Journal of the American Association for Laboratory Animal Science
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Vol 46, No 6
November 2007
Pages 21–28

Effect of Prolonged Ketamine Exposure on Cardiovascular Physiology in Pregnant and Infant Rhesus Monkeys (*Macaca mulatta*)

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Physiologic measurements in nonhuman primates usually are collected from animals that are chemically or physically restrained. Both types of restraint may affect the parameters measured, and those effects can vary with age. Heart rate, respiratory rate, oxygen saturation, expired CO_2, blood pressure, temperature, blood glucose, hematocrit, and venous blood gasses were measured in rhesus monkeys that were either infused intravenously with ketamine for 24 h or were cage-housed and physically restrained for sample collection. The subjects were pregnant monkeys at gestational day 120 to 123, infants 5 to 6 d old, and infants 35 to 37 d old. Heart rate and blood pressure were lower in ketamine-treated monkeys than physically restrained monkeys. Heart rate was higher in infants than adults, whereas blood pressure was lower in infants. Respiratory rate was higher in infants than adults and higher in physically restrained infants than ketamine-sedated infants but was not affected by ketamine in pregnant adults. Hematocrit was decreased in older infants. In summary, both physical restraint and ketamine sedation altered several physiologic parameters in pregnant and infant rhesus macaques. Investigators should consider these effects when designing experiments and evaluating experimental outcomes in monkeys.

Abbreviations: CON, conscious control; GD, gestational day; KET, ketamine-treated; PND, postnatal day

The rhesus monkey (*Macaca mulatta*) is a commonly used model for human physiology and pathology. Due to the complexity of the primate brain, the monkey is often the model of choice for neurologic and behavioral experiments.[24] Recent investigations have shown that some anesthetic drugs induce neurodegeneration if administered during critical periods of brain development.[19,20,33] To understand the effect of anesthetics on brain development, the effects of the anesthetic chemical must be distinguished from those of the physiologic changes that occur during anesthesia (for example, alterations in brain metabolism).

The effects of ketamine sedation and conscious restraint on cardiovascular parameters in adult monkeys are well known,[4,9,10,13-15,22,27,32,37] but little normative information is available for infants and pregnant monkeys. Furthermore, ketamine typically is administered as a single injection, and little information is available about the effects of long-term infusion. As an adjunct to an investigation of the neurotoxic effects of extended ketamine exposure during development,[34] we monitored cardiovascular parameters of pregnant (gestational day [GD] 120 to 123) and infant (postnatal day [PND] 5 to 6 and PND 35 to 37) rhesus monkeys that received 24-h intravenous ketamine infusion and compared those measures with those obtained from conscious, restrained animals.

Materials and Methods

Animals. All animal procedures were approved by the institutional animal care and use committee. The breeding colony consisted of natural-habitat–reared rhesus macaques (*Macaca mulatta*; age, 4 to 9 y) housed at a facility on a 12:12-h light:dark cycle and accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care International. Monkeys were provided with water ad libitum, were fed a commercial diet (High Protein Monkey Diet Jumbo 5047, PMI Nutrition International, Richmond, IN) twice daily, and were supplemented with fresh fruit 3 times a week. The colony was negative on routine screens for tuberculosis, internal and external parasites, *Salmonella*, *Shigella*, and *Campylobacter.* The monkeys were negative for *Herpesvirus simiae* and simian retroviruses on receipt but were not tested subsequently. Except when used for breeding, female monkeys were housed individually with enrichment devices. Males were housed continuously in multilevel breeding cages. Menstrual cycles were monitored with daily vaginal swabs (day 1, first day of blood). Females were transferred to a male's cage for days 11 to 13 of the cycle. Pregnancy was confirmed by ultrasonography at 30 to 40 d of gestation. After confirmation of pregnancy, the first day of exposure to the male was designated GD0. Ketamine and other pharmaceutical agents were not administered to pregnant or potentially pregnant females. Dams were allowed to deliver naturally, and the day of birth was designated as PND 0. Infants remained with their mothers until the start of study, at which time they were separated for the duration of the experiment.

Treatment groups. Animals of 3 ages were evaluated under 24-h exposure to ketamine: adult female monkeys at GD122 (range, GD120 to 123) and infants at PND5 (range, PND5 to 6) and PND35 (range, PND35 to 37). For each age and exposure, 3 animals were assigned randomly to the ketamine-treated group (KET), and 3 were assigned to the conscious control group (CON). Ketamine hydrochloride (Ketaset, Fort Dodge Animal Health, Fort Dodge, IA) was diluted in lactated Ringer solution (final concentration, 2.5 mg/ml) for intravenous infusion.

