Sevoflurane Enhances Negative Inotropic Action of Pilsicainide and Flecainide

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Abstract

Pilsicainide and flecainide, which have a relatively low negative inotropic action, are sometimes used for the treatment of intraoperative atrial fibrillation. Sevoflurane, commonly used for general anesthesia, also has a negative inotropic action. The use of sevoflurane in combination with antiarrhythmic agents can lead to increased negative inotropic effect. The present study was undertaken to evaluate the effects of sevoflurane used in combination with pilsicainide or flecainide on myocardial contractility, using isolated rat hearts.

Each isolated heart was perfused by the Langendorff method and paced at a rate of 300 bpm to measure left ventricular systolic pressure (LVSP). The LVSP recorded after hemodynamic stabilization served as the baseline LVSP. LVSP was measured again 20 minutes after the start of perfusion with a solution of pilsicainide or flecainide at concentrations of $10^{-9}$, $10^{-8}$, $10^{-7}$, and $10^{-6}$M. In the sevoflurane-added groups, baseline LVSP was measured about 10 minutes after treatment with 1.4% sevoflurane using a vaporizer, i.e., after stabilization of LVSP following a sevoflurane dose. Immediately after baseline LVSP measurement, pilsicainide or flecainide was added to the perfusion system at the concentrations given above. Twenty minutes later, LVSP was measured. The baseline LVSP did not differ between any two groups. The lowest drug concentration causing significant reduction of LVSP was higher in the non-combined pilsicainide treatment group than in the non-combined flecainide treatment group. However, when each of these two drugs was administered in combination with sevoflurane, the negative inotropic effect of pilsicainide did not differ significantly from that of flecainide.

The results suggest that negative inotropic effect is lower with pilsicainide than with flecainide, but that this difference was not seen when each of the two drugs was administered individually together with sevoflurane. Thus, we conclude that careful hemodynamic monitoring is necessary when the antiarrhythmic drug is administered under sevoflurane anesthesia.

Key Words

pilsicainide, flecainide, sevoflurane, negative inotropic action, atrial fibrillation

Introduction

Prevention of myocardial ischemia and control of arrhythmias are important elements of perioperative cardiovascular management. Atrial fibrillation is one of the tachycardiac arrhythmias encountered relatively frequently during routine clinical practice, and its incidence rises as the patient age increases. Following recent advances in operative procedures, anesthetic management and monitoring devices, there has been a growing tendency for anesthesia to be performed for elderly patients or those with poor preoperative conditions. A basic strategy for anesthetic management in patients with atrial fibrillation is to maintain an appropriate depth of anesthesia while suppressing the sympathetic reflex. If...
Atrial fibrillation assumes the form of paroxysmal atrial fibrillation during surgery, class la or Ic anti-arrhythmic agents are sometimes used. In Japan, sevoflurane (volatile anesthetic) is commonly used for general anesthesia. However, sevoflurane and many other volatile anesthetics agents have a negative inotropic effect of varying degrees. It is therefore possible that the negative inotropic effect of antiarrhythmic agents might be augmented if these agents are used in combination with volatile anesthetics.

Both pilsicainide and flecainide are antiarrhythmic agents of class Ic, according to the Vaughan Williams classification. Pilsicainide with relatively low negative inotropic effect is now used only in Japan. According to the Guidelines on Drug Therapy for Atrial Fibrillation, published in 2001, oral-dose pilsicainide is one of the first-line drugs for the Management of Patients with Atrial Fibrillation prepared in 2002 by the ACC/AHA/ESC (American College of Cardiology, American Heart Association, and European Society of Cardiology), intravenous treatment with class III antiarrhythmics or class Ic antiarrhythmics (propafenone and flecainide) is recommended as the first-line drug therapy for atrial fibrillation. At present, the Japanese Rhythm Management Trial on Atrial Fibrillation (J-RHYTHM) is being carried out in Japan, to collect evidence of the validity of management under the situation currently prevailing in Japan. However, none of these surveys and studies was designed to explore or evaluate therapeutic strategies for atrial fibrillation during general anesthesia. To date, no report has been published concerning the influence of sevoflurane on the myocardial effects of pilsicainide or flecainide.

