The Effect of Anesthetic on Hemodynamics Measurements in a Rat Model of Monocrotaline-Induced Pulmonary Arterial Hypertension

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Abstract

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Monocrotaline (MCT)-induced pulmonary arterial hypertension (PAH) in rats is a well characterized animal model. MCT administration results in damage of the pulmonary arterial vascular endothelium, pulmonary hypertension, right ventricle hypertrophy and failure. In this study, we compared the hemodynamic parameters from PAH rats anesthetized with isoflurane vs. ketamine/xylazine. Male Sprague-Dawley rats were injected subcutaneously on day 0 with 60 mg/kg monocrotaline. On day 28, animals were anesthetized by intra-muscular injection of ketamine/ xylazine (Ket; 80/10 mg/kg) or connected to a vaporizer that delivers 1-2% MAC isoflurane (Iso) driven by 100% oxygen. A Millar catheter was inserted into the femoral artery to measure arterial blood pressure. The pulmonary artery and right ventricular pressures were measured via venous approach using a curved 3.5 French umbilical vessel catheter. Hemodynamics were monitored for 15-20 minutes. Iso anesthetized rats exhibited systolic, diastolic and mean pulmonary arterial pressure values (32±3.8, 25±2.4 and 28±3.1 mmHg, respectively p>0.05) comparable with the Ket anesthetized rats (38±4.5, 22±2.4 and 29±3.3 mmHg, respectively). Systemic pressures were also comparable, Iso –SAP 93±2.7, DAP 67±2.3 and MAP 79±2.1 mmHg (p>0.05); and Ket- SAP 95±3.6, DAP 68±3.5 and MAP 80±3.9 mmHg. Heart rate was similar in both groups, 361±41.2 bpm (Iso) vs 278±8.5 bpm (Ket). Isoflurane anesthesia is similar to ketamine for evaluating hemodynamic function of monocrotaline-induced pulmonary hypertension in rats.

Introduction

Pulmonary arterial hypertension (PAH) is a chronic disease characterized by sustained elevation of pulmonary arterial pressure that leads to right ventricle failure and death. Pulmonary arterioles in PAH undergo progressive narrowing and/or occlusion. Currently approved therapies for PAH are directed primarily at relief of symptoms by interfering with vasoconstrictive signals, but do not halt the microvascular cytoproliferative process. The industry is focused in improving the available therapies to treat PAH however clinical relevant models are crucial for testing new articles.

Monocrotaline (MCT)-induced pulmonary arterial hypertension (PAH) in rats is a well characterized animal model. MCT administration results in damage of the pulmonary arterial vascular endothelium, pulmonary hypertension, right ventricle hypertrophy and failure.

In this study, we compared the hemodynamic parameters from PAH rats anesthetized with isoflurane vs. ketamine/xylazine.

Objectives

In this study, we compared the hemodynamic parameters from PAH rats anesthetized with isoflurane vs. ketamine/xylazine.

Methods

Experimental Plan: Male SD rats (270-370 g) were injected subcutaneously on Day 0 with 80 mg/kg body weight monocrotaline, the toxic alkaloid of C. spectabilis, (1 mL/kg dissolved in DMSO, Sigma Aldrich, St. Louis, MO). On days 1 – 28, rats were dosed via oral gavage (5 mL/kg) with vehicle (0.5% methylcellulose in deionized water).

Hemodynamic Measurements: On day 21, animals were anesthetized by intra-muscular injection of ketamine/xylazine (80/10 mg/kg) or connected to a vaporizer that delivered 1-2% MAC isoflurane driven by 100% oxygen. Animals were placed on a heating pad to maintain body temperature at 37°C. A Millar catheter 1.4 French (Millar Instruments, Houston, TX) was inserted into the femoral artery to measure arterial blood pressure. Additionally, the pulmonary artery pressures were measured as described previously (Stinger et al., 1981). Briefly, a 3.5 French umbilical vessel catheter (Utah Medical Products LTD, Midvale, Utah), angled to 90° over the distal 1 cm and curved slightly at the tip, was introduced into the right external jugular vein, with the angle directed interiorly, the catheter was inserted proximally, which placed the catheter in the right atrium. The catheter was rotated 90° counterclockwise and inserted further, which placed the catheter in the right ventricle, and then advanced approximately 1.5 cm, into the pulmonary artery. Placement at each stage was confirmed by monitoring the respective pressure contours. Hemodynamics were monitored for 15-20 minutes and values were automatically calculated by a physiologic data acquisition system.

