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# Physiologic Measures of Nonhuman Primates During Physical Restraint and Chemical Immobilization

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## SUMMARY

The arterial acid-base balance and other selected physiologic measures of physically restrained and chemically immobilized nonhuman primates from the families Callithricidae, Cebidae, Cercopithecidae, and Pongidae were compared. The physically restrained primates had significantly lower pH, $pCO_2$, and base excess values, but they had significantly higher $pO_2$ values, rectal temperatures, and pulse and respiration rates.

Of 56 physically restrained primates, 30 (54%) experienced severe metabolic acidosis, with pH values less than 7.2; 15 (27% of total) had pH values less than 7.1.

Two types of behavior were observed during the physical restraint of golden marmosets. Some of the marmosets were excited during restraint, with a great deal of struggling and vocalizing. The other marmosets were quiet and calm, with minimal struggling. The excited group had significantly lower pH, $pCO_2$, and base excess values, but significantly higher $pO_2$ values, rectal temperatures, and pulse and respiration rates.

Primates immobilized with ketamine or tiletamine-zolazepam had a near normal acid-base balance and were handled more easily than the physically restrained animals.

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THE ROUTINE HEALTH CARE and management procedures commonly performed on nonhuman primates often require physical restraint or chemical immobilization. In general, the technique utilized is based on the primate's size and strength, the expertise of the handler, and the procedure to be performed. The choice is usually one of convenience for the people involved. However, the stresses placed on a primate by a particular restraint or immobilization technique must be recognized if the procedure is to be considered a safe and reliable one, especially when the primate is a patient suffering from concurrent disease.

Our own experiences with Père David's deer *(Elaphurus davidianus)* indicated that the handling that animals received prior to and during restraint would alter their acid-base balance.[1,2] In this study, the arterial acid-base balance of physically restrained and chemically immobilized primates was evaluated in an effort to detect any physiologic alterations that may have resulted from the techniques used. Certain alterations to the animals' cardiovascular, respiratory, or metabolic functions are reflected by changes in the acid-base status and the use of appropriate nomograms enables the identification of the origin and degree of any impairments to homeostasis.

## Materials and Methods

During the study period, 237 episodes of physical restraint or chemical immobilization involving 137 individual primates were evaluated. Twenty-three species of the primate families Callithricidae, Cebidae, Cercopithecidae, and Pongidae were included in the study.

The variety of procedures necessitating these episodes of restraint included routine physical examination, tattooing, electroejaculation, rectal palpation for pregnancy examination, routine tuberculin testing, fracture repair, laceration treatment, electrocardiography, and radiography.

Physically restrained animals were manually held throughout the procedures necessitating restraint. Chemically immobilized primates were given 1 of 2 dissociative anesthetics: either ketamine hydrochloride[a] or the combination of 2 compounds, tiletamine hydrochloride and zolazepam,[b] prepared in a 1:1 mixture. Both ketamine and tiletamine-zolazepam have been widely used for the immobilization of primates.[1,3-6]

Prior to restraint or immobilization, the animals were netted or transferred into small squeeze cages. The physically restrained animals were removed from the nets or cages and manually held in as near dorsally recumbent position as was possible. The immobilizing drugs were administered intramuscularly, using a plastic disposable hand syringe. The larger species, which could not be netted or shifted to smaller cages were given injections by use of a syringe pole or a projectile syringe fired from a $CO_2$-powered pistol.[c] The dosages of ketamine and tiletamine-zolazepam used are listed (Table 1). After injection of the agents, the primates were left alone in a quiet environment during the induction period.

As soon as the animal was restrained, arterial blood samples were collected for pH and blood gas analysis. The samples were drawn anaerobically from the femoral artery, using a 1-ml heparinized[d] disposable tuberculin syringe. After thorough mixing of the sample, it was introduced into a pH/blood gas analyzer.[e] Values for pH, $pCO_2$, and $pO_2$

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[a] Ketaset, Bristol Laboratories, Syracuse, NY.

[b] Telazol (CI-744), Parke-Davis and Company, Ann Arbor, Mi.

[c] Cap-Chur Gun, Palmer Chemical and Equipment Company, Inc, Douglasville, Ga.

[d] Sodium heparin, 1,000 USP units/ml, Riker Laboratories, Inc, Northridge, Ca, and Wolins Pharmacal Corporation, Melville, NY.