The present study was undertaken to evaluate the effects of sevoflurane, used in combination with pilsicainide or flecainide, on myocardial contractility, using isolated rat hearts.

Materials and Methods

1. Materials and Preparation of Isolated Heart Samples

Nine-week-old male Wistar rats, weighing 300–360 g, were intraintraperitoneally injected with pentobarbital (Nembutal®, Dainippon Pharmaceutical Co., Ltd.) at a dose of 25 mg/kg body weight, then the heart was immediately removed.

Each isolated heart was perfused with Krebs-Ringer solution (NaCl 108 mM, KCl 4.75 mM, MgSO4 1.19 mM, KH2PO4 1.19 mM, CaCl2 2.54 mM, glucose 10 mM and NaHCO3 22.5 mM) at 37°C. After incision of the left atrium, a latex balloon was inserted into the left ventricle to measure left ventricular systolic pressure (LVSP) and left ventricular end-diastolic pressure (LVEDP). A needle electrode was inserted into the right atrium and ventricle to keep the heart rate constant at 300 beats/min, using an electric stimulator (SEN-101J, Nihon Kohden Corporation) in combination with an isolator (SS-101J, Nihon Kohden). During the experiment, the perfusion pressure was set at 60 mmHg, and the LVEDP was kept at 5 mmHg by adjusting the balloon pressure within the left ventricle.

2. Administration of sevoflurane

Sevoflurane was passed together with a mixture of 95%O2+5%CO2 through a calibrated vaporizer (Sevotec3, Omeda Co., Ltd.), specially designed for sevoflurane. The gas was then guided into the Krebs-Ringer solution at a rate of 5 l/min for perfusion through the isolated heart. The sevoflurane concentration was set at 1.4%, equivalent to 1 MAC for rats.

3. Dose of pilsicainide and flecainide

The present study was undertaken to evaluate the effects of sevoflurane, used in combination with pilsicainide or flecainide, on myocardial contractility, using isolated rat hearts.
hearts for which no drug was administered. LVSP was measured 20 minutes later (20-minute LVSP).

2) For some isolated hearts, either pilsicainide or flecainide was administered at varying concentrations. And LVSP was measured as same as above.

3) In the sevoflurane group, sevoflurane (1.4%) was administered using a vaporizer at 37°C, and baseline LVSP was measured about 10 minutes after the start of perfusion, i.e., after stabilization of LVSP. This was immediately followed by administration of pilsicainide or flecainide at varying concentrations. Twenty-minute LVSP was also measured.

Each parameter was expressed as the mean±SD. Data were analyzed using one-way analysis of variance with Cochran-Cox post hoc test for multiple comparisons significant differences were considered if the P value was <0.05.

This study protocol was assessed and approved by the Experimental Animal Committee of St. Marianna University School of Medicine prior to starting the experiments.

Results

1. LVSP on baseline

Table 1 summarizes the effects of flecainide or pilsicainide (with or without concomitant administration of sevoflurane) on LVSP. There was no significant difference in LVSP on baseline between any two groups (including the control group).

2. Changes of LVSP by pilsicainide or flecainide

The effects of flecainide or pilsicainide on 20-minute LVSP are shown in Table 1. Both pilsicainide and flecainide decreased LVSP in a dose-dependent manner, and the minimum dose causing significant reduction of LVSP was lower with flecainide than with pilsicainide (p<0.05).

3. Changes of LVSP by pilsicainide or flecainide in combination with sevoflurane

Both pilsicainide with sevoflurane and flecainide with sevoflurane decreased LVSP at doses of pilsicainide or flecainide over 10−4 M. Pilsicainide with sevoflurane significantly decreased LVSP than pilsicainide alone at any concentration (p<0.05). Flecainide with sevoflurane decreased LVSP than flecainide alone at 10−4 M and 10−3 M (p<0.05).

When percent change in LVSP was analyzed at each dose of pilsicainide or flecainide administered in combination with sevoflurane, in comparison with pilsicainide or flecainide alone (Figs. 1 and 2), pilsicainide with sevoflurane significantly reduced percent change of LVSP at all doses except 10−3 M (p<0.05), but no significant difference in percent change of LVSP was seen at any dose of flecainide.

