Evaluation of Digital Implantable Telemetry in Multiple Social Housing Paradigms for Cynomolgus Monkey

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Abstract

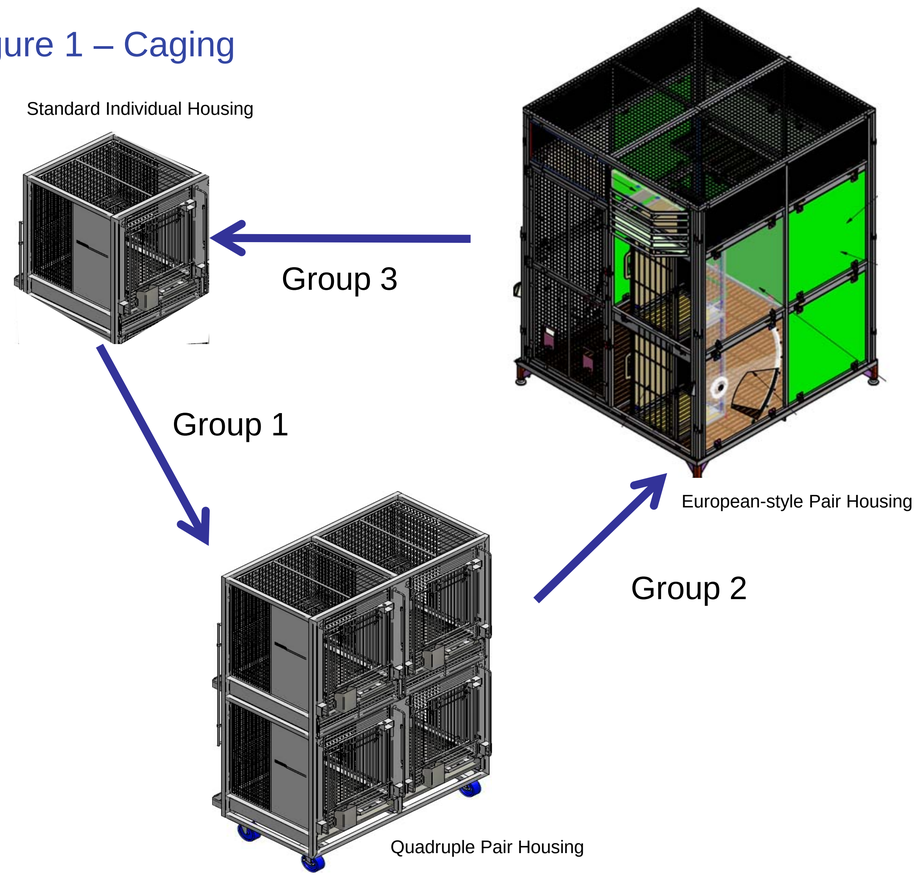
Proactive efforts to socialize laboratory animals are a contemporary initiative for enhancing animal welfare. Telemetry-implanted cynomolgus monkeys have been traditionally considered exclusionary criteria for socialization during repeat-dose or standalone safety pharmacology toxicology studies with safety pharmacology endpoints. Our objective was to evaluate the effect of implementing cynomolgus monkeys implanted with a digital L-11 PhysioTel device (Data Sciences International) in different housing paradigms. Six animals were randomized and rotated (control for time bias) into three different housing conditions (standard individual [SI], quad-paired caging [QP], and European-compliant paired caged [EU]) and dosed on consecutive days with sterile water and subsequently with 100 mg/kg moxifloxacin. Cardiovascular parameters were recorded for 24 hours on each occasion using PhysioTel-Digital and hematology parameters were measured. All animals demonstrated similar diurnal rhythms in heart rate (HR) and blood pressure (BP) parameters per housing type (dark photoperiod/resting HR for SI =105 ± 2 BPM; QP=105 ± 3 BPM; EU=109 ± 3 BPM) with a similar trend in mean BP (MAP, SI and QP= ~75 mmHg; EU=~79 mmHg). Leukocyte profiles did not indicate differences in stress responses between housing conditions (total white cell counts were within 10% regardless of housing condition). Moxifloxacin administration resulted in an expected 20 ms prolongation in individually rate-corrected QT (QTca) with no notable differences between housing conditions. Furthermore, QA intervals tracked consistently with expected patterns of sympathetic stimulation. These data support the sensitivity of PhysioTel digital to detect expected pharmacological and/or physiological changes in the ECG and hemodynamic parameters. Taken together, the different housing paradigms resulted in minimal hematological differences and concurrently, no differences in the detection of hemodynamic or ECG interval changes including QTca.

