trial. However, as in other studies, no change caused by propofol was observed in the anterograde and retrograde effective refractory periods of the fast and the anterograde effective refractory periods of the slow AV nodal pathway.

These results do not point to any evidence that propofol may act directly on the electrophysiological properties of the AV node in patients with AVNRT. Likewise, propofol did not prevent an induction of programmed tachyarrhythmias during EPS and did not interfere with the diagnosis of these tachyarrhythmias.

However, Wu et al.,[16] in their study in animals, found that propofol prolonged AV conduction (AH interval) conduction interval and suggested that, at relevant clinical doses, this drug may directly change AV conduction and potentially interfere with the induction of SVTs during the EPS. Wu et al.[25] also reported about a series of nine pediatric patients with ectopic atrial tachycardia in which it was not possible to sustain tachycardia in 4 (44%) during the use of propofol. Similarly, Lai et al.[17] presented a series of 150 patients with 152 tachyarrhythmias, in which most (148/152) SVTs remained inducible with propofol. However, in this series, in 4 out of 7 (57%) pediatric patients with

TABLE VII.

Mean Drug Doses

Fentanyl (mg)	64.16 ± 11.04
Midazolam (mg)	8.25 ± 3.49
Propofol (mg kg^{-1} min^{-1})	60.0 ± 00

Values are means ± SD.

ectopic atrial tachycardia, this stopped after the infusion of propofol and could not be induced, even with isoproterenol infusion.

This seems to indicate that, probably, propofol may interfere with automatic SVT (at least in children), but not with tachyarrhythmias in which the mechanism is that of reentry as in AVNRT or in AV reentrant tachycardia dependent upon an accessory bundle.

This study had some limitations. First, the size of this sample was small; however, the statistical analysis showed that, for a difference by up to 25 ms between effective refractory periods, the statistical power was 80%. Second, the washout time established here did not allow us to affirm that the serum drug concentration was zero during the use of placebo in series B, as such concentration was not measured. However, the work by Hughes et al.,[26] as well as the description by several authors[27,28] for a waking time of 4–10 minutes after the infusion has ceased, allowed to estimate that the target concentration in the studied organ was at subclinical doses during data collection. Third of all, the "additive effect" on the AV node with the other sedative drugs that were being taken by the patients during the period of ablation could have occurred; nevertheless, we have tried to minimize this disproportion with the study design. In such way, each case is under control and the two series wind up with the same sedation level, as well as with the same sedation drugs and doses.

Conclusions

This study demonstrated that propofol provided suitable sedation levels, maintained hemodynamic stability, and enabled a fast and pleasant recovery for patients, without interfering with the electrophysiological properties of the AV node or preventing AVNRT induction. As a result, it is possible to say that this drug is efficacious and efficient for this group of patients with AVNRT subjected to RF ablation.

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