[e] IL Model 213 pH/Blood Gas Analyzer, Instrumentation Laboratories, Inc, Lexington, Ma.

TABLE 1—Dosages and Total Immobilization Times for Primates Given Ketamine or Tiletamine-Zolazepam

| Species | Ketamine | | | Tiletamine-zolazepam | | |
|---|---|---|---|---|---|---|
| | No. | Dosage* | Immobilization time** (min) | No. | Dosage* | Immobilization time** (min) |
| Cebidae | | | | | | |
| *Ateles fusciceps* (Black spider monkey) | 20 | 23.0 (9.6–28.7) | 28 to 45 | 7 | 3.6 (1.8–5.0) | 22 to 34 |
| *Alouatta villosa* (Black howler monkey) | | Not used | | 4 | 3.9 (3.1–4.8) | 27 to 34 |
| *Lagothrix cana* (Woolly monkey) | 4 | 12.2 (9.4–15.0) | 20 to 31.5 | 3 | 3.3 (3.0–3.5) | 16 to 38 |
| *Aotus trivirgatus* (Douroucouli) | 2 | 8.8 (8.3–9.4) | 24 to 29 | | Not used | |
| *Cacajao rubicundus* (Red-faced ukari) | | Not uaed | | 4 | 3.2 (2.2–4.4) | 16 to 30 |
| Cercopithecidae | | | | | | |
| *Macaca sylvana* (Barbary ape) | 12 | 15.0 (11.0–18.2) | 26 to 72 | 3 | 3.5 (2.2–4.3) | 28 to 35 |
| *Macaca silenus* (Lion-tailed macaque) | 11 | 11.0 (9.2–13.8) | 21 to 44 | 3 | 2.6 (2.5–2.7) | 23 to 29 |
| *Macaca nemestrina* (Pig-tailed macaque) | 3 | 9.8 (9.2–10.7) | 20 to 38 | | Not used | |
| *Cynopithecus niger* (Celebes ape) | 1 | 17.1 | 37 | 3 | 3.6 (2.8–4.4) | 20 to 88 |
| *Theropithecus gelada* (Gelada baboon) | 2 | 7.2 (6.3–8.1) | 42 to 46 | 9 | 2.5 (2.1–4.4) | 20 to 67 |
| *Erythrocebus patas* (Patas monkey) | 2 | 11.3 (10.0–12.6) | 28 to 36 | | Not uaed | |
| *Presbytis senex* (Purple-faced langur) | 5 | 7.4 (5.5–10.0) | 25 to 64 | 2 | 3.4 (3.3–3.6) | 31 to 34 |
| *Colobus guereza* (Black and white colobus monkey) | 6 | 10.1 (9.0–11.0) | 20 to 27 | 4 | 2.7 (2.1–3.3) | 18 to 33 |
| *Cercopithecus aethiops sabaeus* (Green monkey) | 2 | 14.5 (8.8–19.0) | 20 to 33 | | Not used | |
| *Cercopithecus diana roloway* (Diana roloway guenon) | 9 | 12.4 (7.7–23.2) | 21 to 83 | 3 | 3.0 (2.4–3.5) | 23 to 31 |
| *Cercopithecus neglectus* (DeBrazzae monkey) | 3 | 9.8 (9.4–10.1) | 28 to 33 | | Not used | |
| *Cercopithecus* sp (Spotnose monkey) | 2 | 9.0 (8.3–9.7) | 32 to 39 | | Not used | |
| Pongidae | | | | | | |
| *Hylobates concolor* (White-cheeked gibbon) | 10 | 15.8 (9.8–22.0) | 18 to 52 | 9 | 3.4 (2.5–4.1) | 26 to 40 |
| *Pongo pygmaeus* (Orangutan) | 1 | 5.9 | 27 | 8 | 3.6 (1.7–4.4) | 26 to 85 |
| *Pan troglodytes* (Chimpanzee) | 3 | 10.7 (8.4–14.6) | 26 to 35 | 1 | 2.5 | 28 |
| *Gorilla gorilla* (Lowland gorilla) | | Not used | | 16 | 2.4 (1.6–3.1) | 20 to 65 |
| *Sympholangus syndactylus* (Siamang gibbon) | | Not used | | 4 | 3.9 (2.2–4.9) | 27 to 58 |

* Values given as mean and range. ** Immobilization times are given aa ranges of valuea of time from injection until primate ahowed signs of a righting reflex.

were then recorded at the instrument's temperature of 37 C. When the analyzer was not immediately available, the sample was placed in an ice bath and analyzed within 3 hours. Measurements of respiration rate, pulse, and rectal temperature were taken at the time the sample was drawn. In some instances, additional arterial samples were drawn within 15 to 30 minutes after the 1st sample was collected. In order to utilize the various acid-base nomograms, hemoglobin values were required. During physical restraint, the arterial blood sample was used for the hemoglobin determinations. During chemical immobilization, a venous blood sample was collected from the jugular vein.