Methods

The following dimensions of single and social animal housing and were evaluated during the study:

Caging Type	Width (in.)	Depth (in.)	Height (in.)	Floor (ft^2)	Volume (ft^3)	Volume/animal (ft^3)
Standard	27	28	32	4.9	13.9	13.9
Modified Quad (Pair Housed)	54	28	68	14.7	55.4	27.7
European Cage (Pair Housed)	66.5	51	76	23	157.8	78.9

Figure 1 – Caging



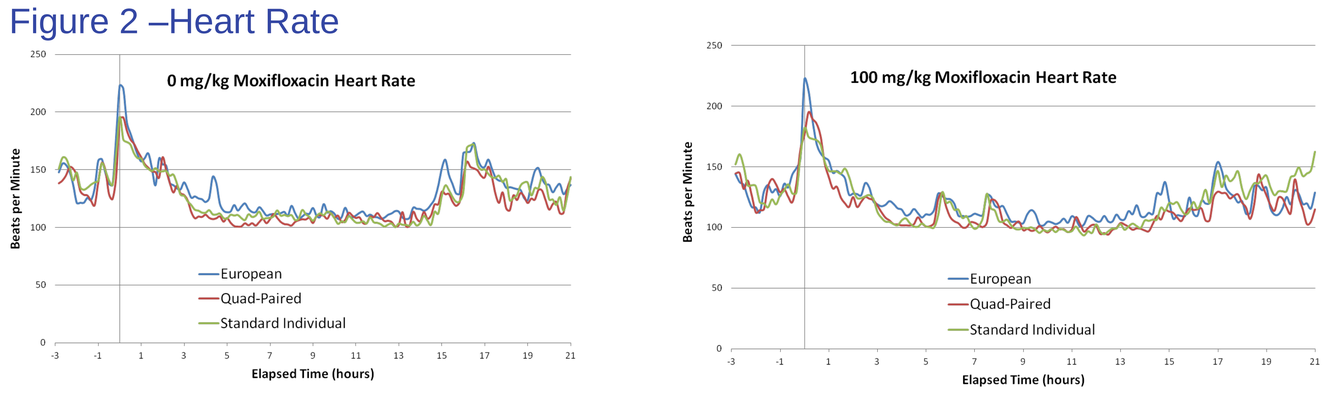
Caging rotation was alternated by group to minimize time bias. Starting caging is indicated by group, such that Group 1 started the study in single housing, and ended in European-style housing, and Group 3 started in European-style housing and ended in modified quad caging (as indicated). All groups proceeded through caging styles depicted above in a counter-clockwise fashion.

Methods/Experimental design

1) 4 male and 2 female monkeys were implanted with L-11 Telemetry devices.
2) Animals were assigned to 3 dose groups, pair housed to verify compatibility.
3) Animals were rotated through caging types 1-3 (Figure 1) on Days -4-3, 3-10, and 10-33. The final rotation was longer compared to the first 2 due to a technical difficulties that required an additional recording session.
4) Telemetry data were recorded for 24 hours on each occasion.
5) Control dose administration occurred at time = 0 hours on Days 1, 8, and 30.
6) Moxifloxacin (100 mg/kg) dose administration occurred at time = 0 hours on Days 2, 9, and 31.
7) Blood samples were collected at the initiation and completion of each housing rotation.
8) Individual animal QT rate corrections were determined during the initial control dose for each group. Individual rate corrections were applied to all data (all caging types) to correct for QT variations associated with heart rate.

