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Original Article

Dose-dependent effects of isoflurane on cardiovascular function in rats

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ABSTRACT

Objectives: Isoflurane is a widely used anesthetic in clinical practice and animal experiments. It exerts cardioprotective effects by pre- and postconditioning but also has dose-dependent cardiovascular side effects. In this article, we aim to characterize the hemodynamic effects of isoflurane.
Materials and methods: We used a pressure–volume catheter to evaluate the hemodynamic changes in adult Sprague–Dawley rats ($n = 6$) given increasing concentrations of inhaled isoflurane anesthesia. The concentration was started at 0.5% (baseline) and gradually increased. Data on cardiovascular variables were recorded at each concentration.
Results: Heart rate, blood pressure, and left ventricular systolic and diastolic function decreased as isoflurane concentration increased. At a concentration of 3%, isoflurane significantly decreased myocardial contractility, blood pressure, and heart rate, and impaired left ventricular diastolic function.
Conclusion: High-dose isoflurane resulted in unfavorable hemodynamics. Old age and dehydration may predispose animals to the unfavorable hemodynamic effects of isoflurane. Determining the optimal isoflurane concentration for anesthesia or preconditioning is important. The effects of isoflurane anesthesia on aged and/or volume-depleted animals should be further investigated.

1. Introduction

Isoflurane is a common inhalational anesthetic in animal experiments and clinical practice. Thus, the cardiovascular characteristics of this agent should be carefully investigated. Isoflurane affects several hemodynamic parameters, which result in various cardiovascular side effects. It alters cardiac electrophysiological function and may cause arrhythmia and decrease cardiac contractility [1,2]. Furthermore, isoflurane decreases peripheral vascular resistance [3], leading to hypotension. Because it is a potent coronary vasodilator, isoflurane may, under certain conditions, cause a coronary steal phenomenon in ischemic regions [4]. However, isoflurane also has a dose-dependent cardioprotective effect. It can protect the heart against ischemia–reperfusion injury and may limit myocardial infarct size to an extent similar to that seen in ischemic preconditioning.

The cardioprotective mechanisms of volatile anesthetics have been extensively studied [5], but the mechanisms responsible for cardioprotection are not well understood. Phosphatidylinositol 3-kinase has a role in myocardial protection from both anesthetic and ischemic preconditioning [6]. Isoflurane has been used during cardiac surgery to exert a preconditioning protective effect [7]. However, the optimal isoflurane concentration for preconditioning may have undesirable hemodynamic effects on patients. Therefore, the effect of dose dependency on hemodynamics during isoflurane anesthesia should be investigated.

Pressure–volume analysis is a useful approach for examining *in vivo* intact ventricular function in all loading conditions. The reliability and reproducibility of pressure–volume catheters for simultaneous, real-time measurement of left ventricular (LV) pressure and volume make them useful for evaluating LV function

Conflicts of interest: none.

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[8]. This technique has been widely used in humans and large animal studies since the mid-1980s. Recent advances in the development and validation of microconductance pressure–volume catheters have made it possible to use this approach to assess cardiac and pharmacological interventions in small animals. A technique for LV pressure–volume analysis in rats was recently introduced. However, only limited normative data are available [9].

We used a pressure–volume loop system to investigate the hemodynamic effects of different concentrations of inhalational isoflurane anesthesia in adult rats.

2. Materials and methods

2.1. Animals

Male Sprague–Dawley rats ($n = 6$; age 8–12 months; weight, about 600 g) were purchased from BioLASCO Co., Ltd. (Taipei, Taiwan). The rats were kept in cages (2 rats per cage) in our laboratory animal center and fed with standard laboratory diet and tap water *ad libitum* on a 12-h/12-h light/dark cycle. All study procedures were performed in accordance with the guidelines of the Institutional Animal Care and Use Committee of Tzu Chi University, Hualien, Taiwan.

