Long term measurements of temperature, activity and heart rate in laboratory rats using data loggers as a minimally invasive and low-cost screening tool

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BACKGROUND

Preclinical safety pharmacology and toxicology studies use several tools such as Implantable telemetry and jacketed external telemetry to evaluate 24-h endpoints. There exists a need that enables cardiovascular (CV) screening using minimally invasive and low-cost solutions.

OBJECTIVES

Leadless data loggers from Star-Oddi were explored as an alternative to traditional telemetry for three typical physiological signals; temperature, heart rate and activity for three weeks. Correlation between signals was compared, quality of HR estimated and physiological response to a series of husbandry and protocol-defined activities occurring during light cycle were evaluated.

METHODS

Data was used from twelve laboratory rats, implanted subcutaneously with two data loggers on the flank of the animal, one on each side. One data logger measures temperature and ECG derived heart rate (DST micro-HRT) implanted on the right side and one measures temperature and accelerometer derived activity (DST micro-ACT), implanted on the left side (see Fig 1). Both devices measured for 20 days with an 8-minute fixed sampling interval (Fig 2). The heart rate measurement is from ECG recording sampled at 700Hz for ~1 sec (Fig 4). The activity measurement is based on an average from 3-axis accelerometer measurement recorded over 1 minute at 1Hz. Animals were individually housed under 12:12h light:dark cycle, in Techniplast cages with food and water ad libitum.

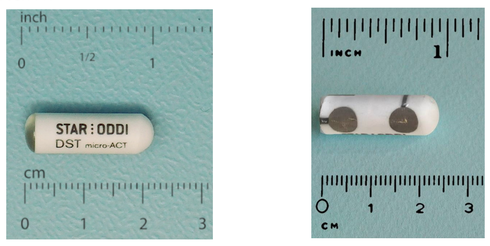

Fig 1: (Left) DST micro-ACT (3.3g), (right) DST micro-HRT (3.3g).

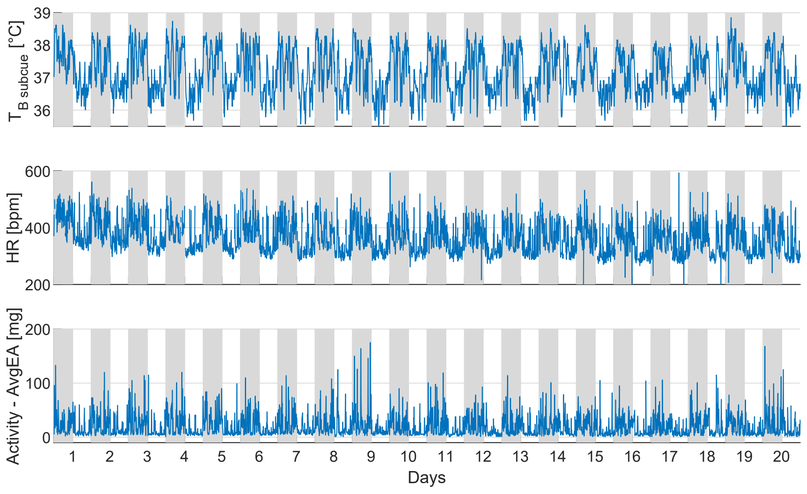

Fig 2: Raw data from a single animal, showing body temperature (top), HR (center) and average activity (bottom) for 20 days. 12h:12h light cycle is showed in gray.

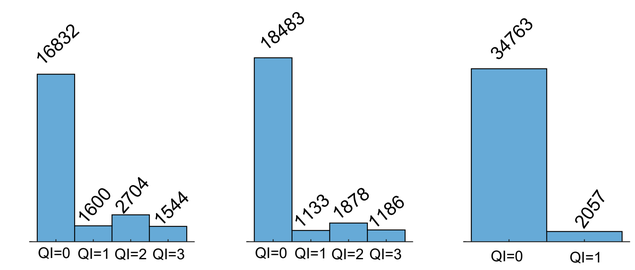

Fig 3:QI distribution for the heart rate recordings, (left) Lights off, (center) Lighs on and (right) the post processed data.

RESULTS

Heart rate recordings were processed based on quality index (QI) and threshold. Recordings with QI=2&3 were eliminated and HR above 600bpm and below 140bpm were deleted from the dataset. This provided an average of 81.5% of all HR data recorded being used (see Fig 3). The logger with the highest quality provided 96% of reliable HR recordings while lowest quality was 42%. Fig 4 shows the QI distribution where QI=0 is the highest quality and QI=3 is the lowest quality ECG recording.