The $pCO_2$ and $pO_2$ values were corrected to correlate with the primates' body temperatures, using line charts prepared for dogs and man.[11] Values for pH were adjusted by adding or subtracting 0.0147 pH units per 1 C difference below or above, respectively, the instrumental temperature of 37 C.[9] Base excess (BE) was estimated, using an alignment nomogram.[10]

## Results

The mean dosages of ketamine and tiletamine-zolazepam that were used to immobilize the primates are listed (Table 1). For both drugs, induction time was approximately 2 to 5 minutes, rarely exceeding 8 minutes. The longest induction times were in orangutans *(Pongo pygmaeus)* and gorillas *(Gorilla gorilla)*. Visual effects accompanying induction included head sagging, loss of grip, and moderate salivation. In the larger primates, atropine[f] in dosages of approximately 0.0015 mg/kg body weight was effective for reducing the salivation. In most cases, the degree of relaxation was adequate for the procedures performed. Tiletamine-zolazepam produced better muscle relaxation than did ketamine. Additionally, tiletamine-zolazepam was a more potent agent than ketamine. Ten times the amount of ketamine was required to produce comparable levels of sedation.

The immobilized primates began to awaken 20 to 90 minutes after injection, depending on the dosage used. The mean dosages provided an average of 25 to 40 minutes of immobilization time before the primate began to show signs of a righting reflex. In general, the duration of immobilization was dosage-dependent for both drugs. Total immobilization times for each of

[f] Atropine-Sulfate, Med-Tech, Inc, Elwood, Ks.

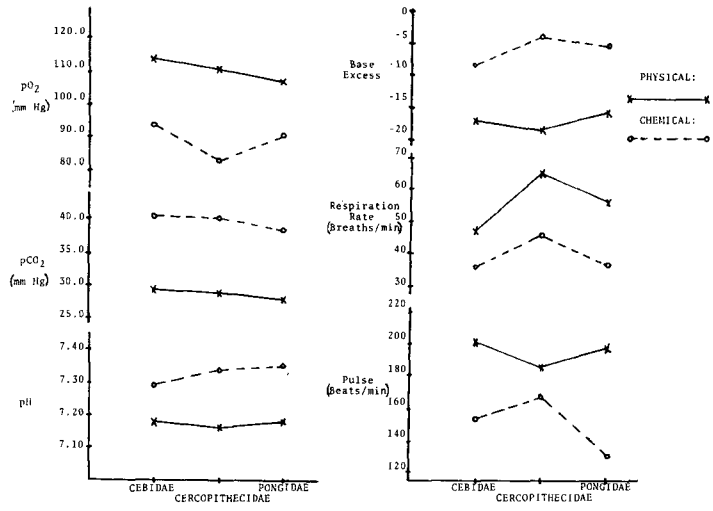


Fig 1—Comparison of acid-base and other physiologic data obtained from members of 3 primate families during physical restraint and chemical immobilization. Data are expressed as mean values.

the species studied, with each of the immobilizing agents, are listed (Table 1).

There were no significant differences between the acid-base and other physiologic measures obtained from the ketamine-immobilized and the tiletamine-zolazepam-immobilized primates. Consequently, data obtained from the drug immobilizations with both of the agents were combined to obtain figures for chemical immobilization in general. The mean pH, $pCO_2$, and $pO_2$ values obtained during physical restraint and chemical immobilization of species from 3 primate families (Cebidae, Cercopithecidae, and Pongidae) are compared (Fig 1). The values for pH and $pCO_2$ were significantly ($P < 0.01$) lower, and the $pO_2$ values were significantly ($P < 0.01$) higher, in the physically restrained animals. Values for BE, respiration rate, and pulse were also compared (Fig 1). The BE was significantly ($P < 0.01$) lower (more negative) in the physically restrained primates, indicating a greater base deficit, and both the respiration and pulse rates were more rapid. The base deficits of physically restrained primates were found to be two- to threefold greater than the deficits in chemically immobilized animals. All of the differences were observed at the species level as well as at the family level.

