Effects of Propafenone Associated with Propofol on Myocardial Contractility, Heart Rate, Coronary Flow, and the Incidence of Arrhythmia in Isolated Hearts of Rats

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Objective - *To study the influence of propafenone associated with propofol on myocardial contractility (dP/dt and heart rate), coronary flow, and the incidence of arrhythmia in isolated rat hearts.*

Methods - *Forty albino rats were anesthetized with sulfuric ether, a modified Langendorff method was performed, and the rats were fed with Krebs-Henseleit (K-H) solution, (95% O_2, 5% CO_2, pH 7.4±0.1, perfusion pressure between 90 and 100cm of water, and temperature 37± 0.5°C). Control records were obtained after a stabilization period and rats were distributed into the following 4 groups: I (control), II (100mcg propafenone), III (25mcg propofol), and IV (propafenone-propofol).*

Results - *A decrease ($P<0.05$) in the heart rate in groups II and IV was observed, with a greater decrease in group II. A decrease was noted in the dP/dt ratio ($P< 0.05$) in groups II and IV, during all periods. Group III experienced depression from the 1st to the 3rd minute. Coronary flow had a decrease ($P<0.05$) in all groups, compared with the control group, especially in group IV with a decrease from 14mL/min to 11mL/min. Arrhythmogenic effects of propafenone (pro-arrhythmia) were verified in 50% of group II. In the association with propofol (group IV), no significant difference occurred, and arrhythmias (pro-arrhythmic effect) were observed in 40% of the hearts.*

Conclusion - *The association propafenone-propofol was not harmful to the use of propafenone solely, regarding the effects observed in myocardial contractility, coronary flow, and in the incidence of arrhythmias.*

Keywords: myocardial contractility, propafenone, propofol

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Cardiac rhythm disturbances are a frequent finding in patients with heart diseases, and are responsible for the development of increasing clinical and experimental research. To recognize and treat arrhythmias correctly is of utmost importance because they are risk factors for sudden cardiac death. Since the study by Wenckeback [1], at the beginning of the 20th century, about the efficiency of antiarrhythmic therapy, several studies have been conducted demonstrating that the control of rhythm disturbances is essential in the prevention of sudden cardiac death and in the reduction of mortality because of acute myocardial infarction [2-5].

Maintenance of arrhythmia control usually demands additional care, and chronic treatment is still a challenge, especially in light of evidence of the arrhythmogenic effects of most known medications [6-9]. The clinical decision to treat patients with cardiac arrhythmias involves careful analysis and knowledge of the elected antiarrhythmic medication.

Among the most commonly used antiarrhythmic medications in our country for the treatment of ventricular and supraventricular arrhythmias, propafenone stands out, classified as an IC drug according to Vaughan Willians [10,11]. 2-3 hydrochloride (hydroxy-2 propylamine) 3 propoxy phenyl (propafenone) was synthesized in 1970 and has been widely used in the suppression of supraventricular and ventricular arrhythmias. The medication contributes to the reduction of the permeability of the cellular membrane to sodium and to a lesser extent to calcium, disrupting the action potential of myocardial fibers [12,13]. It also has an antiadrenergic effect to block nonselective beta-adrenergic receptors. These mechanisms suggest negative inotropic and chronotropic effects especially if the dose exceeds that predicted.

Because of specific studies [14-17] that demonstrated the antiarrhythmic efficiency of propafenone, it has been used in patients with heart diseases that can be surgically treated.

Regarding anesthesia in cardiovascular surgery, the severity of heart diseases leads to concern about the level of myocardial depression caused by most anesthetic medications.

Propofol (2,6-diisopropyphenol) is an intravenous

anesthetic agent for use in the induction and maintenance of an anesthetized state with rapid action and elimination and is widely used in cardiovascular surgeries. Intravenous injection of a therapeutic dose produces hypnosis rapidly with minimal excitation. Propofol binds to plasma proteins above 95% with elimination through hepatic metabolism, forming inactive compounds that are eliminated in the urine[18]. Studies of propofol [19-20] have demonstrated decreases in systolic and diastolic blood pressure and in the cardiac index, in addition to the decrease in peripheral vascular resistance without a significant alteration in heart rate. The negative inotropic effect has been presented both in clinical studies and in experimental models in animals [21-24].