Right Ventricular Hypertrophy Measurements: At the end of the study, rats were euthanized by pentobarbital overdose and hearts were isolated, flushed with saline and dissected to separate the right ventricle (RV) from the left ventricle+septum (LV+S). Dissected samples were weighed and the ratio of the RV weight to body weight [RV/BW] for each heart was calculated to obtain an index of RV hypertrophy.

Statistical Methods: All data are expressed as mean ± S.E.M. The different experimental groups were analyzed by unpaired t-test, significance was fixed at $p<0.05$. All statistical analyses were conducted with GraphPad Prism.

Summary

- Isoflurane anesthetized rats exhibited systolic, diastolic and mean pulmonary arterial pressure values not significantly different then ketamine anesthetized rats.
- Systemic pressures and heart rate were also not significantly different in isoflurane anesthetized rats as compared to ketamine.
- Animals in both groups also show same degree of right ventricular hypertrophy, as measured by RV/LV + S and RV/BW ratio).

Effect of Isoflurane and Ketamine Anesthesia on Pulmonary Arterial Pressures in Monocrotaline-Induced Pulmonary Hypertension in Rats

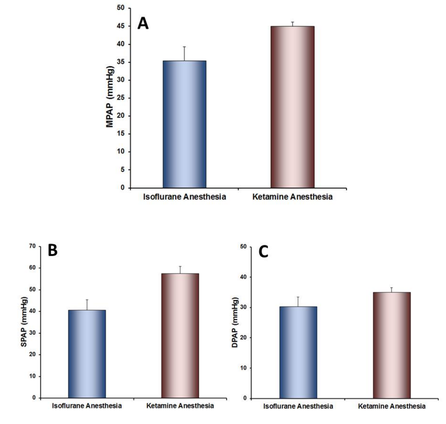

Figure 1. *Effect of isoflurane and ketamine anesthesia on hemodynamics in monocrotaline (MCT) induced pulmonary hypertension in rats. A- Mean pulmonary arterial pressure (PAP). B- Systolic pulmonary arterial pressure (SPAP). C- Diastolic pulmonary arterial pressure (DPAP). MCT-injected rats received vehicle for 21 days. Data are presented as mean ± S.E.M. (n=4-6).*

Effect of Isoflurane and Ketamine Anesthesia on Mean Arterial Pressure and Heart Rate in Monocrotaline Induced Pulmonary Hypertension in Rats

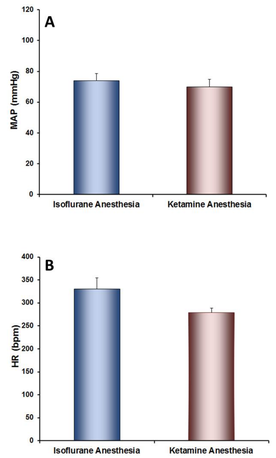

Figure 2. *Effect of isoflurane and ketamine anesthesia on hemodynamics in monocrotaline (MCT) induced pulmonary hypertension in rats. A- Mean arterial pressure (MAP). B- Heart rate. MCT-injected rats received vehicle for 21 days. Data are presented as mean ± S.E.M. (n=4-6).*

Effect of Isoflurane and Ketamine Anesthesia on Right Ventricle to Left Ventricle Ratio and Right Ventricle to Body Weight Ratio in Monocrotaline-Induced Pulmonary Hypertension in Rats

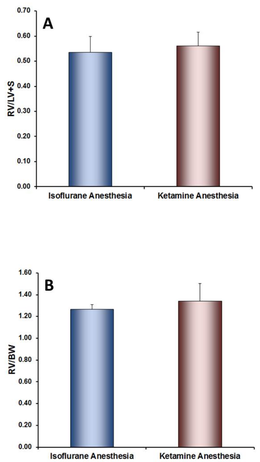

Figure 3. *Effect of isoflurane and ketamine anesthesia on hypertrophy in monocrotaline (MCT) induced pulmonary hypertension in rats. Right ventricle (RV), Left ventricle + septum (LV+S) and body weight (BW). Data are presented as mean ± S.E.M. (n=5-6).*

Conclusions

Isoflurane anesthesia is similar to ketamine for evaluating hemodynamic function of monocrotaline-induced pulmonary hypertension in rats.