The 4th primate family involved in this study was Callithricidae. All of the members of this family are small in size and were involved in physical restraint episodes only. The evaluation of 20 physical restraint sessions with 1 species of this group, the golden marmosets *(Leontideus rosalia)*, revealed 2 different reactions to the restraint procedure. One group of marmosets became extremely excited during the episode, with much struggling and vocalizing. The other group consisted of semi-tame animals that were relatively calm during the restraint procedure; they offered little resistance and vocalized less than the others.

Significant ($P < 0.01$) differences were found between the acid-base and other physiologic measures of the 2 groups. The excited group had mean values for pH, 7.14 ± 0.03 (mean ± standard error); $pCO_2$, 29.8 ± 1.2; $pO_2$, 100.8 ± 2.0; and BE, −16.8 ± 1.4. Mean respiration rates, pulse, and rectal temperatures in this group were 112 ± 7 breaths/minute, 277 ± 17 beats/minute, and 39.6 ± 0.3 C, respectively. The calm group had mean values for pH, 7.38 ± 0.01; $pCO_2$, 34.3 ± 0.8; $pO_2$, 95.2 ± 2.6 mm of Hg; BE, −5.6 ± 1.4; respiration rate, 78 ± 6 breaths/minute; pulse, 218 ± 38 beats/minute; and rectal temperatures, 38.9 ± 0.2 C.

On several occasions, the primate was initially physically restrained and a blood sample was drawn for blood gas analysis. Then the animal was given either ketamine or tiletamine-zolazepam and additional arterial blood gas studies were performed. Values for pH, $pCO_2$, $pO_2$, BE, respiration rate, and rectal temperature obtained during such a procedure with a Barbary ape *(Macaca sylvana)* are traced (Fig 2). In this case, typical of those handled in this manner, the physical restraint lasted approximately 4 minutes, at which time ketamine was given at a dosage of 16 mg/kg body weight. The animal was handled 2½ minutes after injection, and an arterial blood sample was drawn. A 3rd arterial sample was obtained 15 minutes later, at 19 minutes after injection. The pH, $pCO_2$, and BE values, which increased during the transition from physical restraint to chemical immobilization, are shown (Fig 2). Values for $pO_2$, respiration rate, and rectal temperature decreased over the same period. The 1st sample, taken during physical restraint, indicated a status of severe metabolic acidosis (pH of 7.18). The 3rd sample, collected during ketamine immobilization, showed an acid-base balance that was approaching normal (pH of 7.31).

Of the 56 physically restrained primates, 30 (54%) had pH values ≤ 7.2; half of these (27%) had values < 7.1. Physical restraint in the primates led to severe metabolic acidosis, with pH values as low as 6.8 in highly excited animals. In general, values for pH and $pCO_2$ were lower, and values for $pO_2$ higher, in physically restrained primates, when compared with chemically immobilized animals. In addition, the handheld group had more rapid respiration and pulse rates, higher rectal temperatures, and larger base deficits.

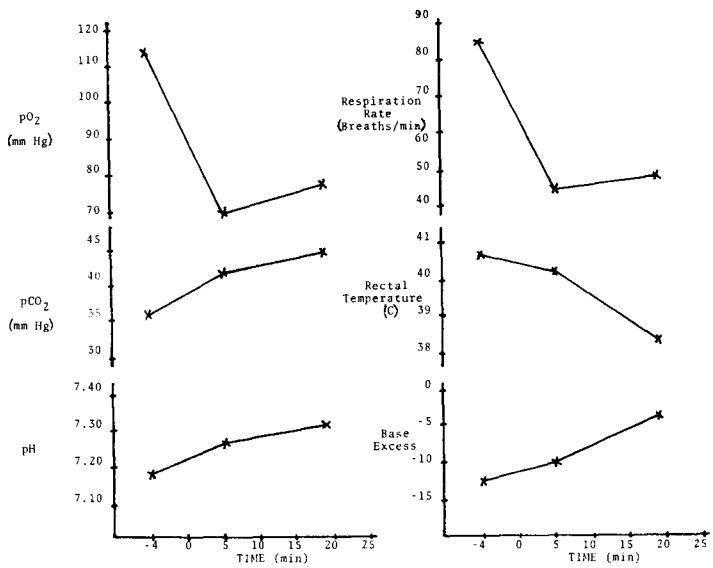


Fig 2—Acid-base and other physiologic data of a Barbary ape during physical restraint, prior to administration of ketamine at time 0, and during ketamine immobilization.