Experimental procedure. At the initiation of experimental

Received: 11 Jun 2007. Revision requested: 11 Jun 2007. Accepted: 21 Jul 2007.
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treatment, each animal was removed from its home cage and transferred to the procedure room. Animals in the CON group were maintained individually in a study cage with water but no food between sampling times. For physiologic measurements, these animals were removed from the study cage and restrained manually (infants) or in a restraint chair (pregnant adults). For animals in the KET group, ketamine was given as an initial intramuscular injection (20 mg/kg) followed by continuous intravenous infusion at a rate of 20 to 50 mg/kg hourly to effect. Animals were maintained in a light surgical plane of anesthesia for 24 h in an incubator with a circulating-water heating pad and heat lamp to maintain body temperature. Dextrose (5%, 5 to 15 ml/kg hourly) was administered by stomach tube (infants), by water bottle (conscious pregnant adults), or intravenously (ketamine-treated pregnant adults) to maintain blood glucose. Glycopyrrolate (0.01 mg/kg intramuscularly) was administered every 6 h during the experimental period to reduce salivary secretions, which are increased by ketamine.[2]

Physiologic measurements. Pulse oximetry (N-395 Pulse Oximeter, Nellcor, Pleasanton, CA), capnography (Tidal Wave Hand-held Capnograph, Respironics, Murrysville, PA), noninvasive sphygmomanometry (Critikon Dynamap Vital Signs Monitor, GE Healthcare, Waukesha, WI), and a thermal probe were used to monitor the physiologic condition of the animals. Pulse rate, respiratory rate, oxygen saturation of hemoglobin, expired CO_2 concentration, and rectal temperature were recorded every 15 min in KET animals and every 2 h in CON animals. Systolic, diastolic, and mean arterial blood pressure were recorded every 30 min in KET animals and every 4 h in CON animals. Blood (approximately 0.25 ml) was collected at 1- to 4-h intervals for the measurement of ketamine, venous blood gasses (Rapidlab, East Walpole, MA), glucose (Ascensia Elite XL Blood Glucose Meter, Bayer Diagnostics, Tarrytown, NY), and spun hematocrit.

Statistical analysis. Two-way analysis of variance was used to evaluate interaction effects of stage of development and ketamine treatment, with time after initiation of treatment included in the model as a repeated measure; Tukey post hoc analysis was used to correct for multiple comparisons. Parameters were determined to change over time if the slope of the regression line was significantly different from zero. The null hypothesis was rejected at a probability level of $P < 0.05$.

Results

All monkeys tolerated the procedures and recovered from anesthesia uneventfully. Table 1 summarizes the differences in physiologic parameters with regard to age and ketamine administration. Some parameters showed a significant increase or decrease throughout the 24-h experimental period.

Respiratory rate was higher in infants than in pregnant adults (Figure 1). In the infants, the rate was lower in the KET monkeys than in the CON animals. In CON PND35 monkeys, respiratory rate decreased over time. In KET PND5 animals the rate decreased over time, whereas in KET GD122 animals, it increased. Further regression modeling revealed a quadratic fit for KET GD122 ($P = 0.0002$) and KET PND35 ($P = 0.017$) monkeys, indicating a decrease initially followed by an increase toward the end of the infusion period for both of these groups.

End-tidal expired CO_2 concentration was lower in PND35 infants than in PND5 infants or GD122 adults (Figure 2). Consistent with differences in respiratory rate, expired CO_2 was higher in KET infants than in CON infants. CO_2 tended to increase over time in KET PND5 and CON PND35 infants but decreased over time with ketamine treatment in PND35 and GD122 monkeys. Further analysis revealed a significant quadratic fit for PND35 monkeys, both CON ($P = 0.036$) and KET ($P = 0.0002$).

Heart rate decreased over time in all groups and was lower with ketamine treatment at all ages (Figure 3). Of the KET monkeys, PND35 animals had the fastest heart rate and GD122 the slowest. Oxygen saturation of hemoglobin measured by pulse oximetry was significantly lower in KET monkeys when calculated as a main effect and was specifically lower in KET PND35 monkeys compared with the corresponding CON monkeys (Table 1). Oxygen saturation tended to increase over time in CON PND5, CON PND35, and KET PND5 monkeys.

Body temperatures did not vary significantly among groups (Table 1) but did vary significantly with time. Specifically, temperature decreased over time in PND35 and GD122 CON animals. Data from CON PND5 and GD122 monkeys showed a significant quadratic fit ($P = 0.036$ and $P = 0.0004$, respectively). Although a heat lamp was used to maintain body temperature in KET monkeys, temperatures nevertheless decreased over time in both PND35 groups and increased over time in the KET PND5 monkeys.

In general, blood pressure was lower in infants than adults and was lower in KET monkeys than in CON monkeys at PND5 and GD122 (Figure 4). In addition, among KET monkeys, mean and systolic blood pressures were lower in PND5 than in PND35 monkeys. Systolic blood pressure decreased over time in PND5 and PND35 KET monkeys, whereas mean and diastolic blood pressures decreased in PND35 and GD122 KET monkeys.