Discussion

1. Suppression of myocardial contractility following treatment with pilsicainide or flecainide alone

In the present study, both drugs, administered independently without sevoflurane, exerted negative inotropic effect in an approximately dose-dependent manner. Generally, class I antiarrhythmic agents are known to exert a dose-dependent negative inotropic effect. A similar result was also obtained in the study conducted by Kihara et al. designed to evaluate the effects of these two drugs on the contractility of canine right ventricular myocardium.

Asaike et al. also reported a dose-dependent reduction in myocardial contractility following treatment of guinea pig papillary muscle with pilsicainide hydrochloride, identical to the results obtained in the present study.
In this study, myocardial contractility was significantly lower in the pilsicainide group than in the control group at pilsicainide doses of $10^{-7}\text{M}$ and higher. The same parameter was significantly lower in the flecainide group than in the control group at flecainide doses of $10^{-8}\text{M}$ and higher ($P<0.05$).

Both pilsicainide and flecainide are class Ic antiarrhythmic agents and Na channel blockers. According to the prevailing view on the mechanism underlying the negative inotropic effect of these two drugs, the drugs reduce intracellular Na$^+$ levels, and the resultant decrease in Ca$^{2+}$ flow into cells and decrease in Ca$^{2+}$ stores within the sarcoplasmic reticulum lead to a decrease in the release of Ca$^{2+}$ and suppression of contractility\textsuperscript{11}. Two major mechanisms known to determine Ca stores are: (1) Na$^+/\text{Ca}^{2+}$ exchange, and (2) Ca$^{2+}$ influx via the Ca$^{2+}$ channel. The influx of extracellular Ca$^{2+}$ serves not only as a factor determining the amount of Ca$^{2+}$ stored in the sarcoplasmic reticulum but also as a factor triggering the release of Ca$^{2+}$ from the sarcoplasmic reticulum, thereby regulating the amount of Ca$^{2+}$ released\textsuperscript{12}. According to a previous report dealing with the effects of pilsicainide and flecainide on this Ca$^{2+}$ channel (L type Ca$^{2+}$ channel), treatment with $10^{-4}\text{M}$ flecainide suppressed the peak Ca$^{2+}$ current to about 35% of the control level, while treatment with the same concentration of pil-
pilsicainide suppressed it to only about 70% of the control level\(^4\). This result suggests that the negative inotropic effect of class I antiarrhythmic agents depends not only on Na\(^+/\)Ca\(^{2+}\) exchange but also on some other mechanisms, and that the difference in the effect on Ca\(^{2+}\) channels between the two drugs reflects a difference in negative inotropic effect between these drugs. Kihara et al. additionally reported that the magnitude of negative inotropic effect at doses of 10\(^{-5}\) and 10\(^{-4}\) M was significantly higher with flecainide than with pilsicainide\(^4\). Although the present study used an experimental model different from that employed by Kihara et al., negative inotropic effect, as compared with that of the control group, was lower in the pilsicainide group than in the flecainide group. However, the lowest concentration of these drugs exerting negative inotropic effect was lower in the present study than in the aforementioned previous studies. This discrepancy between the present and previous studies may be associated with a difference in the animal species tested (rat in our study and canine by Kihara et al.) and/or a difference in the experimental system (whole heart in our study and papillary muscle by Kihara et al.). Another factor possibly responsible for the discrepancy is a difference in the frequency of stimulation (0.33 Hz stimulation of isolated muscle by Kihara et al. and stimulation of isolated heart at a pacing rate of 300/min in our study), which can have different impacts on the frequency-dependent blocking effect of Na channel blockers. Frequency-dependent blocking effect means that the suppressive effect is higher against cells undergoing frequent, i.e., repeated, excitation. It seems likely that drugs with high affinity for Na channel-activated conditions (e.g., pilsicainide and flecainide) exert more potent suppression on cells with higher frequency of excitation.

2. **Myocardial contractility following pilsicainide or flecainide in combination with sevoflurane**

When administered in combination with sevoflurane, pilsicainide and flecainide each significantly reduced myocardial contractility at doses over 10\(^{-4}\) M as compared with the control group.