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## Discussion

Ketamine and tiletamine-zolazepam proved to be effective agents for the restraint and immobilization of primates. Both agents are cyclohexylamines that induce profound analgesia and cataleptoid anesthesia.[13] Ketamine and tiletamine-zolazepam were characterized in this study by rapid induction times and intact corneal, palpebral, and swallowing reflexes. The eyes of the primates remained open during the immobilizations. Tiletamine-zolazepam induced better muscle relaxation than did ketamine and provided adequate immobilization with smaller dosages. There were no serious alterations of the acid-base balance of the primates immobilized with ketamine and tiletamine-zolazepam.

In contrast, physical restraint of primates resulted in severe alterations to their acid-base balance, which led to serious metabolic acidosis. The metabolic acidosis during these episodes of physical restraint was probably related to increased blood concentrations of lactic acid. The energy of muscular work is largely obtained from the oxidation of carbohydrates and fats. During heavy work or exercise, the individual is not capable of supplying and utilizing the large amounts of oxygen needed to satisfy the increased energy requirements. Consequently, anaerobic oxidative mechanisms become important in providing the necessary energy to perform the work. The metabolites of anaerobic metabolism in the form of fixed acids, mainly lactic acid, then diffuse into the bloodstream. These increased acid concentrations then decrease the blood pH. During this study, the pH values of physically restrained primates dropped to as low as 6.8 after only 2 to 6 minutes of restraint. Assuming a normal pH of 7.4, the average decrease from normal was 0.2 to 0.3 pH units during physical restraint. Similarly, in athletic men, 2 to 5 minutes of exhausting work caused the pH to decrease from 7.4 to 7.0, accompanied by an increase in lactic acid concentration from 1 mEq/L to 22 mEq/L.[14] Therefore, increased lactic acid concentrations in the primates fighting restraint probably accounted for the metabolic acidosis. The calm, nonexcited golden marmosets, which had minimal muscular exercise through struggling, had pH values near normal during physical restraint.

Increased respiration rates due to physical restraint have been reported in primates.[2] The hyperventilation observed during physical restraint in this study led to decreased $pCO_2$ and increased $pO_2$ in these animals. The increased exercise and work of the struggling primates during physical restraint generated body heat, which accounts for the higher rectal temperatures.

Not all physically restrained animals became excited and struggled during the procedures. As with the golden marmosets, most handheld primates could have been separated into 2 categories: calm and excited. The excited animals invariably had lower blood pH values and greater metabolic acidosis. Similarly, not all of the chemically immobilized primates had near-normal acid-base values. Some had low pH values and moderate acidosis. However, these animals were generally more excited prior to administration of the chemical immobilizing agent than were those with the normal acid-base values. Several minutes of a chase or excitement before injection would have been sufficient time for metabolic acidosis to develop. Thus, the acidemia in the first arterial sample of such an individual was assumed to be related to the pre-administration exercise rather than to the drug itself.

For healthy primates, recovery from the metabolic acidosis of physical restraint is rapid and efficient. After an animal is released, it adopts normal respiratory and presumably metabolic functions. The liver removes the lactic acid from the bloodstream and the blood pH rises toward normal. In human beings, recovery from exhaustive work is rapid enough that he (she) may perform well again in less than an hour.[14] In stressed animals, however, recovery may not be as efficient. Physical restraint may provide additional stress, which may be lethal to an already debilitated animal. If the animal has an occult hepatic or renal disorder, a normally rapid recovery from restraint may not be possible. Studies have been conducted on the pH and blood gas values of samples obtained from physically restrained zebra *(Equus burchelli)* and blesbok *(Damaliscus dorcas phillipsi)* after forced exercise.[7,8] In those studies, severe metabolic acidosis contributed to postcapture myopathy and to other postcapture problems, including death. Thus, unless the animal is relatively tame, and therefore calm during the procedures, chemical immobilization may be indicated as an alternative when handling stressed animals.

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