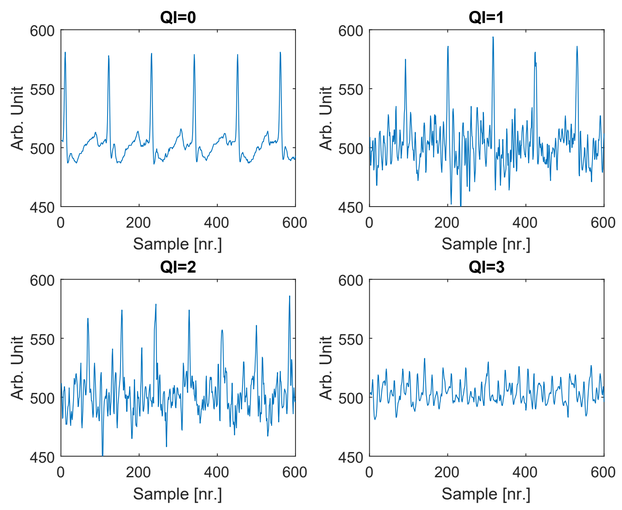

Fig 4: Example of the ECG signals recorded and how the QI is reflected for one data logger.

Average daily waveforms (20d) and cosinor rhythmometry was calculated (see Fig 5) from the raw data for the three variables, for all the animals (n=12). The rhythm characteristics are presented in Table 1. HR acrophase was 23:45 followed by temperature at 0:05 and Activity at 0:45.

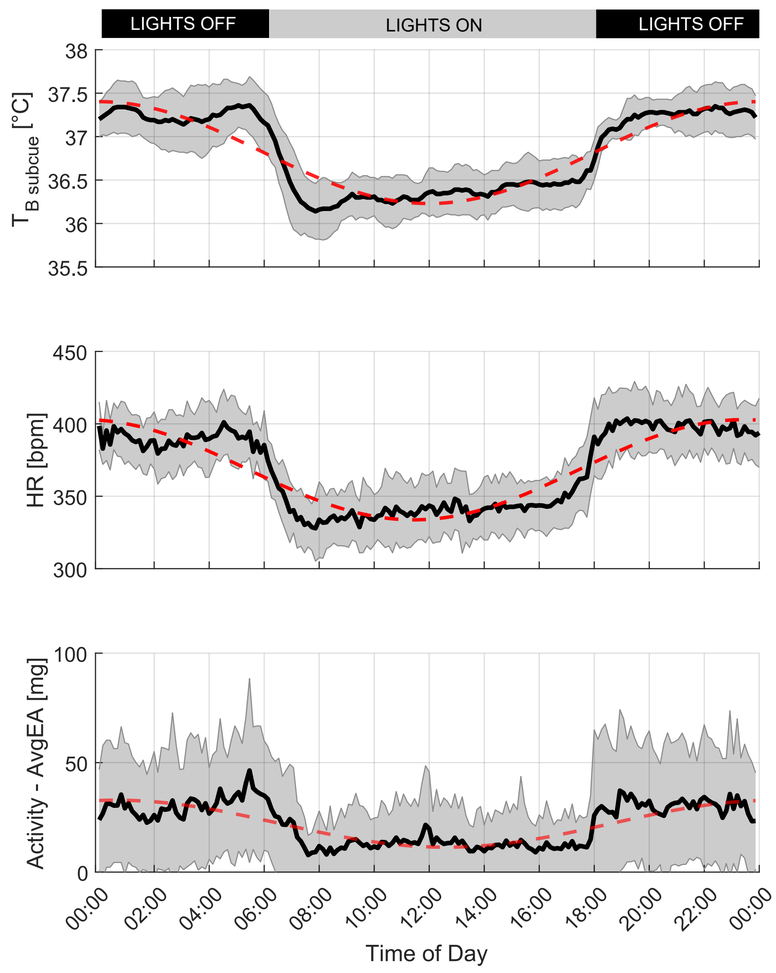

Fig 5: Average daily waveform (± SD) for all the animals (n=12) of body temperature (°C), heart rate (bpm) and Activity - AvgEA (mg) throughout the experiment. The broken red line shows the cosinor fit.

Variable	Mesor	Amplitude	Acrophase
T (°C)	36.81	0.586	0:05
HR (bpm)	368.31	34.58	23:45
Activity - AvgEA (mg)	22.12	10.73	0:45

Table 1: Mesor (the rhythm-adjusted mean), Amplitude (the difference between the peak and mesor) and Acrophase (the timing of peak value reaccuring).

Temperature and heart rate were weakly correlated both during Lights ON (T_{AVG}= 36.44 ± 0.36 °C, HR_{AVG}= 343.8 ± 20.3 bpm R^2=0.77) and Lights OFF (dark) cycle (T_{AVG} = 37.25 ± 0.2 °C, HR_{AVG} = 393.8 ± 16.09 bpm R^2= 0.54) see Fig 6(A). Temperature and activity (AvgEA) were weakly correlated during the Light ON (AvgEA= 14.92 ± 9.76 mg, R^2=0.59) but not during Ligths OFF (dark) cycle (AvgEA = 30.73 ± 7.15mg, R^2 = 0.15) see Fig 6(B). Comparison of activity (AvgEA) and HR show weak correlation during Lights on (R^2=0.47) while there is no correlation during Lights off (dark) cycle (R^2 = 0.18) see Fig 6(C)