A special concern is that patients with heart diseases who use propafenone may undergo cardiac surgery and receive propofol, because both medications are myocardial depressors with the possibility of an enhancing effect concerning myocardial contractility. As studies in the literature about the possible enhancing effect of interaction of these medications were not found, the present experimental investigation was conducted aiming at studying the heart's performance, assessing the variables: myocardial contractility, heart rate, coronary flow, and incidence of arrhythmias.

Methods

Forty adult albino Wistar rats housed in the vivarium at the Medical School of Barbacena – UNIPAC, were studied without regard to sex, with weights ranging from 210 to 350g (mean, 280g). All animals were treated according to the "Ethical Principles in Animal Research" adopted by the Brazilian College of Animal Experimentation (COBEA) [25], and by the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health - USA [26].

After anesthesia with inhalation of sulfuric ether, the animals underwent a wide thoracotomy. The anterior thoracic wall was reflected, and the heart and the great vessels were exposed. After that, 500 UI of sodium heparin were administered in the posterior vena cava to prevent thrombosis. The animal's aorta was isolated and repaired with a 2.0 cotton thread, and cannulated with a 20G-caliber plastic catheter, making sure that the integrity of the aortic valve was maintained during introduction of the catheter. The catheter was then fixed to the aorta with another 2.0 cotton thread. Next, the left ventricle was drained with the introduction of a fenestrated 18G-caliber plastic cannula through the left atrium and was taken out through the cardiac apex, avoiding greater coronary vessel lesions. The heart was released by cutting the vena cava, pulmonary artery, and the aorta above the cannulation region and was immediately connected to the coronary perfusion system.

The method used was the modified Langendorff [27,28], using Krebs-Henseleit solution for perfusion (composition: NaCl 126mM/l, $NaHCo_3$ 25mM/l, KH_2PO_4 1.2mM/l, KCl 4.8mM/l, $MgSO_4$ 1.2mM/l, $CaCl_2$ 2.5mM/l, and glucosin 11.5mM/l), gassed with a mixture containing 95% O_2 and 5% CO_2, obtaining 7.4±0.1 pH and 37±0.5°C temperature with the use of a heating unit for thermal permutation (COMEX Ind. Com. Ltda, Belo Horizonte, MG). The solution was filtered with a CardioPro monofilament filter (American BioTech Corporation, New York, NY, USA) with holes of 3 micra, placed right after the deposit of the Krebs-Henseleit (K-H) solution. Perfusion pressure was kept constant, between 90 and 100cm H_2O.

After heart perfusion for 15 minutes, for the purpose of recovering and stabilizing cardiac activity, an empty plastic balloon was introduced into the left ventricle through a hole in the left atrium. The mitral valve was preserved, and the balloon was connected to a monitor (model DH 073, BESE-Bioengenharia, Belo Horizonte, MG) with the help of a metal cannula. Systolic and diastolic pressure, heart rate, and an electrocardiogram were recorded (printer Epson LX-810). Diastolic pressure was adjusted to 5±2 mmHg, through movements of introduction and withdrawal of redistilled water in the latex balloon in all periods of group I; in groups II, III, and IV, the diastolic pressure was not adjusted except in t_1 period (fig. 1). Coronary flow was determined by the assessment of the drained volume of the right and left cavities in 1 minute, collected in a graduated glass bottle. The incidence of arrhythmia was assessed by observing cardiac rhythm, recorded on the electrocardiogram in D_2 derivation by 2 electrodes placed on the heart.

The 40 hearts were distributed into 4 groups and prepared according to the method described. The groups were perfused with a Krebs-Henseleit solution at 37°C temperature for 30 minutes, and the parameters were recorded in the control (t_0), after the 1st (t_1), 3rd (t_2), 5th (t_3), 10th (t_4), and 15th (t_5) minute. The groups can be characterized as follows: group I- control: 10 hearts without medication; group II - propafenone: 10 hearts differing from the control group due to the administration of 100mcg of propafenone diluted in 0.1 mL of the K-H solution via a proper lateral route above the bulb of the cannula inserted into the aorta; 10 hearts differing from the control group because of the administration of 25mcg of propofol diluted in 0.1 mL of the K-H solution via a proper lateral route above the bulb of the cannula inserted into the aorta; group IV - propafenone: 10 hearts differing from the previous groups by the administration of 0.1 mL of the K-H solution containing 100mcg of propafenone in an appropriate lateral vein above the cannular bulb inserted in the aorta followed by 0.1 mL of the solution containing 25 mcg of propofol by the same route.