Hematocrit was lower in KET monkeys as a main effect, but specific contrasts were not significant. Hematocrit was lower in PND35 than in PND5 monkeys under both treatment conditions and was lower than in GD122 monkeys as a main effect. Hematocrit decreased over time in CON GD122 monkeys. Blood glucose was significantly ($P < 0.05$) lower overall in KET monkeys than in CON monkeys as a main effect but did not vary significantly as a function of age.

Venous pH was higher in KET animals, especially at PND5 (Table 1). Venous pH increased over time in KET PND5 animals and decreased in KET GD122 monkeys. Venous CO_2 partial pressure was higher overall in PND5 animals than in PND35 or GD122 monkeys as a main effect, but specific contrasts were not significant. Venous O_2 partial pressure and O_2 saturation were higher in KET animals than in CON animals, and venous O_2 saturation was higher in GD122 monkeys than in PND5 infants. In CON GD122 monkeys, these parameters increased over time.

Discussion

Nonhuman primates are valuable animal models for several reasons. They are genetically the most similar animals to humans, and with modern experimental techniques, data from multiple endpoints can be collected from individual animals. However, factors other than the experimental treatment can affect several of these outcomes. The data presented here demonstrate that restraint, whether chemical or physical, affects several physiologic parameters. This information will aid in the decision of the appropriate method of restraint for a specific protocol, as well as provide normative data for several physiologic measurements.

Both physical restraint and ketamine treatment affect physiologic parameters in nonhuman primates, and the effects vary with the age of the subject and the duration of ketamine-induced anesthesia. Restraint causes excitement, as evidenced by increases in heart rate, blood pressure, and respiratory rate.[4,10,14,37]

Table 1. Physiologic values in physically (CON) and chemically (KET) restrained monkeys

					P		
		GD122 (maternal)	PND5 (infant)	PND35 (infant)	GD122 vs PND5	GD122 vs PND35	PND5 vs PND35
Respiratory rate (breaths per min)	CON	30 ± 5	65 ± 13	72 ± 20	0.0001	<0.0001	NS
	KET	36 ± 11	43 ± 16	46 ± 25	0.006	0.0004	NS
	P (CON vs KET)	NS	<0.0001	0.0001			
Expired CO_2 (mm Hg)	CON	29 ± 6	24 ± 2	22 ± 3	0.034	0.002	NS
	KET	31 ± 7	33 ± 6	28 ± 5	0.007	0.003	<0.0001
	P (CON vs KET)	NS	<0.0001	0.0004			
Heart rate (beats per min)	CON	197 ± 32	219 ± 25	212 ± 34	0.006	NS	NS
	KET	130 ± 16	158 ± 26	171 ± 22	<0.0001	<0.0001	0.0001
	P (CON vs KET)	<0.0001	<0.0001	<0.0001			
O_2 saturation (%)	CON	94 ± 4	96 ± 3	97 ± 2	NS	NS	NS
	KET	94 ± 4	94 ± 3	94 ± 3	NS	NS	NS
	P (CON vs KET)	NS	NS	0.006			
Temperature (°C)	CON	37.3 ± 0.8	36.9 ± 0.5	36.8 ± 0.9	NS	NS	NS
	KET	37.2 ± 0.9	37.2 ± 0.8	37.2 ± 0.7	NS	NS	NS
	P (CON vs KET)	NS	NS	NS			
Mean arterial pressure (mm Hg)	CON	85 ± 13	63 ± 16	58 ± 16	0.001	0.0004	NS
	KET	68 ± 14	47 ± 10	53 ± 12	<0.0001	<0.0001	0.027
	P (CON vs KET)	0.003	0.0008	NS			
Systolic blood pressure (mm Hg)	CON	112 ± 14	85 ± 19	74 ± 17	0.001	<0.0001	NS
	KET	87 ± 17	66 ± 10	74 ± 16	<0.0001	0.0004	0.005
	P (CON vs KET)	0.0005	0.0007	NS			
Diastolic blood pressure (mm Hg)	CON	68 ± 14	54 ± 16	50 ± 15	0.012	0.003	NS
	KET	54 ± 13	38 ± 8	42 ± 10	<0.0001	<0.0001	NS
	P (CON vs KET)	0.004	0.0003	NS			
Glucose (mg/dl)	CON	58 ± 15	65 ± 12	59 ± 27	NS	NS	NS
	KET	48 ± 19	56 ± 17	58 ± 15	NS	NS	NS
	P (CON vs KET)	NS	NS	NS			
Hematocrit (%)	CON	42 ± 3	46 ± 5	40 ± 6	NS	NS	0.017
	KET	42 ± 4	43 ± 8	36 ± 2	NS	NS	0.019
	P (CON vs KET)	NS	NS	NS			
Venous pH	CON	7.35 ± 0.07	7.30 ± 0.08	7.35 ± 0.07	NS	NS	NS
	KET	7.38 ± 0.07	7.38 ± 0.06	7.38 ± 0.04	NS	NS	NS
	P (CON vs KET)	NS	0.012	NS			
Venous pCO_2 (mm Hg)	CON	39 ± 7	44 ± 10	36 ± 7	NS	NS	NS
	KET	38 ± 6	44 ± 9	42 ± 7	NS	NS	NS
	P (CON vs KET)	NS	NS	NS			
Venous pO_2 (mm Hg)	CON	31 ± 12	26 ± 18	28 ± 19	NS	NS	NS
	KET	44 ± 14	38 ± 15	45 ± 17	NS	NS	NS
	P (CON vs KET)	NS	NS	0.020			
Venous O_2 saturation (%)	CON	53 ± 17	35 ± 18	43 ± 19	0.038	NS	NS
	KET	73 ± 19	66 ± 18	73 ± 17	NS	NS	NS
	P (CON vs KET)	0.009	0.0006	0.0005			

