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Left Ventricular, Systemic Arterial, and Baroreflex Responses to Ketamine and TEE in Chronically Instrumented Monkeys

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Effects of prescribed doses of ketamine five minutes after application and influences of transesophageal echocardiography (TEE) on left ventricular, systemic arterial, and baroreflex responses were investigated to test the hypothesis that ketamine and/or TEE probe insertion alter cardiovascular function. Seven rhesus monkeys were tested under each of four randomly selected experimental conditions: (1) intravenous bolus dose of ketamine (0.5 ml), (2) continuous infusion of ketamine (500 mg/kg/min), (3) continuous infusion of ketamine (500 mg/kg/min) with TEE, and (4) control (no ketamine or TEE). Monkeys were chronically instrumented with a high fidelity, dual-sensor micromanometer to measure left ventricular and aortic pressure and a transit-time ultrasound probe to measure aortic flow. These measures were used to calculate left ventricular function. A 4-element Windkessel lumped-parameter model was used to estimate total peripheral resistance and systemic arterial compliance. Baroreflex response was calculated as the change in R-R interval divided by the change in mean aortic pressure measured during administration of graded concentrations of nitroprusside. The results indicated that five minutes after ketamine application heart rate and left ventricular diastolic compliance decreased while TEE increased aortic systolic and diastolic pressure. We conclude that ketamine may be administered as either a bolus or continuous infusion without affecting cardiovascular function 5 minutes after application while the insertion of a TEE probe will increase aortic pressure. The results for both ketamine and TEE illustrate the classic "Hawthorne Effect," where the observed values are partly a function of the measurement process. Measures of aortic pressure, heart rate, and left ventricular diastolic pressure should be viewed as relative, as opposed to absolute, when organisms are sedated with ketamine or instrumented with a TEE probe.

Previous experiments conducted in our laboratory have focused on investigation of microgravity and hypergravity effects on cardiovascular function (1), using head-down tilt (2, 3) and centrifuge (4) models. In those studies, a single bolus of ketamine was injected to lightly sedate nonhuman primates and/or allow insertion of a transesophageal echocardiography (TEE) probe for measuring atrial and ventricular volumes.

Use of ketamine as an anesthetic agent and application of TEE have been well documented. Investigators have reported that ketamine causes hypertension and tachycardia with variable effects in humans (5, 6), dogs (7), and cats (8). In those studies, ketamine was administered as a single bolus injection or a continuous infusion. It is unclear whether bolus injection or continuous infusion of ketamine has different effects on cardiovascular function. We proposed testing the hypothesis that bolus and continuous infusion of ketamine alter cardiovascular function five minutes after application.

Due to its superior imaging capabilities, use of TEE in evaluating cardiac function has increased through the years. The passing of a transesophageal probe through the esophagus, though invasive, provides better images and feature recognition than do transthoracic echocardiography techniques. Its use in diagnosing valvular dysfunction (9), regional myocardial ischemia (9, 10), and pulmonary emboli (9), as well as assessing blood flow velocity, cardiac output, and ventricular diastolic function (11) have been investigated. However, we are unaware of any investigations that revealed effects of TEE on cardiac, systemic, and baroreflex responses. Subsequently, we proposed testing a second hypothesis that TEE insertion alters cardiovascular function.

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Materials and Methods

Subjects. Seven domestically born and raised adult male rhesus monkeys *(Macaca mulatta*), seronegative for *Herpesvirus simiae* and simian retrovirus 2 and weighing between 4.5 and 8 kg, were selected as candidates for the study. These monkeys had been prepared for a prior study (2), and were available for additional assignment to the present study. All monkeys were individually housed in indoor caging in a climate controlled (temperature, 22°C; relative humidity, 50%; light cycle, 12:12 h), AAALAC-approved, vivarium facility. The monkeys received water ad libitum from automatic waterers, and were fed a commercial primate ration (Monkey Chow #5038, Ralston-Purina, St Louis, Mo.) twice daily. The environmental enrichment program for individually caged monkeys mandated provision of food treats, in-cage manipulanda, and foraging boards. All cages were situated to maximize visual and aural interactions between conspecifics. All experimental procedures and protocols were reviewed and

approved by the Institutional Animal Care and Use Committee (Brooks AFB, San Antonio, Tex.).