Generally, volatile anesthetics reduce myocardial contractility in a dose-dependent manner\(^1\). Mechanisms which have been proposed to explain this effect include: (1) reduction of the intracellular Ca\(^{2+}\) level due to suppression of Ca\(^{2+}\) influx via the L type Ca\(^{2+}\) channel, (2) decrease in the amount of Ca\(^{2+}\) ion stored in the sarcoplasmic reticulum due to suppression of Ca-ATPase activity, and so on\(^6\). In the present study, pilsicainide or flecainide at each dose in combination with sevoflurane significantly reduced the LVSP as compared to the control group. This indicates that although suppression of Ca\(^{2+}\) influx via the L type Ca\(^{2+}\) channel is less severe with pilsicainide than with flecainide, the negative inotropic effect of these two drugs was enhanced by concomitant administration of sevoflurane (a drug suggested to suppress Ca\(^{2+}\) influx via the L type Ca\(^{2+}\) channel, as a possible mechanism of myocardial contractility suppression).

Several mechanisms have been proposed to explain suppression of myocardial contractility by sevoflurane\(^2\)\(^-\)\(^7\). However, considering that negative inotropic effect in the pilsicainide with sevoflurane group was comparable to that in the flecainide with sevoflurane (more potent L type Ca\(^{2+}\) channel blocker) group in the present study, it seems likely that sevoflurane suppresses myocardial contractility primarily through its action on the L type Ca\(^{2+}\) channel. In the present study, the value of LVSP measured 20 minutes after the start of perfusion was compared with the baseline LVSP, in view of the report by Nishikido et al. that the sevoflurane level in perfused solution had reached equilibrium by 20 minutes after administering a dose of the drug and did not differ between measurements at 20 minutes and 30 minutes\(^6\). Sevoflurane was administered at a concentration of 1.4% in the present study because treatment with sevoflurane alone at this level reportedly does not significantly suppress myocardial contractility\(^6\).

3. **Effects of sevoflurane on the activities of pilsicainide and flecainide at each dose level evaluated on the basis of percent change in LVSP**

This analysis revealed significant suppression of myocardial contractility following combined administration at most doses of pilsicainide but no significant suppression at any dose of flecainide, as compared with administration using these drugs alone. This result also suggests that the influence of simultaneously administered sevoflurane (known to possibly modify the negative inotropic effect of antiarrhythmic agents by suppressing Ca\(^{2+}\) influx via the L type Ca\(^{2+}\) channel) was greater with pilsicainide, which is known to cause less suppression of Ca\(^{2+}\) influx through the same channel than flecainide.

During clinical practice, hemodynamic parameters of patients with atrial fibrillation may sta-
bilize if reentry is stopped. In the present study, negative chronotropic effect was not analyzed, since we focused on the negative inotropic effect of pilscia
cainide and flecainide and because the study in-
volved heart pacing. To allow application of the findings from this kind of study to clinical settings, it seems desirable to measure the magnitude of both negative inotropic and chronotropic effects. Other limitations of the present study are: (1) the study was in vitro, (2) the influence of systemic vascular resistance was not considered, and (3) retrograde perfusion (perfusion in a non-physiological di-
rection) was employed. We should also point out that
if data on conduction systems and coronary blood
flow had been available, a more detailed analysis
based on comprehensive data assessment would
have been possible.

In conclusion, the results of the present study
suggest that although suppression of myocardial
contractility is less severe following pilscia
cainide alone than following flecainide alone, the magni-
tude of suppression is approximately the same for
these two drugs when used in combination with
sevoflurane. The results also suggest that careful
hemodynamic monitoring is necessary when antiar-
rhythmnic drug is administered under sevoflurane
anesthesia.

