WALIA journal 30(1): 62-64, 2014
Available online at www.Waliaj.com
ISSN 1026-3861

Effects of ketamine on left ventricular ejection fraction in mixed breed dog

Mehdi Tavana *, Seyedeh Zeinab Peighambarzadeh, Bahador Bardshiri

Veterinary Medicine Department, Faculty of Agriculture, Shoushtar Branch, Islamic Azad University, Shoushtar, Iran

Abstract: Anesthesia is a useful element of experimental Veterinary Medicine procedures. Ketamine is one of the agents that commonly used to induce anesthesia in animals. The cardiovascular effects of these anesthetic agents are diverse, and the response of global myocardial function is unknown. Methods In this study in the ten clinically healthy dogs, echocardiography measurements of left ventricular ejection fraction (LVEF) were obtained before the animals received anesthesia (baseline), after an intramuscular injection of ketamine. The mean LVEF of an unanesthetized dog was 49 ± 2%. There was a significant decrease in the mean LVEF after administration of ketamine to 42.5±7.5% (P value = 0. 0 11). Six of the dogs had an increase in their LVEF with sympathetic stimulation.. In our experimental model the administration of ketamine was associated with decreased LV function. The decrease may be largely secondary to a blunting of sympathetic tone. A significant number of animals had returned to preanesthesia LV function with sympathetic stimulation.

Key words: *Ketamine; Ventricular ejection; Mixed breed dog*

1. Introduction

Anesthesia is frequently required during the clinical management of animals for both therapeutic procedures and experimental models. The response of the cardiovascular system to anesthetic agents can be highly variable, based on agent selection, dosing, and the experimental model (Gross, 2009). Commonly used induction and maintenance anesthesia protocols involve agents that are known to effect the sympathetic and parasympathetic nervous systems, vascular tone, and contractile properties of the myocardium (Kunst et al. 1999). Ketamine, a derivative of phencyclidine and cyclohexamine, is a NMDA antagonist that is frequently used to induce anesthesia in dog experimental models. It acts on the thalamocortical, reticular activating, and limbic systems (Bergman, 1999). Limited models exist to describe the complex cardiovascular effects of ketamine which include increased heart rate, cardiac output, and vascular resistance. A model using isolated chick embryo hearts suggests that this agent decreases myocardial contractile amplitude (Berry, 1974). Descriptions of the effects of these agents on global myocardial function are limited to isolated muscle preparations or different animal models (Hettrick et al, 1996). The specific effects of this agent on global systolic myocardial function in vivo have not been fully evaluated and are critical to understanding the physiologic responses to general anesthesia. The hypothesis of this work is that global myocardial systolic function is affected by ketamine. In this analysis we use standard echocardiography techniques to evaluate the changes in left ventricular ejection fraction after exposure to ketamine in a dog model.

2. Material and Methods

10 clinically healthy dogs, weighing 10 to 14 kg, were used in this study. The anesthesia protocol has been previously published (Link et al, 2001). Dogs were sedated with intramuscular ketamine at a concentration of 12 milligrams per kilogram of body weight. Each animal was placed prone in a sling to approximate physiologic cardiac anatomy and hemodynamics. The anesthesia protocol and experimental design described here are part of a larger research program evaluating sudden death due to low-energy chest-wall impact (commotio cordis) (Link et al, 2001).Echocardiography was performed at the start of the study prior to ketamine administration, while the animal was being held on the stretcher (baseline). Views included parasternal short and long axis, and apical 2 and 4 chamber. Echocardiography was repeated 5 minutes after ketamine administration, and then again 5 minutes after isoflurane administration. After induction of ventricular fibrillation by ball impact and defibrillation, echocardiography was repeated (Link et al, 2001). Heart rates were obtained at each echocardiographic study for each subject. Echocardiograms were reviewed by a single board certified echocardiographer (N.P.) who was blinded to dog specific data and to the stage of the experimental protocol. The global left ventricular ejection fraction (LVEF) was quantitatively assessed

* Corresponding Author.

as well as the presence or absence of wall motion abnormalities.

