

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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Introduction

Pulmonary arterial hypertension (PAH) is a chronic disease characterized by elevated elevation of pulmonary arterial pressure that leads to right ventricular failure and death. Pulmonary arteries 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.

Currently approved therapies for PAH however clinical relevant models are crucial for testing new treatments. 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 ventricular hypertrophy and failure.

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 6 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 1–26, rats were dosed twice weekly with 80 mg/kg monocrotaline in 0.5% methylcellulose in deionized water. Monocrotaline (MCT)-induced pulmonary hypertension (PAH) in rats is a well-characterized animal model. PAH was induced on Day 0 by injecting monocrotaline intraperitoneally. Animals were euthanized on Day 28 at 1 minute before the end of the study. Rats were anesthetized by intraperitoneal injection of ketamine/xylazine (Ket: 80/10 mg/kg) with vehicle (0.5% methylcellulose in deionized water).

Hemodynamic Measurements: On day 21, animals were anesthetized by intramuscular injection of ketamine/xylazine (80/10 mg/kg) at centered in a cage that delivered 1-2% isoflurane driven by 100% oxygen. Animals were placed on a heating pad and 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 (Ringler et al., 1984). Briefly, a 1.5 French unsublotted (20g) 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 inferiorly, the catheter was inserted proximally, which placed the catheter in the right atrium. The catheter was created 90° counter-clockwise 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 percutaneous overloads 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) was calculated as the ratio of right ventricular weight to body weight (BW). Dissected samples were weighed and the ratio of the RV weight to body weight (RV/BW) was calculated as the ratio of right ventricular weight to body weight (BW).

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.

Conclusions

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

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

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

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

Summary

- Isoflurane anesthetized rats exhibited systolic, diastolic and mean pulmonary arterial pressure values not significantly different than 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/19W ratios.

Effect of Isoflurane and Ketamine Anesthesia on Pulmonary Arterial 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). D. Mean arterial pressure (MAP). E. Heart rate (HR). F. Systemic arterial pressure (SAP). G. Body weight (BW). Data are presented as mean ± S.E.M. (n=6).

Figure 2. 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). Data are presented as mean ± S.E.M. (n=6).

Figure 3. 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). Data are presented as mean ± S.E.M. (n=6).

Figure 4. 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). Data are presented as mean ± S.E.M. (n=6).