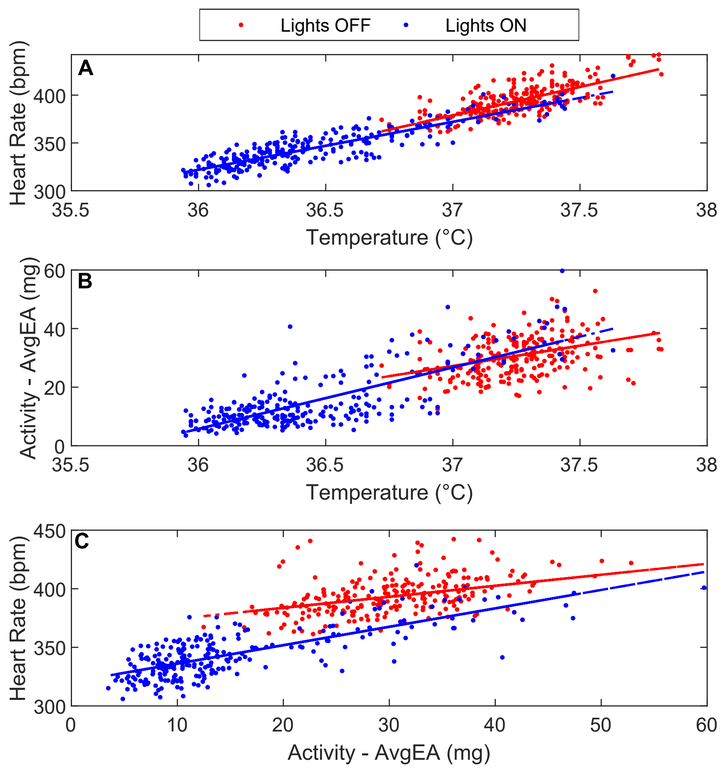

Fig 6: Relationship between (A) daily temperature and heart rate, (B) daily temperature and Activity - AvgEA and (C) daily recorded Activity AvgEA and Heart Rate.

Relationship	R^2 - Lights OFF	R^2 - Lights ON
T vs HR	0.54	0.77
T vs AvgEA	0.15	0.59
AvgEA vs HR	0.18	0.57

Table 2: R^2 relationship between daily temperature and heart rate, daily temperature and activity - AvgEA and daily Activity-AvgEA and HR.

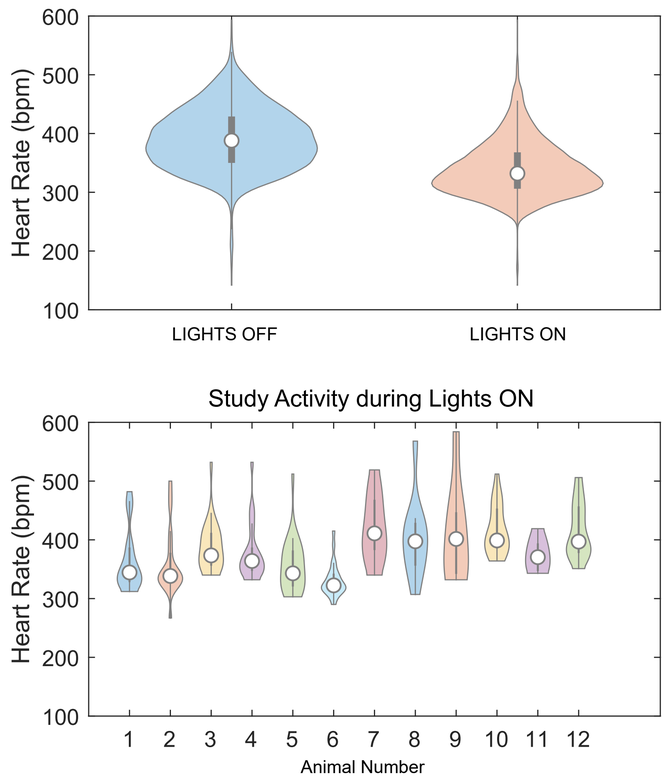

Fig 6: Violin plots for all raw heart rate recordings during lights off and lights on (top) and individual violin plots of heart rate for each animal during a study activity that took place during daytime (bottom).

Individual study activites were visualized with violin plots and compared to routine values (Fig 6) white circles represent median values $HR_{LIGHTS\ OFF}$ = 388bpm, $HR_{LIGHTS\ ON}$ = 332bpm. Bottom plot shows a 2.5h time period while the activity took only 45 minutes. Median value for the group was 370bpm with ten out of twelve animals reaching heart rates of 500bpm or more.

All animal procedures were approved by the Pfizer Institutional Animal Care and Use Committee, and followed the Guide for the Care and Use of Laboratory Animals.

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FINDINGS & CONCLUSIONS

1. Weak correlation between the variables indicates added information not revealed by heart rate alone.
2. The animals are most active during the dark (Lights OFF) cycle creating a more complex assessment then during the resting light (Lights ON) cycle.
3. Compared to traditional telemetry, the loggers don´t offer continuous ECG collection, however as a CV screening tool the loggers offer further refinement of reduced surgical duration and invasiveness.
4. Extended battery capacity and elimination of any restriction with cage type or group housing creates opportunities for a novel study systems.