NS, not significant ($P > 0.05$).

Values are given as mean ± 1 standard deviation across all time points for 3 monkeys per group.

The increased respiration causes CO_2 to be expelled at a greater rate, such that a lower concentration of CO_2 is expelled with each breath. Struggling against restraint may increase lactic acid production due to muscle contractions and can increase metabolic rate sufficiently to raise body temperature.[4] Conversely, anesthetics tend to decrease metabolic rate, body temperature,

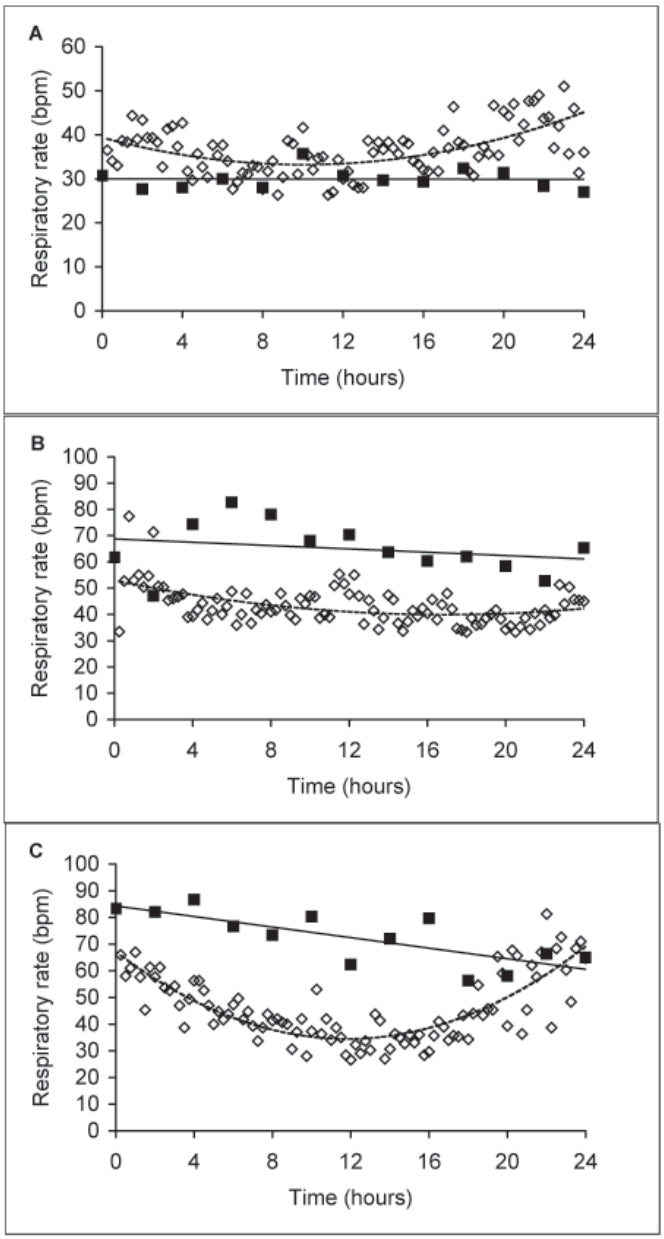

Figure 1. Respiratory rate (breaths per min, bpm) over a 24-h period in rhesus monkeys infused intravenously with ketamine (KET, open diamonds) or physically restrained (CON, closed squares). Each point represents mean of 3 monkeys. (A) GD122 pregnant females, (B) PND5 infants, and (C) PND35 infants.