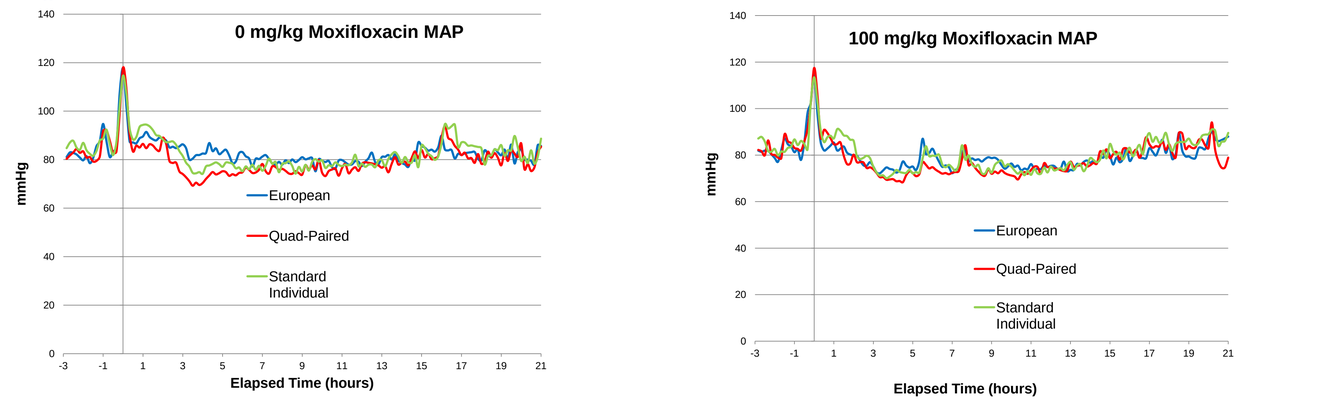
Results

Figure 2 –Heart Rate



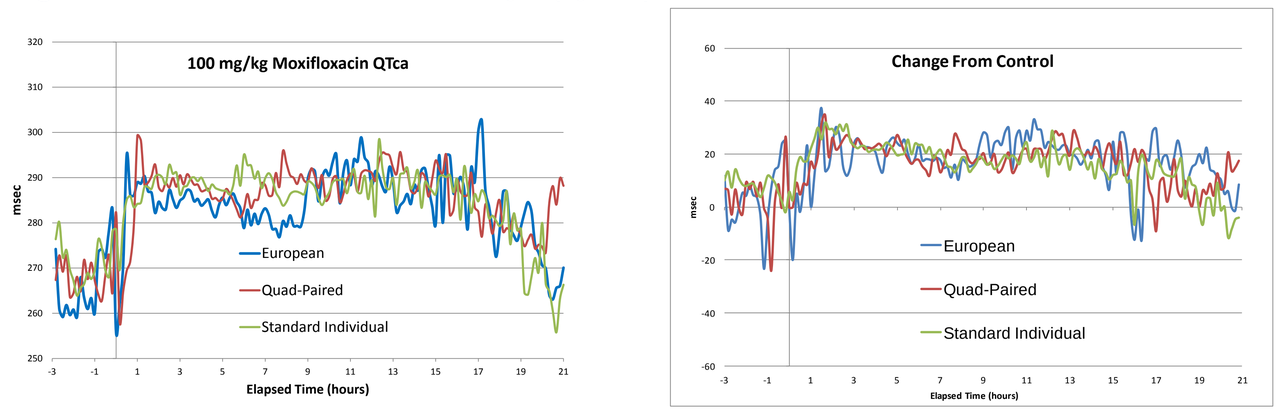
There were no discernible effects of caging types on heart rate collected with PhysioTel Digital®. A normal diurnal rhythm is evident in all caging types indicated by decreased heart rate from 3-15 hours post dose (dark photoperiod).