2.2. Experimental protocol

Anesthesia induction was performed with a mixture of 5% isoflurane and oxygen in an induction chamber. After induction, the animals were placed on a heating pad in the supine position. A tracheostomy was performed, and the animals were ventilated with a mixture of 1.5% isoflurane and oxygen by a Harvard rodent ventilator (Model 683; Harvard Apparatus, Holliston, MA, USA) during the instrumentation procedure. The ventilator was set at a tidal volume of $6.2 \times M^{1.01}$ (where M denotes the animal mass in kg) and a frequency of 70 ventilations/minute. The right carotid artery was exposed, and a pressure–volume catheter (SPR-901; Millar Instruments, Inc., Houston, TX, USA) was inserted into it and advanced into the LV while being guided by real-time pressure and volume signals. A polyethylene tube was inserted into the left jugular vein for administration of fluids. The signals were continuously recorded by a PowerLab data acquisition system and LabChart software (AD Instruments, Mountain View, CA, USA). Then, four different isoflurane concentrations—0.5% (baseline), 1%, 2%, and 3%—were given as the interventions. The experiment started at an isoflurane concentration of 0.5%, and the concentration was increased every 3 minutes. Heart rate, blood pressure, maximum first derivative of LV pressure over time (dP/dt max), and minimum first derivative of LV pressure over time (dP/dt min) were recorded continuously at each concentration and compared with values obtained at other concentrations. Inferior vena cava compression was performed at every isoflurane concentration, and the end-systolic pressure–volume relation (ESPVR) was recorded.

2.3. Statistical analysis

Descriptive statistics are expressed as means ± standard deviations for all hemodynamic variables. The Friedman test was used to evaluate the effects of different concentrations. A p value of < 0.05 indicated statistical significance. If the result was significant, the Dunn *post hoc* test was used to compare the difference between the value at baseline and the value at a given isoflurane concentration.

3. Results

3.1. Heart rate

Hemodynamic characteristics, including heart rate, blood pressure, and dP/dt, are shown according to isoflurane concentration in Table 1. The heart rate increased when the isoflurane concentration was increased from 0.5% to 1% and then progressively decreased with increasing isoflurane concentration. The difference in heart rate at a concentration of 1.5% (standard) versus 0.5% isoflurane (baseline) was not significant. However, heart rate significantly differed between the baseline concentration and the concentration of 3% (high dose; Fig. 1).

3.2. Blood pressure

Systolic blood pressure, diastolic blood pressure, and mean arterial pressure increased as the isoflurane concentration was increased from 0.5% to 1% and then progressively decreased with increasing isoflurane concentration. As compared with baseline, these variables were significantly lower at a concentration of 3%. However, LV end-diastolic pressure did not significantly change in relation to isoflurane concentration. The difference between diastolic aortic pressure and LV end-diastolic pressure (DBP − Ped), which represents coronary perfusion pressure, was also significantly lower than the baseline value at a concentration of 3% ($p < 0.001$).

3.3. Cardiac systolic function

At a concentration of 3%, dP/dt max, the maximum rate of pressure change in the ventricle, was significantly lower than at baseline. However, dP/dt max is load-dependent and, therefore, a

Table 1
Cardiovascular characteristics of rats according to the concentration of isoflurane anesthesia.

	ISO 0.5% (baseline)	ISO 1%	ISO 1.5%	ISO 2%	ISO 3%
Heart rate (bpm)	325.0 (16.9)	341.0 (29.1)	321.0 (23.4)	278.2 (31.7)	234.8 (21.8)*
SBP (mmHg)	154.2 (13.3)	160.0 (26.4)	126.2 (27.3)	100.4 (25.6)	85.0 (16.1)*
DBP (mmHg)	118.4 (9.7)	120.0 (24.2)	92.6 (33.1)	62.5 (30.1)	49.4 (23.1)*
MAP (mmHg)	130.3 (10.7)	133.3 (24.9)	103.8 (31.1)	75.1 (28.3)	61.3 (20.6)*
DBP − Ped (mmHg)	113.1 (10.0)	114.4 (24.1)	86.8 (33.6)	56.8 (29.8)	42.9 (22.3)*
Pes (mmHg)	154.5 (14.7)	158.9 (28.5)	127.8 (27.4)	103.9 (27.9)	86.0 (14.6)*
Ped (mmHg)	5.3 (2.0)	5.6 (1.4)	5.8 (1.6)	5.7 (2.0)	6.6 (2.8)
dP/dt max (mmHg/s)	10,278.2 (1278.6)	10,321 (717.7)	8424.5 (1784.9)	5782.8 (2249.1)	4312.5 (1315.9)*
dP/dt min (mmHg/s)	8009.5 (392.0)	7988.5 (907.8)	6537.3 (1757.2)	4736.0 (1911.8)	3663.2 (1200.6)*

Data are presented as mean (SD).
*$p < 0.05$ versus ISO 0.5% (baseline).
DBP = diastolic blood pressure; ISO = isoflurane; MAP = mean arterial pressure; Ped = left ventricular end-diastolic pressure; Pes = left ventricular end-systolic pressure; SBP = systolic blood pressure.