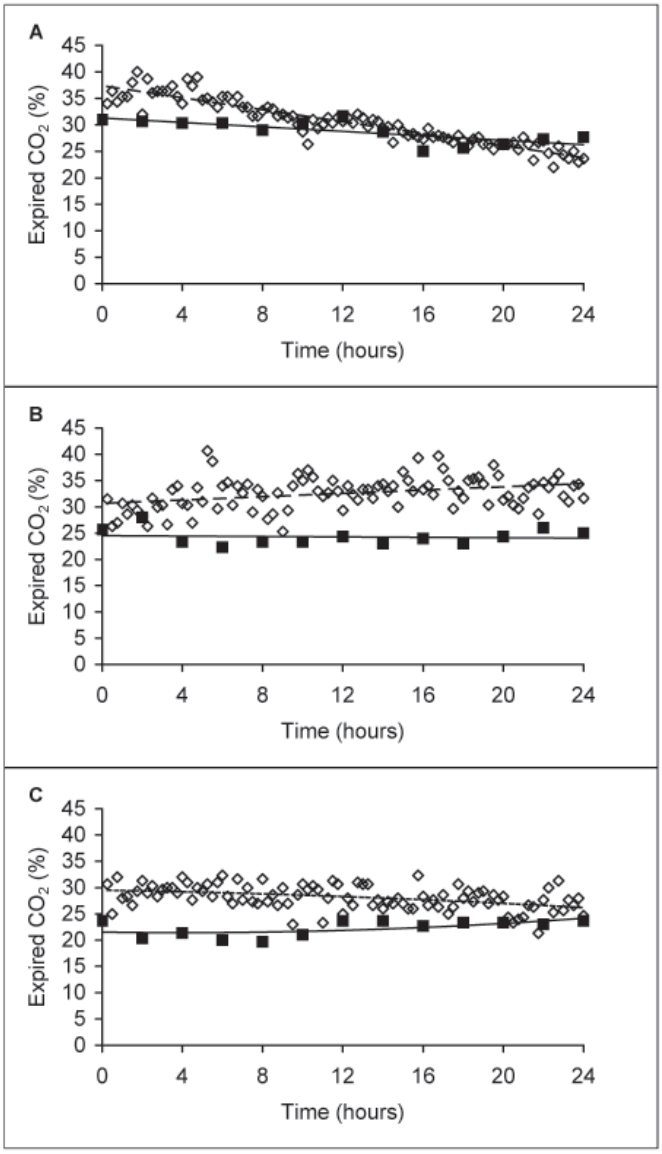

Figure 2. Expired CO_2 (%) over a 24-h period in rhesus monkeys infused intravenously with ketamine (KET, open diamonds) or physically restrained (CON, closed squares). Each point represents mean of 3 monkeys. (A) GD122 pregnant females, (B) PND5 infants, and (C) PND35 infants.

and respiratory rate. Although most anesthetics also decrease heart rate, ketamine increases cardiac rate, as well as systemic and pulmonary vascular resistance, resulting in increased systemic and pulmonary blood pressure.[2]

In monkeys instrumented with telemetry, ketamine treatment clearly increases heart rate compared with that of a resting state.[15,27] However, the increase in heart rate in response to restraint stress is greater than the response to ketamine in both rhesus[10] and cynomolgus[14] monkeys, such that the heart rate in ketamine-treated monkeys consistently is lower than in physically restrained monkeys,[4,22] as was seen in the present study. Heart rate decreased in the conscious animals as they became acclimated to restraint, consistent with previous reports.[9,10,13] A similar decrease also occurred in the ketamine-treated monkeys; this finding is novel, given that extended infusions of ketamine have not been studied in monkeys. The heart rates reported here for KET infants and pregnant adults are consistent with those reported for ketamine-sedated young adult males, but the heart rates for restrained CON monkeys reported here are significantly higher than those measured by telemetry in unrestrained conscious monkeys.[15]

Our results for ketamine-sedated pregnant rhesus are similar to those reported for pregnant rhesus monkeys anesthetized with halothane,[32] which yielded a heart rate of 124 ± 18 beats per min, respiratory rate of 29 ± 10 breaths per min, and femoral blood pressure of 69 ± 11 mm Hg. Approximately 42% of halothane-anesthetized animals became hypotensive, which was reversible with fluid administration in most cases.[32] Although blood pressure fell during anesthesia in the pregnant animals in our study, the depression was less marked than that caused by halothane. This difference could be attributed to either fluid administration or the lesser effect of ketamine on hemodynamics.