Results are presented as mean ± standard deviation unless otherwise specified. Data were analyzed using Two-Sample Independent t tests. Statistical significance was set at a probability value of $P<0.05$ with a two sided confidence interval and assuming equal variance. The statistical analyses were run using SPSS Version 17.0.

3. Results

Prior to anesthesia the mean heart rate of the dog was 134 ± 23 and the mean LVEF was 49 ± 2%. No wall motion abnormalities were identified at baseline (Table 1).

After ketamine the mean heart rate was unchanged at 147 ± 14 bpm (= n s) . As compared to baseline, there was a significant decrease in the mean LVEF to 42.5 ± 7.5%, (= 0.011). A decrease in LVEF was observed in 6 of the 10 (60%) subjects, with 4 subjects showing no change in global left ventricular function. In these animals, the LVEF decreased by a mean value of 11.92 ± 12.28% from the baseline. There were no wall motion abnormalities evident after ketamine administration. After initiation of ventricular fibrillation by baseball strikes to the chest wall and defibrillation, 7 of the 15 animals had a return to preanesthesia LVEF (Table 1).

Table 1: Animal Data. Ejection fraction (EF) measurements were made using standard echocardiography techniques. Pulse rate was recorded using standard ECG techniques and is presented as beats per minute.

Num.	Pre-ket EF	Pre-ket pulse	Post-ket EF	Post-ket pulse
1	0.50	146	0.42	162
2	0.44	156	0.45	138
3	0.43	154	0.35	144
4	0.45	152	0.42	146
5	0.43	140	0.40	150
6	0.46	144	0.38	160
7	0.45	128	0.40	140
8	0.45	142	0.44	146
9	048	144	0.44	150
10	049	156	0.45	160

4. Discussion

Ketamine is frequently used in experimental animal models to induce and maintain anesthesia. Ketamine has significant and varied effects on cardiovascular physiology. The contractility and global LVEF changes documented in this dog model are consistent with a report by Schulte-Sasse et al. that showed short-term elevation of filling pressures with ketamine use in human subjects undergoing coronary artery bypass operations (Schulte-Sasse U et al, 1982). The data presented here suggest that this rise in filling pressure is largely related to a decrease in global left ventricular systolic function. Numerous reports in various animal models have worked to define these changes. In one dog model, for example, there appeared to be an overall increase in stress-related hormones (Ambrisko et al. 2005). Experiments on rats and guinea pigs have noted that ketamine tends to not only increase blood pressure and heart rate but also decrease left ventricular diastolic pressure. The latter changes have been linked to cation movement, specifically magnesium, and associated kinase pathways (Saranteas et al, 2005).

Recent molecular work might offer further insight for the cardiodepressive effects of ketamine. Specifically, Kawano et al. have demonstrated in an in vitro model that ketamine induces inhibition of sarcolemmal K + ATP sensitive potassium channels (Kawano et al., 2005). Blockade of these channels has long been associated with decreased contractility (Gramolini and Renaud, 1997). Additionally, recent descriptions in a cat model demonstrate increased histamine release, which has also been linked to global cardiovascular depression (Costa-Farré et al., 2005).

The overall short-term myocardial depressive effects of ketamine on the dog myocardium have important experimental implications. This short-term changes should be considered when interpreting experimental hemodynamic changes. Additionally, while there have not been systematic evaluations of this agent and its short-term effects on human systolic function, it is reasonable to hypothesize that the human heart undergoes similar short-term changes when exposed to these agents. Lastly, arrhythmic, ischemic, and heart failure disease states in human research studies are all independently associated with decreasing left ventricular ejection fraction (Strauer, 1977). It is reasonable to interpret results from experimental models such as those within the framework of a somewhat reduced ejection fraction, not in the context of the starting, preanesthetic ejection fraction.