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Reference

1) Yamada T. Atrial Fibrillation and Anesthetic
Management. J Clin Anesth (Jpn) 2004; 28:
1059–1063.
2) Matsumoto M and Yamashita T. The Treat-
ment of Atrial Fibrillation Based on Clinical
3) Toyama J and Nakazawa H. Drug Treatments
Guidelines of Atrial Fibrillation. Jpn Circ J
2001; 65: 931–998.
4) Fuster V, Ryden LE, Asinger RW, Cannom
DS, Crijns HJ, Fyne RL, Halperin JL, Kay
GN, Klein WW, Levy S, Menamara RL,
Prystowsky EN, Wann LS and Wyse DJ. ACC
/AHA/ESC Guidelines for the Management of
Patients With Atrial Fibrillation. Circulation
5) Yamashita T, Ogawa S, Aizawa Y, Atarashi H,
Inoue H, Ohe T, Okumura K, Kato T, Kama-
kura S, Kumagai K, Kurachi Y, Kodama I,
Koretsune Y, Saikawa T, Sakurai M, Sugi K,
Nakaya H, Nakayama T, Hirai M, Fukatani
M, Mitamura H and Yamazaki T. Investigation
of the Optimal Treatment Strategy for
Atrial Fibrillation in Japan —The J-
RHYTHM (Japanese Rhythm Management
Trial for Atrial Fibrillation) Study Design. Circ
6) Hanouz JL, Vivien B, Gueugniaud PY, Lecarp-
pentier Y, Coriat P and Riou B. Comparison
of the Effects of Sevoflurane, Isoflurane and
Halothane on Rat Myocardium. Br J Anaesth
7) Yokota M, Miyahara T, Enomoto N, Inagaki
H, Goto J, Hayashi H, Toyama J and Tobata
I. Pharmacokinetics and Pharmacodynamics
of SUN 1165, a Novel Antiarrhythmic Agent,
after Administration of a Single Oral Dose.
8) Sugiyama A, Takehana S, Kimura R and
Hashimoto K. Negative Chronotropic and
Inotropic Effects of Class I Antiarrhythmic
Drugs Assessed in Isolated Canine Blood-
perfused Sinoatrial Node and Papillary Muscle
9) Kihara Y, Inoko M, Hatakeyama N, Momose
Y and Sasayama S. Mechanisms of Negative
Inotropic Effects of Class Ic Antiarrhythmic
Agents: Comparative Study of the Effects of
Flecainide and Pilsicainide on Intracellular
Calcium Handling in Dog Ventricular Myocar-
10) Aisaka K, Hidaka T, Inomata N, Hamazaki S,
Ishihara T and Morita M. N- (2,6-Dimethyl-
phenyl)-8-Pyrrolizidineacetamide Hydrochlor-
ide Hemihydrate (SUN1165): A New Potent
and Long-acting Antiarrhythmic Agent.
Arzneim-Forsch/Drug Res 35(II), 8, 1239–1245
(1985).
11) Hiraoka M. Electro Pharmacology of Na+
Channel Blockers with Slow Kinetics of Disso-
12) Park WK, Pancrazio JJ, Suk CK and Lynch
CIII. Myocardial Depressant Effects of Sevo-
13) Bosnjak JZ, Supan FD and Rusch NJ. The
Effects of Halothane, Enflurane, and Isoflurane

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セボフルランはビルジサイニドおよびフレカイニドの陰性変力作用を増強する

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抄 録

ビルジサイニドは陰性変力作用が少なく術中の心房細動の治療に用いられることがある。一方、全身麻酔薬として一般的に用いられているセボフルランは陰性変力作用を有し、抗不整脈薬を併用すると陰性変力作用が増強される可能性がある。そこで、ラット摘出心を用いてセボフルランがビルジサイニドあるいはフレカイニドの心収縮力に及ぼす影響を検討した。

Langendorff法により摘出心を灌流して300 bpmでベーシングし、室壁収縮圧 (LVSP) を測定した。循環動態安定後のLVSPをbaselineとした。ビルジサイニド、フレカイニドをそれぞれ10⁻⁷M、10⁻⁷M、10⁻⁸M、10⁻⁹Mを投与後20分灌流した後にLVSPを測定した。セボフルラン投与群では1.4％のセボフルランを投与し10分間灌流後の圧をbaseline値としてLVSPを測定した。その直後、ビルジサイニドあるいはフレカイニド各濃度を投与し20分後にLVSPを測定した。Baselineにおいて全群間で有意差は認められなかった。ビルジサイニド単独群ではフレカイニド単独群より高濃度でLVSPを有意に低下させた。一方、セボフルラン投与下ではビルジサイニドとフレカイニドの陰性変力作用に差は無かった。

ビルジサイニドはフレカイニドより陰性変力作用は少ないが、セボフルラン投与下では差が無く使用に際して注意深い循環動態の観察が必要であると考えられた。