Instrumentation. The monkeys were instrumented with chronically-implanted left ventricular and right atrial access catheters, a transit-time ultrasound flow sensor on the proximal ascending aorta, and pericardial electrocardiogram leads. The left ventricular catheter provided an access site for insertion of a high-fidelity, dual-sensor 3-F micromanometer (Millar Instruments, Houston, Tex.) for simultaneous measurement of left ventricular pressure (LVP) and aortic pressure (AoP), as described (12). An active redirectional transit-time (ART^2) probe (Triton Technology, San Diego, Calif.) was used to measure aortic flow (AoF) (13). Electrocardiography was done, using medical-grade stainless steel wire leads sutured to the pericardium, and the right atrial catheter provided an access site for administration of the anesthetic agent (ketamine). Implantation of all transducers and access catheters was accomplished via median sternotomy, as described (2). The monkeys were allowed one month of postoperative recovery before the start of the test protocol.

The dual-sensor aortic and left ventricular micromanometers were pre- and post-calibrated against a known pressure standard at the start and end of the study, as described (2, 12, 14). Electrical DC-equivalent voltage calibrations were performed for aortic flow (0 to 8 L/min). Pressure transducer outputs were amplified with fixed-gain differential DC amplifiers (Ectron, San Diego, Calif). Aortic flow signal conditioning was accomplished, using a commercial transit-time module (Triton Technologies, San Diego, Calif). These conditioned analog signals were then fed into a signal distribution unit for channeling outputs to multiple data acquisition units. The primary data acquisition unit was an A/D station composed of antialaising filters (Precision Filters, Phoenix, Ariz.), A/D board (National Instruments, Austin, Tex.), desktop computer (Zeos, Nampa, Idaho), and A/D support software (National Instruments, Austin, Tex.). Data were low pass filtered at 60 Hz (linear phase) and sampled at 250 Hz.

Experimental design. Monkeys were tested in each of the four randomly selected treatment conditions: intravenous bolus dose of ketamine (0.5 ml), continuous infusion of ketamine (500 mg/kg of body weight/min), continuous infusion of ketamine (500 mg/kg/min) with TEE, and (4) control (no ketamine or TEE). Each monkey was tested under each of the four treatment conditions. The order of the testing was randomized for each monkey, with no two monkeys subjected to the same order. The between testing crossover periods consisted of 24 h of ambulatory control.

Prior to testing, each monkey was transferred to a sealed cage where it was sedated with isoflurane (3% isoflurane in 100% oxygen) prior to insertion of the high-fidelity pressure micromanometers during cardiac fluoroscopy. Once the micromanometer transducers were properly positioned within the left ventricle and aorta, the monkeys were placed in prone position on a custom-built confinement bed and allowed to fully recover from the isoflurane sedation for a period of 60 min, during which blood pressure and aortic flow were monitored to ensure homeostasis. Sedation time with isoflurane totaled between 5 and 10 min for all monkeys.

For the ketamine bolus treatment condition, a single bolus of ketamine (0.5 ml) was administered through the right atrial access catheter. Five minutes after the bolus injection, it was assumed that a steady state was achieved, then a continuous five-minute recording of left ventricular and systemic arterial measurements was made. For the control, continuous infusion, and continuous infusion plus TEE treatment conditions, the same experimental sequences of baseline and nitroprusside infusions were used. For the continuous infusion treatment condition, a constant, continuous infusion of ketamine (500 mg/kg/min) was administered through the right atrial access catheter. Once again, five minutes after initiation of the continuous infusion, it was assumed that a steady state had been achieved, and ventricular and systemic arterial measurements were recorded for five minutes.

For the continuous infusion plus TEE treatment condition, the experimental sequence (five-minute baseline and nitroprusside infusion) was repeated with the addition of a TEE probe inserted through the esophagus and left in the monkey throughout the duration of the experiment. For each treatment condition, baroreflex response measurements were continuously recorded during increasing graded concentrations of nitroprusside infused from (1) t = 0 to 2 min (1.75 μg/kg/min), (2) t = 2 to 4 min (3.50 μg/kg/min), and (3) t = 4 to 6 min (5.25 μg/kg/min). Baroreflex testing was conducted after all static measures of cardiovascular performance were completed.