The variations of heart rate in bpm, of the velocity of circumferential cardiac fiber shortening (dP/dt in $mmHg.s^{-1}$), of coronary flow (mL/min), and the incidence of arrhythmias were studied. For statistical analysis, we used the Student *t* test for paired data (significance level: $P<0.05$) and single-factor analysis of variance with the same significance level.

Results

Heart rate decreased ($P<0.05$) in groups II and IV (1st to 15th min), and in group III, only in the 3rd and 10th minutes; however, no statistically significant difference existed in group I.

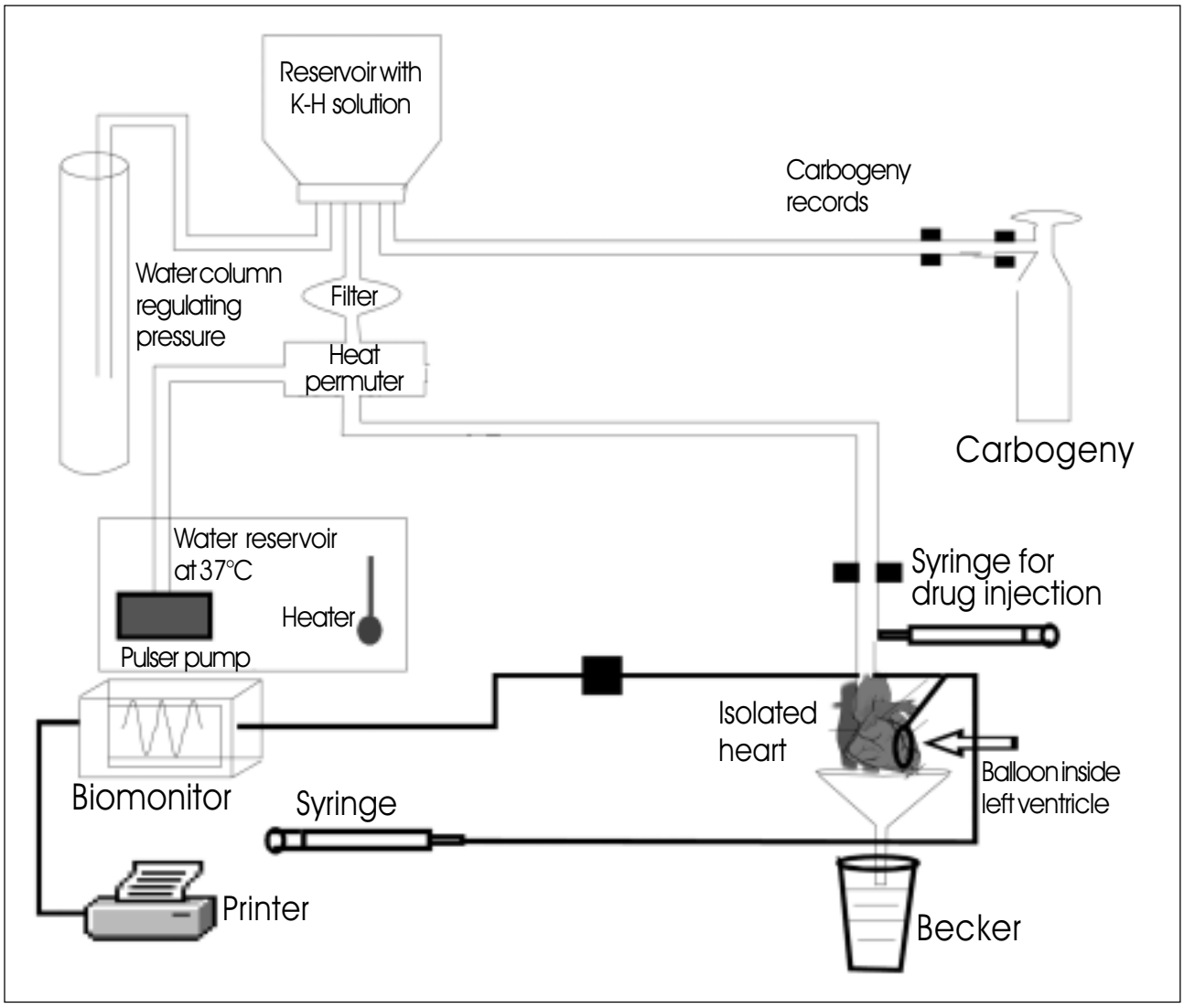

Fig. 1 - Diagram of the isolated heart preparation used in the Langendorff @ method.

In group II, a decrease was recorded from 100% (control) to 71% (1st min), 68% (3rd min), 71% (5th min), 83% (10th min), and 78% (15th min); in group IV decreases occurred from 100% to 77% (1st min), 69% (3rd min), 70% (5th min), 76% (10th min), and 80% (15th min), on average. In the comparison between groups, groups II and IV demonstrated significant variation compared with the control group; however, they did not have significant variation when compared with each other. Heart rate had a significant variation ($P<0.05$) only in the first minute in the comparison between groups II and III (fig. 2 and tab. I). The dP/dt decreased in group II (from the 1st to the 15th min), in group III (1st and 3rd min), and in group IV (from the 1st to the 15th min). In percentage values, in groupII, a decrease was recorded from 100% (control) to 62% (1st min), 75% (3rd min), 80% (5th min), 78% (10th min), and 76% (15th min). In group III, a percentage decrease occurred from 100% (initial) to 77% (1st min), and 86% (3rd min). In group IV, a percentage decrease occurred from 100% (initial) to 54% (1st min), 62% (3rd min), 68% (5th min), 73% (10th min), and 76% (15th min). All these decreases demonstrated in mean