Investigation of environmental and biological factors on cardiovascular and ECG data

Elham Ataei Alizadeh, Thomas Trautmann, Pieter-Jan Guns*, Brian Guth, Michael Markert

Department of Drug Discovery Sciences, Boehringer Ingelheim Pharma GmbH & Co KG
** Laboratory of Physiopharmacology, University of Antwerp, Antwerp, Belgium*

ABSTRACT

In safety pharmacology studies, potential side effects of a drug are detected and evaluated, detected, and investigated prior to its introduction into clinical trials. Cardiovascular functions are among the primary vital functions assessed during safety pharmacology studies. [1]
Detecting possible drug-induced cardiovascular side effects requires consideration of environmental and biological factors.
The purpose of this study was to analyze the influence of biological (sex, strain, and age) and environmental factors (cage size, housing condition, location, and seasonal factors) on the variability of ECG, aortic pressure (AP), and left ventricular pressure (LVP) in male and female dogs (Beagles, Labradors, Mongrel/Labradors), female non-human primates (Cynomolgus monkeys), and female minipigs (Göttingen) in safety pharmacology studies.

METHODS

A total of 4,751 hours of beat-by-beat data over 20 years were analyzed. 592 single experiments were performed on dogs (164 on Beagles, 296 on Labradors, 132 on Mongrel/Labradors), 107 single experiments on primates and 95 on mini-pigs were used. The cardiovascular data were collected from vehicle control studies (animals receiving placebo) and combined with the biological and environmental information. Statistical data analysis and visualization were performed using R studio® and Spotfire®. To assess the effect of factors over a period of time, ANOVA and Mann-Whitney U tests were conducted with significance levels of 0.05. Identifying and removing outliers was also possible. Several types of graphs were used to summarize the results, including box plots, bar charts, pie charts, and linear graphs.

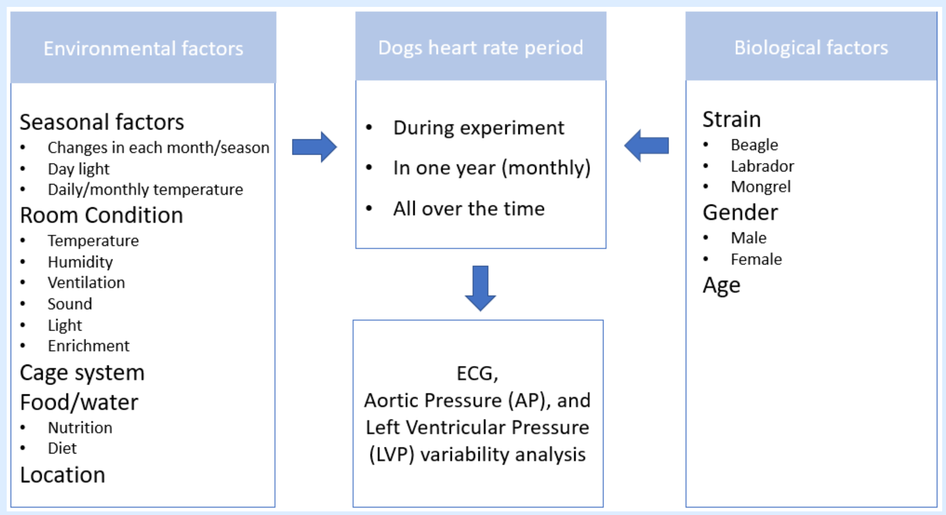
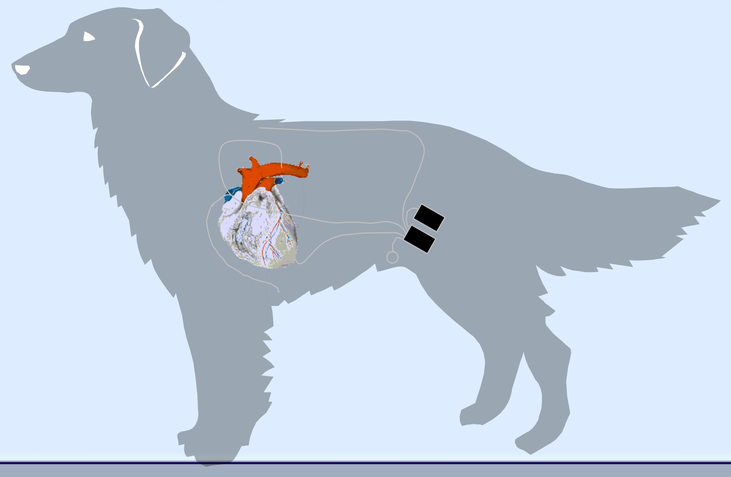


Figure 1. The framework for investigating the impact of available environmental and biological factors.