Data reduction. Cardiovascular data were analyzed, using custom-designed software developed in Matlab (MathWorks, Natick, Mass.). Peak aortic pressure (AoPsys), minimal aortic pressure (AoPdia), left ventricular end-diastolic pressure (LVPdia), peak-positive slope of left ventricular pressure waveform (dP/dt), and heart rate (HR) were determined for every beat within each data set for all experimental conditions. Left ventricular diastolic compliance (LVdC), which was assumed to be constant during cardiac filling, was calculated by dividing the change in LV volume by the change in LV pressure from end-diastole to begin-diastole (LVPed - LVPbd). The change in LV volume during ejection or stroke volume (SV) was calculated by integrating aortic flow for that beat. This calculation assumes the volume that was ejected during systole was the same volume that had filled the ventricle during diastole. Cardiac output (CO) was calculated as SV times HR. A four-element Windkessel model (15) was used to estimate the lumped arterial parameters, total peripheral resistance (TPR), and systemic arterial compliance (SAC), using Essler's frequency domain analysis technique (16). The baroreflex response was calculated as the change in R-R interval divided by the change in mean aortic pressure measured during administration of graded concentrations of nitroprusside. All left ventricular and systemic arterial parameters were estimated on a beat-to-beat basis. All statistical calculations were performed by use of SAS statistical software (Cary, N.C.).

Statistical analysis. A one-way (treatment condition) randomized block (monkeys) analysis of variance (ANOVA) was used to statistically evaluate differences between the four treatment conditions across 11 dependent variables. The statistical model coincides with the experimental design in which all seven monkeys were subjected to each of the four treatment conditions. When overall statistical differences between treatment conditions were detected, Tukey's honestly significant difference (HSD) was used to evaluate pairwise differences between treatment means. The HSD indicates how much difference must exist between any two treatment means, before a statistical difference is obtained ($\alpha = 0.05$). Standard errors of the mean (SEM) are presented as raw values and are not adjusted for subject-to-subject variation.

Results

The four treatment condition means, SEM, *P*-values associ-

ated with the overall statistical tests, and HSD values for the 11 dependent variables are presented in Table 1. Compared with the continuous infusion condition, systolic and diastolic aortic pressures were increased when the TEE was in place (i.e., TEE effect). The TEE increased aortic systolic pressure by an average of 13.4 mmHg and aortic diastolic pressure by an average of 10.9 mmHg. Although the means were not statistically different due to higher experimental error, left ventricular diastolic pressure also had the same pattern of increased pressure with insertion of the TEE. Heart rate in the continuous infusion condition was 16 beats/min (bpm) less than that during the control condition and was consistently lower than that of the control across all three ketamine conditions. There was an average decrease across bolus, continuous infusion, and continuous infusion plus TEE of 0.36 ml/mmHg in LVdC, compared with that of the control condition (i.e., ketamine effect). There were no other statistically discernible effects among the remaining dependent variables. In summary, insertion of the TEE increased arterial pressure whereas ketamine decreased HR and LVdC. Also, differences between the continuous infusion and bolus treatment conditions were small and not statistically discernible.

Discussion

Administration of ketamine is believed to have a direct myocardial and peripheral vasculature effect, as well as an indirect effect administered through direct sympathetic activity. Studies have indicated that ketamine is a direct myocardial depressant (17, 18) and may cause peripheral vasodilatation (19) in the absence of autonomic control. It also has been documented that ketamine induces sympathetic effects that can cause vasoconstriction (18, 20), increased contractility (21), and increased HR (21). These sympathetic effects are thought to be mediated through direct stimulation of the central nervous system (22, 23). The sympathetic effects of ketamine usually mask the direct effects on the heart and peripheral vasculature, causing either unchanged or increased contractility and TPR (24, 25).

In this study, ketamine administered to rhesus monkeys as a bolus dose or continuous infusion caused tachycardia, which has been commonly reported by others (7, 26-30), and specifically in rhesus monkeys when ketamine was administered as a single bolus (31). An unexpected finding was a 20% reduction in LVdC observed for bolus dose, continuous infusion, and continuous infusion plus TEE, compared with that for the control condition. Increased ventricular diastolic stiffness could be caused by increased SV, reduced ventricular filling pressure, or increased contractility as previously suggested. However, changes in SV or ventricular filling pressures were not observed in our animals, and dP/dt, an index of left ventricular contractility, was either unchanged or slightly reduced. The filling properties of the left ventricle may have evoked an increase in filling volume or a decrease in transmural pressure. Unfortunately, the measurements needed to test these hypotheses were not made. Therefore, mechanism(s) associated with reduction in LVdC remain unclear.

Previous experiments indicated hypertension following administration of either bolus dose or continuous infusion of ketamine (7, 24, 26, 27). In contrast to those reports, we did not observe significant alterations in aortic pressure, peripheral resistance, and systemic arterial compliance between control, bolus dose, and continuous infusion of ketamine. Therefore, our data indicated little impact of either technique for administration of ketamine on arterial blood pressure. However, differences in ketamine responses may be species specific. Additionally, the baroreflex response for each of the experimental conditions remained unchanged, supporting previous reports that the origin of cardiovascular stimulation lies in the central nervous system and that ketamine does not act on the baroreceptors (22, 23).