percentile values were statistically significant. In the comparison between groups, the dP/dt ratio was smaller ($P<0.05$) in group II when compared with that in the control group in all periods. Group III had a significant decrease ($P<0.05$) only in the first minute regarding the control group. Group IV had a significant decrease ($P<0.05$) from the first to the fifth minute compared with the control group. In the comparison between groups II and III, the dP/dT ratio did not have a significant decrease. Variations occurred between groups II and IV, and II and IV were not significant (fig. 3 and tab. II).

Coronary flow decreased in groups II and IV (1st to 15th min), and in group III (3rd, 5th, 10th, and 15th min). In terms of percentages, in group II a decreases from 100% (control), to 88% (1st min), 86% (3rd min), 80% (5th min), 75% (10th min), and 72% (15th min) was recorded. In group III, a percentage decrease from 100% (control), to 99% (1st min), 92% (3rd min), 89% (5th min), 84% (10th min), and 77% (15th min) was recorded. In group III, a percentage decrease from 100% (control), to 91% (1st min), 88% (3rd min), 85% (5th min), 79% (10th min), and 74% (15th min) was recorded.

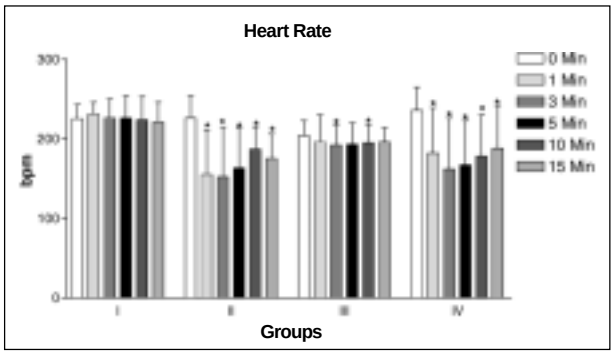

Fig. 2 - Group I: control; group II: propofol; group IV: propofol+propafenone. Values obtained in table I (mean and standard deviation). *P<0.05 - Student *t* test.

Table I - Heart rate variation (bpm) in the groups studied

Groups	Períods t_0	t_1	t_2	t_3	t_4	t_5
I	225±18	231±15	226±24	226±28	224±29	221±25
II	226±28	155±56	152±63	163±50*	187±28*	175±31*
III	204±19	196±34	192±26*	193±27	195±23*	196±18
IV	236±29	182±57*	162±64*	167±56*	178±52*	188±54*

Group I: control; group II: propafenone; group III: propofol; group IV: propofol+propafenone; control(t_0), 1st min (t_1), 3rd min (t_2), 5th min (t_3), 10th min (t_4), 15th min(t_5).*P<0.05 - Student *t* test.