Figure 3 –Blood Pressure



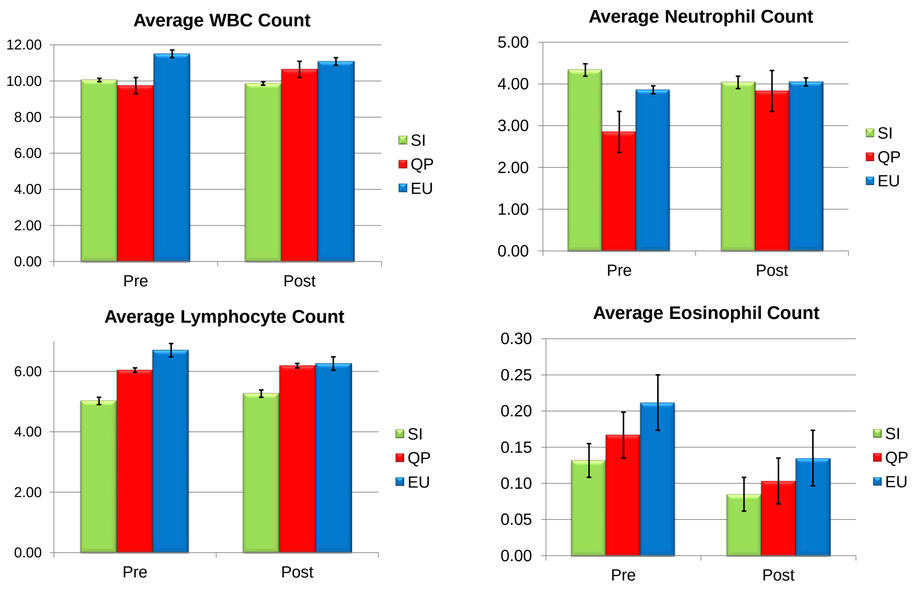
There were no discernible effects of caging types on mean arterial blood pressure (MAP) collected with PhysioTel Digital®. A normal diurnal rhythm is evident in all caging types as indicated by decreased MAP from 3-15 hours post dose (dark photoperiod).

Figure 4 –Heart rate-corrected QT (QTca)



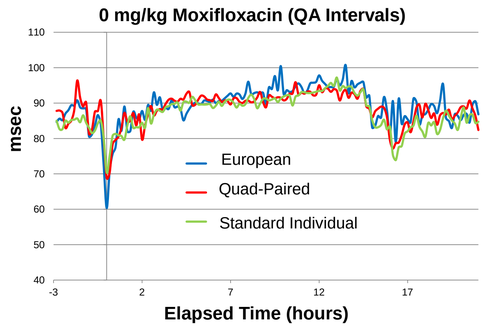
There were no effects of caging types on the detection of the expected increase in individually heart rate-corrected QT interval (QTca). There were no intergroup differences in these intervals irrespective of caging type (no inter-group biases, not depicted).

Figure 5 –Effect on Leukocyte Parameters in Different Housing Paradigms



Blood samples collected for hematology analysis were evaluated from all animals in each housing paradigm pre- and post-dose to assess physiological stress of the animals. In each housing paradigm, there were no notable differences in the mean (n=6) leukocyte parameters indicative of physiological stress (i.e.; white cell counts, neutrophil counts, lymphocyte counts, and eosinophil counts).

Figure 6 –QA Interval as a surrogate marker for contractility



There was a trend for QA shortening during expected periods of sympathetic stimulation (i.e., dose administration time =0 and during the initiation of the lights on period), which does potentially suggest that the QA interval is an appropriate surrogate for cardiac contractility analysis.

Conclusions

1) The implantable PhysioTel Digitial® system reliably collected ECG data from freely-moving cynomolgus monkeys in individual and in different social housing paradigms.
2) There were no effects of caging type or social housing status (individual or paired) on of any of the parameters measured, including ECG, heart rate, and hemodynamic profiles.
3) There was no change in the leukocyte panel between the 3 housing paradigms, indicating a similar physiologic stress profile that is independent of the housing type.
4) The PhysioTel Digitial® system detected a similar 20 ms prolongation in individually rate-corrected QT (QTca) following moxifloxacin administration in all caging types.
5) QA interval shortening tracked consistently with expected periods of sympathetic stimulation.
6) Telemetry data are not impacted by caging type/socialization status in properly acclimated animals**.**

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