The primary effect of TEE probe insertion was an increase in aortic systolic and diastolic pressure, with a slight decrease in SV (not statistically significant). It is possible that the TEE probe displaced cardiac filling volume and resulted in reduced SV and increased arterial pressure. Although other investigations indicate that HR increases with TEE insertion (32, 33), our experimental design and statistical analysis suggest that this effect was likely due to ketamine rather than TEE probe insertion.

We have used and continue to use ketamine as an anesthetic agent in animal research. Effects of any anesthetic agent on physiologic function and their influence on outcome variables in an experimental study should be appreciated. It is possible to minimize the impact of anesthetic agents on experimental outcomes by carefully designing each experiment. For example, as previously reported by us, ketamine was used as the anesthetic of choice for a head-down tilt study using rhesus monkeys (2, 3). In this study, ketamine was administered as a bolus dose during hemodynamic recordings and continuous infusion during TEE recordings. To minimize the influence of the anesthetic agents and administration techniques, the study was designed as a randomized, counter-balanced crossover design, in which each test subject was tested across all treatment conditions (i.e., within-subjects design). Subsequently, the influences of anesthetic agent (ketamine) and administration technique (bolus or

Table 1. Treatment means, standard errors of the mean, and test statistics for the 11 dependent effects

	Treatment				Test Statistics	
Dependent variable	Control	Bolus	CI	CI+TEE	P^a	HSD[b]
AoPsys (mmHg)	114 ± 3	116 ± 4	111 ± 5	125 ± 4	0.003	11.9
AoPdia (mmHg)	82 ± 3	79 ± 3	76 ± 4	86 ± 4	0.033	9.7
CO (ml/min)	1,082 ± 208	1,020 ± 163	992 ± 166	949 ± 140	0.518	–
LVPdia (mmHg)	2.6 ± 1.6	1.8 ± 0.9	2.8 ± 0.7	4.5 ± 1.1	0.356	–
SV (ml)	6.8 ± 1.2	6.7 ± 1.1	6.9 ± 1.1	6.2 ± 0.8	0.394	–
HR (bpm)	158 ± 7	149 ± 8	141 ± 8	151 ± 8	0.051	15
D(LVP)/dt (mmHg/s)	3,465 ± 149	3,197 ± 241	3,057 ± 300	3,005 ± 211	0.236	–
CLVD (ml/mmHg)	1.3 ± 0.2	1.0 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	0.001	0.2
SAC (ml/mmHg)	0.10 ± 0.02	0.10 ± 0.02	0.10 ± 0.01	0.14 ± 0.01	0.659	–
TPR (mmHg-min/ml)	0.16 ± 0.07	0.17 ± 0.08	0.15 ± 0.06	0.14 ± 0.06	0.751	–
Slope (R-R vs. AoP)	3.6 ± 0.7	4.2 ± 0.9	2.8 ± 0.6	2.2 ± 0.7	0.106	–

CI = Continuous infusion, TEE = transesophageal echocardiography, HSD = Tukey's honestly significant difference.
[a]3,18 Degrees of freedom.
[b]$\alpha = 0.05$.

continuous infusion), as well as other external factors (time, food) were counterbalanced and did not confound the treatment effects. Although treatment effects are not confounded in such an experimental design, it should be understood that measurements of cardiovascular performance should be viewed as relative rather than absolute. This is not only important in experimental situations, but also clinical settings where clinicians often assume that measurements provide absolute information.

Results of this study illustrate what is commonly called the "Hawthorne Effect". In more technical terms, this effect is referred to as "the reactive effect of experimental arrangements". Since many physiologic experiments require a high degree of physical instrumentation, it is not uncommon for the outcome (i.e., dependent) variable in the experiment to be influenced solely by the measurement process. This in turn effects the external validity (i.e., generalizability) of the findings to physiologic situations where the instrumentation is not present. Proper experimental design and control group manipulation are critical components for separating "true" experimental effects from those resulting solely from the interaction of the organism with the instrumentation. This study also illustrates how the instrumentation can change these values by an unknown constant.

In conclusion, the primary effects of ketamine observed five minutes after bolus injection or start of continuous infusion, and TEE on cardiovascular function in rhesus monkeys were minimal. Ketamine increased HR and reduced LVdC five minutes after administration by either bolus or continuous infusion. There were no statistical differences in cardiovascular function and baroreflex response five minutes after ketamine was administered as a bolus dose or a continuous infusion, indicating that either anesthetic approach can be applied. The primary effect of TEE probe insertion was increased aortic systolic and diastolic pressures.

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