All these decreases where statistically significant, demonstrated in mean percentage values (P<0.05). In the comparison between groups, coronary flow did not decrease in groups II and IV as compared with that in the control group. A significant decrease occurred (P<0.05) in the 10th and 15th minutes of group III, as compared with the control group. No significant difference occurred (P<0.05) between groups II and IV, between groups II and IV, and when group II was compared with group III (fig. 4 and tab. III).

During the study, arrhythmias were not present in groups I (control) and III (propofol). In group II (propafenone), arrhythmias were observed in 5 of the 10 hearts, and in the propofol-propafenone association (group IV) an increase in the arrhythmias were observed in 4 of the 10 hearts studied.

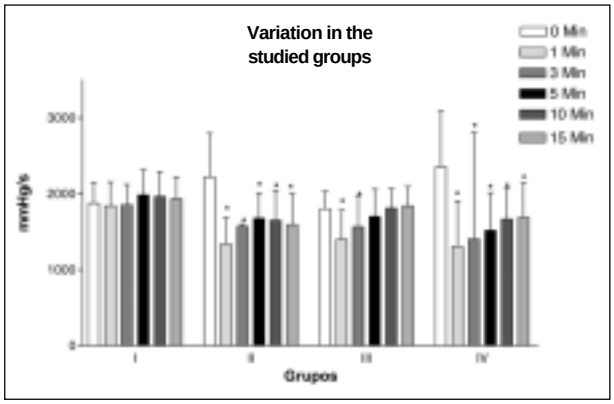

Fig. 3 - Group I: control; group III: propofol; group IV: propofol+propafenone. Values obtained in table II (mean and standard deviation). *P<0.05 - Student *t* test.

Discussion

Despite the great advances in clinical and experimental electrophysiology in the last 20 years, sudden cardiac death is still a complex physiopathologic event. Patients with coronary disease as well as those with congestive heart failure are an important risk group for sudden death [29-31].

Around 75% of sudden deaths are due to episodes of ventricular tachycardia or ventricular fibrillation [32-35]. Patients with congestive heart failure experience severe ventricular arrhythmias and sudden death in up to 50% of cases[36]. Aiming at preventing these severe complications, antiarrhythmic therapeutics are indicated. However, the proper treatment of a cardiac arrhythmia is a challenge in clinical practice due to the adverse effects of antiarrhythmic medications, which may even worsen the congestive heart failure due to the negative effect of myocardial contractility.

With these data, several studies have searched for the ideal antiarrhythmic medication to prevent and treat these arrhythmias. However, despite the studies conducted, some of the available antiarrhythmic drugs, have pro-arrhythmic effects, and may cause myocardial depression and increased mortality [37,38].

The Cardiac Arrhythmia Suppression Trial (CASH) [39], a randomized multicenter study, demonstrated that patients treated with IC antiarrhythmic medications have a greater risk of sudden death compared with the placebo group. Other studies [40,41] demonstrated similar results with the use of IC medications, which led to the use of these antiarrhythmics only in potentially lethal cases, avoiding their chronic use.

The difficulties in approaching clinical treatment of a patient are frequently due to concomitant diseases, which requires the administration of several medications at the same

Table II - ST/Dt variation (mmHg/s) in the groups studied

Groups	Períods t_0	t_1	t_2	t_3	t_4	t_5
I	1876±273	1840±318	1854±269	1983±334	1965±327	1935±285
II	2218±578	1339±350*	1569±30*	1676±333*	1650±397*	1593±410*
III	1800±232	1399±381*	1564±400*	1700±358	1811±255	1840±254
IV	2354±736	1305±601*	1405±404*	1518±498*	1666±411*	1687±455*

Group I: control; group II: propafenone; group III: propofol; group IV: propofol+propafenone; control(t_0), 1st min (t_1), 3rd min (t_2), 5th min (t_3), 10th min (t_4), 15th min(t_5).*P<0.05 - Student *t* test.