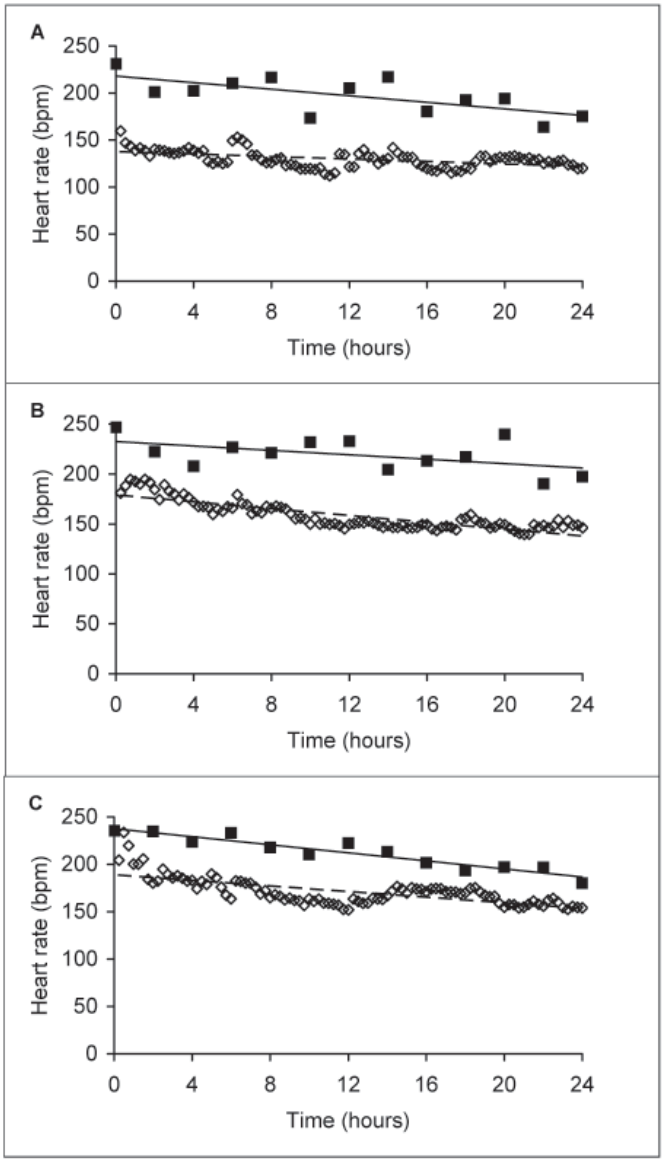

Figure 3. Heart rate (beats per min, bpm) over a 24-h period in rhesus monkeys infused intravenously with ketamine (KET, open diamonds) or physically restrained (CON, closed squares). Each point represents mean of 3 monkeys. (A) GD122 pregnant females, (B) PND5 infants, and (C) PND35 infants.

When cynomolgus monkeys were sedated with ketamine, blood pressure and temperature decreased from the time it was first possible to handle the monkeys until 10 min later,[37] suggesting that handling restraint increased blood pressure. In this experiment, blood pressure was higher in restrained adult monkeys than in ketamine-treated monkeys. Stress elevates blood pressure in both rhesus[10] and cynomolgus monkeys.[14] Blood pressure reportedly decreased in pregnant[13] and non-pregnant[9] adult rhesus with acclimation to restraint over a period of days to weeks; we did not see such a decrease within the course of this experiment.

When measured by telemetry, blood pressure may[27] or may not[15] increase with ketamine treatment. Although less hypotensive than other anesthetic agents, ketamine causes significant decreases in heart rate and blood pressure in neonatal humans, who are perhaps more susceptible to these effects than adults because of cardiovascular immaturity.[11] In contrast, in older children, ketamine led to an increase in blood pressure.[29] This result is consistent with our finding of lower blood pressure with ketamine treatment in PND5, but not PND35, monkeys.

In the infant monkeys, the respiratory rate was higher in conscious, restrained animals than in ketamine-sedated animals. This result is consistent with previous findings in cynomolgus monkeys.[4,22] The fact that respiratory rate was not decreased in the ketamine-treated adults suggests that the difference primarily was due to restraint stress increasing respiration in the more excitable infants, rather than a hypoventilatory effect of ketamine. The decrease over time in CON PND35 and GD122 animals suggests some acclimation to the restraint procedure. In KET monkeys, the respiratory rate decreased initially but increased after 16 or more hours of anesthesia. The most likely decrease was related to the increased length of exposure to ketamine, whereas the increase may have been induced by poor pulmonary oxygenation related to pulmonary congestion. Despite frequent repositioning of the animals, increased lung sounds developed in some ketamine-sedated monkeys, perhaps related to the volume of fluid infused.

Ketamine is a mild respiratory depressant, in that it shifts the CO_2 response curve to the right but does not change the slope of the curve.[2] In infant monkeys, expired CO_2 was higher with ketamine treatment than with physical restraint. This result could be related to decreased respiratory stimulation with higher CO_2 concentrations in ketamine-treated animals, decreased CO_2 in response to hyperventilation in restrained animals, or a combination of both. Changes in expired CO_2 over time corresponded inversely to changes in respiratory rate.

PND35 monkeys showed a small but significant decrease in oxygen saturation of hemoglobin with ketamine treatment. In humans, particularly children, oxygen saturation measured by pulse oximetry may decrease during ketamine anesthesia, but the problem can be corrected by stimulation of the patient or through administration of supplemental oxygen.[2] This scenario is consistent with our experience in infant monkeys. Protective airway reflexes generally remain intact with ketamine treatment, but there have been reports of apnea, airway obstruction, and pulmonary aspiration.[2] Although we did not quantitate it, after several hours of anesthesia it was not unusual to see a drop in oxygen saturation which responded to clearing of the airway and stimulation of the animal. Vomition has been reported as another adverse effect of ketamine;[2] some infant KET monkeys vomited after orogastric feeding.