REFERENCES

1. Lacroix P, Provost D. Basic safety pharmacology: the cardiovascular system. Therapie. 2000 Jan-Feb;55(1):63-9. PMID: 10860003.
2. Markert, M., Trautmann, T., Krause, F., Cioaga, M., Mouriot, S., Wetzel, M., & Guth, B. D. (2018). A new telemetry-based system for assessing cardiovascular function in group-housed large animals. Taking the 3Rs to a new level with the evaluation of remote measurement via cloud data transmission. Journal of Pharmacological and Toxicological Methods, 93, 90–97. https://doi.org/10.1016/j.vascn.2018.03.006
3. Markert, M., Christ, K., Graf, K., Trautmann, T., Ege, A., Krause, F., & Guth, B. (2017). A New Telemetry-based System for Assessing Cardiovascular Function in Large Animals. Journal of Pharmacological and Toxicological Methods, 88, 221. https://doi.org/10.1016/j.vascn.2017.09.174

RESULTS

With the new tool we could find out that the cardiovascular system is affected by both environmental and biological factors (and their combinations).

According to the retrospective evaluations done thus far, the type of cage system used affects heart rate. The median heart rate of Labrador dogs is 47 beats per minute (bpm) in our conventional cage system and 58 bpm in our glass cage system; in contrast, Mongrel/Labradors showed a median HR of 71 bpm in the conventional cage system and 63 bpm in the glass cage system. Concerning the Beagle dogs, no noticeable difference was detected.
(Figure 2)

A further result demonstrates a seasonal effect on primates and minipigs that was not found in dogs (mean heart rate was: 67– 70 bpm in dogs; 156 –172 bpm in primates; 47 –58 bpm in minipigs.)

In addition, body temperature of dogs during the experimental period (in mean range 38.0 – 37.5 °C) decreased, in contrast to primates (mean range: 37.8 – 38.1 °C) and minipigs (mean range: 37.3 – 37.8 °C). (Figure 3)

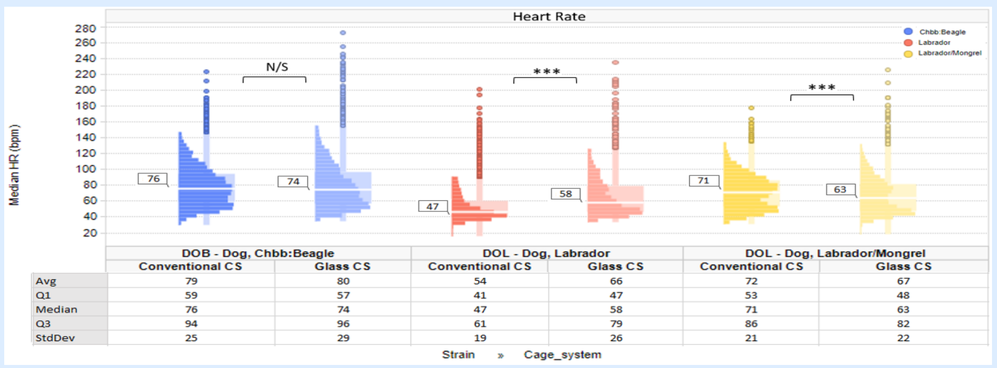


Figure 2. Overview of heart rate median (bpm) ranges and data variation by cage system and strain.

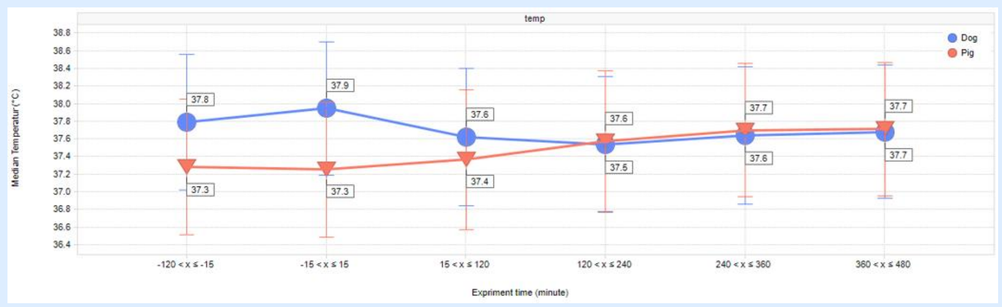


Figure 3. Comparison of the body temperatures of dogs and minipigs during an experimental study

CONCLUSIONS

This novel approach allows an investigator to assess the impact of external effects on cardiovascular data sets generated as part of safety pharmacology studies in a systematic manner. This type of analysis can help to improve the study design and the execution of experiments in cardiovascular safety pharmacology studies to optimize the 3R principles as well as best practices in terms of both the study design and the execution of experiments. [2]

In order to keep up with the ongoing placebo studies of cardiovascular experiments, this approach can continuously store new upcoming placebo case studies and always keep itself up to date.

By enabling online access to the provided platform, the relevant staff members were able to easily access it from their computers and see the easy-to-understand assessment of cardiovascular data directly from the data base.

The remaining biological findings from this study will be published in the near future as part of the upcoming publication of the study.