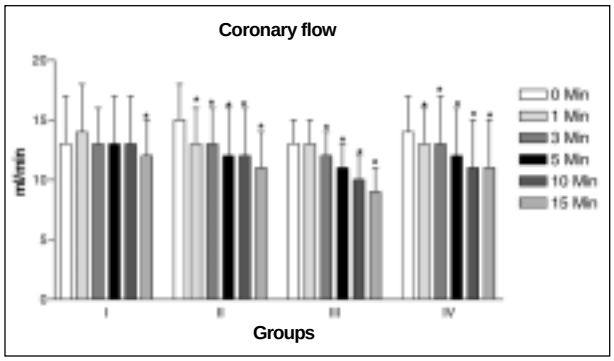

Fig. 4 - Group I: control; group III: propofol; group IV: propofol+propafenone. Values obtained in table III (mean and standard deviation). *P<0.05 - Student *t* test.

Table III - Coronary flow variation in the groups studied (mL/min)

Groups	Períods t_0	t_1	t_2	t_3	t_4	t_5
I	13±4	14±4	13±3	13±4	13±4	12±3*
II	15±3*	13±3*	13±3*	12±4*	12±4*	11±3*
III	13±2	13±2	12±2*	11±2*	10±2*	9±2*
IV	14±3	13±3*	13±4*	12±4*	11±4*	11±4*

Group I: control, group ± I: propafenone; group III: propofol; group IV: propofol+propafenone; control(t_0), 1st min (t_1), 3rd min (t_2), 5th min (t_3), 10th min (t_4), 15th min(t_5).*P<0.05 -Student *t* test.

time. The interaction of these medications may generate unexpected consequences in the initial approach to the patient. Several possibilities of interaction exist, and, therefore, they are an extensive research field, extremely important in clinical practice. The study of the interaction of these medications in clinical trials is difficult, and the use of experimental animal models is essential. In addition to that, the effects of an in vivo medication may be difficult to assess, due to the metabolic interferences of the autonomous nervous system and due to the changes in the heart rate, preload, and afterload.

Among the most commonly used medications in clinical practice, propafenone stands out because of its efficacy in suppressing ventricular and supraventricular arrhythmias. The use of this medication is not rare during surgeries where anesthesia is used, and therefore the possibility of an interactive effect is present.

Propofol is a medication that has been used frequently in cardiovascular surgeries with the possibility of interaction with propafenone. However, studies on the add-on effect of the propafenone-propofol association were not found. Taking into account that the 2 medications have a suppressor myocardial effect, a study is necessary.

Salerno et al [42] reported a decrease in left ventricular function in patients receiving propafenone. Baker et al [43] reported similar results. Meneghin [44] observed that even in healthy hearts, propafenone has a reversible negative inotropic effect. A similar fact was reported by Santana [45], Faraj[46], and Nakamura et al [47], all of whom studied isolated rat hearts.

In the present investigation, propafenone produced significant myocardial depression. However, associated with propofol it did not have an additive effect.

Rouby et al [48], studying the effects of propofol in patients with artificial hearts, concluded that cardiovascular depression of propofol is associated with the venous and arterial vasodilation effect rather than with myocardial depression. However, in the present study the significant depressive myocardial effect of propofol was confirmed.

Heart rate significantly decreased in all assessed periods in the propafenone and propofol groups, contrary to the findings of Riou et al [23] who did not demonstrate significant negative chronotropic effects in the myocardium of rats.

Coronary flow analysis did not demonstrate a significant decrease in groups II and IV in all times assessed, regarding the control groups apart from the 10th and 15th minutes of group II.

The pro-arrhythmic effect of propafenone was reported by Podrid [37] and Zipes [38]. In our investigation, 50% of the hearts studied in group II experienced arrhythmias. However, with the use of propofol, in isolation, arrhythmias were not observed, and an increase in the incidence of arrhythmias associated with the use of propofol and propafenone did not occur.

Based on the results obtained, we conclude that propafenone has negative inotropic and chronotropic effects, with arrhythmogenic effects and decreases in coronary flow. Propafenone-propofol association neither exaggerated the negative inotropic effect of propafenone in isolation nor increased its arrhythmogenic effect.

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