There are several limitations to this work. It should be noted that the baseline values in this study were obtained while the animals were excited as they were without anesthesia. As a result, these values may represent a baseline sympathetic-induced increase in ejection fraction although it is possible that the change in ejection fraction after ketamine injection is due in part to a decrease from a baseline sympathetically elevated ejection fraction, the lack of significant change in heart rate suggests that the dog were unlikely to be significantly sympathetically activated. Importantly, the results here represent only short-term changes associated with the agent. The effects seen here do not allow comment on the effects of ketamine on global systolic function. Ketamine use was associated with a significant short-term decrease in LV function in this experimental dog model. The decrease may be largely due to a blunting of sympathetic tone.

References

Ambrisko T. D., Y. Hikasa, and K. Sato (2005) .Influence of medetomidine on stress-related neurohormonal and metabolic effects caused by butorphanol, fentanyl, and ketamine administration in dogs. American Journal of Veterinary Research, 66(3), 406–412.

Bergman S. A., (1999). Ketamine: review of its pharmacology and its use in pediatric anesthesia Anesthesia progress, 46(1), 10–20.

Berry D. G., (1974). Effect of ketamine on the isolated chick embryo heart. Anesthesia and Analgesia, 53(6), 919–923.

Costa-Farré C., F. García, A. Andaluz, R. Torres, and F. de Mora (2005). Effect of H- and H-receptor antagonists on the hemodynamic changes induced by the intravenous administration of ketamine in sevoflurane-anesthetized cats. Inflammation Research, vol. 54, no. 6, pp. 256–26.

Fabian L. W., (1964). Anesthesia and Circulation, F.A. Davis Company, Arch Street, Pa, USA.

Gross D. R., (2009). Animal Models in Cardiovascular Research, Springer, New York, NY, USA.

Gramolini A. and J. M. Renaud, (1997). Blocking ATP-sensitive K+ channel during metabolic inhibition impairs muscle contractility. American Journal of Physiology, vol. 272, no. 6, pp. C1936–C1946.

Hettrick D. A., P. S. Pagel, and D. C. Warltier, (1996). Desflurane, sevoflurane, and isoflurane impair canine left ventricular- arterial coupling and mechanical efficiency. Anesthesiology, vol. 85, no. 2, pp. 403–413.

Kawano T., S. Oshita, A. Takahashi et al., (2005). Molecular mechanisms underlying ketamine-mediated inhibition of sarcolemmal adenosine triphosphate-sensitive potassium channels. Anesthesiology, vol. 102, no. 1, pp. 93–101.

Kohn D. F., (1997). Anesthesia and Analgesia in Laboratory Animals, Academic Press, San Diego, Calif, USA.

Kunst G., E. Martin, B. M. Graf, S. Hagl, and C. F. Vahl, (1999). Actions of ketamine and its isomers on contractility and calcium transients in human myocardium. Anesthesiology, vol. 90, no. 5, pp. 1363–1371,.

Link M. S., B. J. Maron, B. A. VanderBrink et al., (2001). Impact directly over the cardiac silhouette is necessary to produce ventricular fibrillation in an experimental model of commotio cordis. Journal of the American College of Cardiology, vol. 37, no. 2, pp. 649–654.

Saranteas T., N. Zotos, C. Chantzi et al., (2005). Ketamine-induced changes in metabolic and endocrine parameters of normal and 2-kidney 1-clip rats. European Journal of Anaesthesiology, vol. 22, no. 11, pp. 875–878.

Schulte-Sasse U, W. Hess, and J. Tarnow, (1982). Hemodynamic analysis of 6 different anesthesia induction procedures in coronary surgery patients. Anasthesie Intensivtherapie Notfallmedizin, vol. 17, no. 4, pp. 195–200.

Strauer B. E., K. Beer, K. Heitlinger, and B. Hoefling, (1977). Left ventricular systolic wall stress as a primary determinant of myocardial oxygen consumption: comparative studies in patients with normal left ventricular function, with pressure and volume overload and with coronary heart disease. Basic Research in Cardiology, vol. 72, no. 2-3, pp. 306–313.