Venous pH reportedly increases with ketamine treatment[13,22] and decreases with restraint.[4] These reports are consistent with our finding in PND5 monkeys, and may be related to differences in metabolism: decreased basal metabolism during anesthesia increases pH[22], whereas increased lactic acid production from struggling during restraint results in metabolic acidosis, lowering pH[4]. Venous CO_2 partial pressure is reported to decrease with either ketamine[22] or physical restraint.[4] Our data revealed no difference in CO_2 partial pressure between these 2 conditions. Our finding of lower venous pO_2 and O_2 saturation in restrained animals was unexpected, because pO_2 is expected to increase with hyperventilation.[4] This finding could be an artifact of blood collection. Venipuncture was accomplished more rapidly in anesthetized animals, such that the vein was occluded for a shorter period of time before the sample was obtained.

Body temperature was controlled effectively with external heat sources during the course of this experiment, although some changes over time were detected. In the absence of such control, body temperature would be expected to decrease with any anesthetic, including ketamine.[22,27,37] The changes over time in conscious monkeys were due to either circadian variation[17]

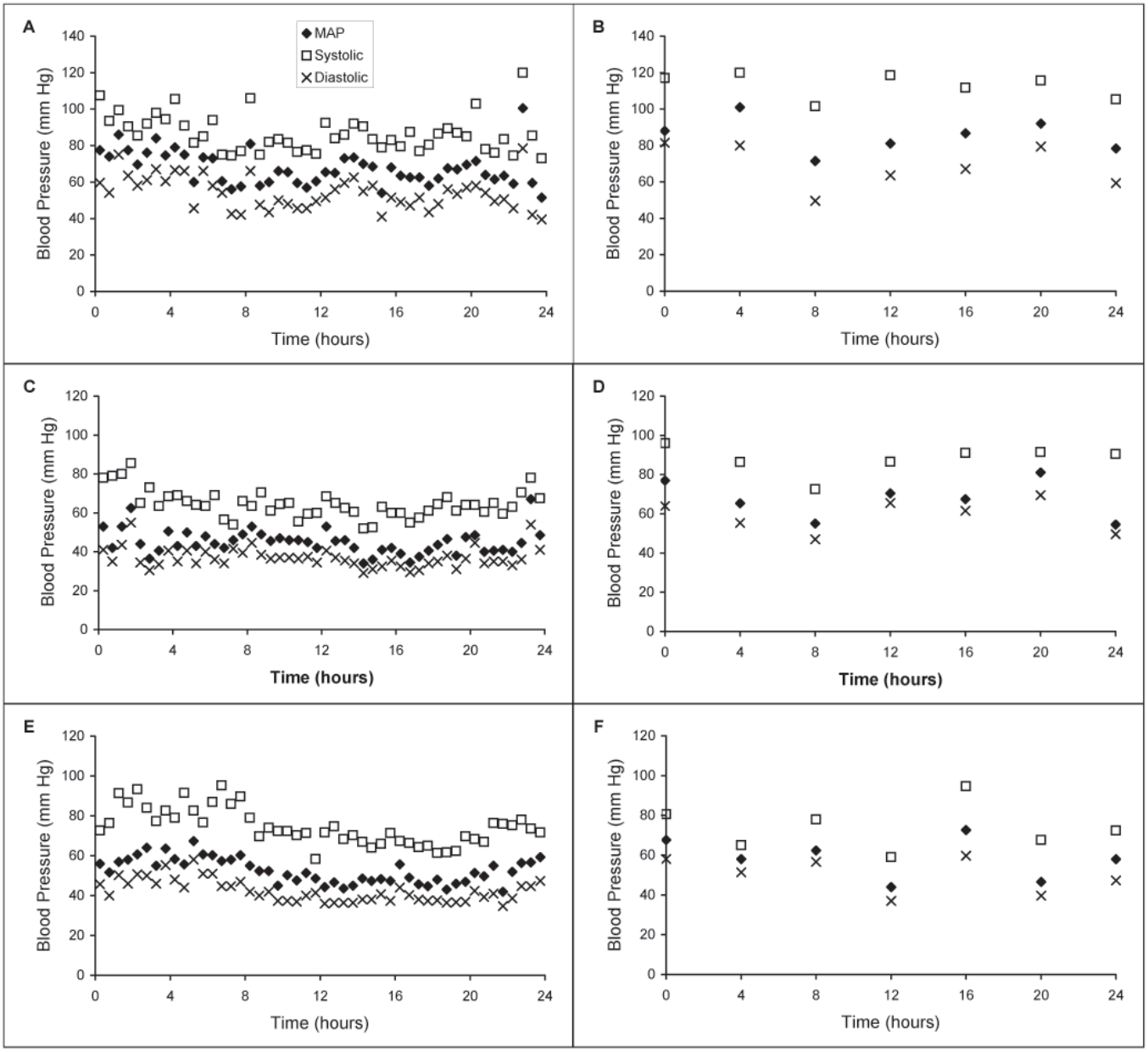

Figure 4. Blood pressure (mm Hg) over a 24-h period in rhesus monkeys infused intravenously with ketamine (A, C, E) or physically restrained (B, D, F). Each point represents mean of 3 monkeys. (A, B) GD122 pregnant females, (C, D) PND5 infants, and (E, F) PND35 infants. MAP, mean arterial pressure (◆); □, systolic pressure; ×, diastolic pressure.

or a decrease in temperature with acclimation to restraint and reduced struggling.[13]

Glucose and hematocrit have been reported to decrease after ketamine sedation as compared with values obtained in conscious, restrained rhesus monkeys.[1] This effect was attributed to a reversal of restraint stress, which is known to cause splenic contraction with increases in the number of circulation erythrocytes, as well as epinephrine-induced hyperglycemia. However, it also has been reported that ketamine does not affect glucose regulation in rhesus monkeys.[21] No differences in glucose or hematocrit related to ketamine administration were statistically significant in the present study.

The effects of restraint and ketamine infusion were superimposed on the differences between infants and adults, specifically pregnant female adults. Respiratory rate was higher in both PND5 and PND35 infants than in adult monkeys but was not different between the 2 groups of infants. This finding is consistent with reports in humans, in whom respiratory rate is higher during the first 2 mo of life than during later months and in adulthood.[8,16,23] Similarly, heart rate is higher in human infants than adults, but the decline is more continuous with age.[8,23] Our data confirm that heart rate is markedly faster in monkey infants than adults. However, our data indicate a significantly faster heart rate at PND35 than at PND5 in ketamine-treated monkeys, which may be due to differing responses to anesthesia at different ages. Heart rate increases during pregnancy in humans,[6,18,30] rhesus monkeys,[13] and marmosets.[12] The values for conscious pregnant rhesus in the current study were higher than those reported for nonpregnant rhesus,[9,10,15] but the values for ketamine-treated pregnant rhesus were similar to those reported for sedated nonpregnant rhesus.[15,32]

The values for blood pressure measured in these conscious pregnant female rhesus were essentially the same as those recorded for nonpregnant physically restrained cynomolgus

monkeys.[5] Due to increased intravascular volume, blood pressure can decrease during pregnancy in humans.[3,6,30] Our data for pregnant rhesus are comparable to those previously reported for pregnant rhesus[13,32] and are lower than blood pressures reported for nonpregnant adult rhesus,[9,10,15] whether under ketamine anesthesia, physically restrained, or as measured by telemetry in conscious, unrestrained monkeys. Blood pressure was even lower in the infant monkeys (conscious or ketamine-treated) than in the pregnant adults, consistent with findings of very low blood pressure in neonatal humans, which increases during the first week of life.[7,28]

The reason for the significant effect of age on expired CO_2 is not obvious and is most likely multifactorial. In the conscious animals, decreased CO_2 is associated with hyperventilation. In the ketamine-treated PND35 animals, the increased respiratory rate may account for the decreased expired CO_2. Conversely, the high expired CO_2 in the ketamine-treated PND5 infants may be due to an immature ventilatory response to hypercapnia.[31]

Hematocrit was lower in PND35 monkeys than in PND5 animals. Hematocrit is high at birth due to the formation of adult hemoglobin while fetal hemoglobin is still present;[25] hematocrit decreases markedly over the first 2 wk of life.[25,36] The decrease in hematocrit in pregnant animals over time more likely was attributable to circadian changes in fluid homeostasis than to loss of blood cells, because no decrease was seen in infants, from which a larger volume of blood relative to the size of the animal was removed. Renal blood flow and urine production decrease at night, preserving electrolytes and water during a time in which there is normally no fluid influx.[26,35] Consequently, the intravenous infusion of fluid resulted in hemodilution in the adult animals, whose circadian rhythms were well established.

In conclusion, several physiologic parameters are affected by ketamine, restraint, age, and pregnancy. In using animal models, investigators must be aware of these effects when evaluating experimental outcomes.

Acknowledgments

This work was supported by National Center for Toxicological Research (NCTR)/FDA, CDER/FDA, and NICHD. The authors would like to thank the Bionetics Animal Care staff for technical assistance. This document has been reviewed in accordance with United States Food and Drug Administration (FDA) policy and approved for publication. Approval does not signify that the contents necessarily reflect the position or opinions of the FDA nor does mention of trade names or commercial products constitute endorsement or recommendation for use. The findings and conclusions in this report are those of the author(s) and do not necessarily represent the views of the FDA.

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