Exploring Waveform Analysis of Radiotelemetric Data to Improve Cardiovascular Safety Pharmacology using SPAR.

Marieke Van Daele[1], Miquel Serna Pascual[2], Manasi Nandi[2], Matt Skinner[3] and Jeanette Woolard[1]

[1]University of Nottingham, Nottingham, [2] King's College London, London, [3]Vivonics Preclinical Ltd, Nottingham

Introduction

Radiotelemetric approaches recording blood pressure in conscious, freely-moving animals are routinely used for preclinical *in vivo* haemodynamic assessments.[1] Typically, minimum, maximum and mean values of these waveforms (i.e., systolic, diastolic and mean arterial pressure (MAP) are examined.[2] More in-depth characterisation of blood pressure waveform data could enhance mechanistic insights in cardiovascular safety liabilities.[2] The Symmetric Projection Attractor Reconstruction (SPAR) is a novel mathematical method that enables such detailed waveform analysis. This method transforms lengthy waveform recordings into contained 2D representations.[3] By subsequent analysis of key features, such as density or length of the loops, detailed information on the effects of a drug on haemodynamic waveforms can be extracted.

Aim

The objective of the present study was to explore in-depth characterisation of *in vivo* blood pressure waveforms, considering changes in morphology and variability after drug administration (in this instance sunitinib, a drug acting as receptor tyrosine kinase inhibitor and associated with a raise in blood pressure), using SPAR.

Methods

1. Radiotelemetry

Male Han Wistar rats were instrumented with Stellar telemetry implants. Arterial blood pressure was recorded continuously over two consecutive days, for at least 1h before and up to 23h after daily administration of sunitinib (7 mg/kg, p.o.) or vehicle control (10 mL/kg, p.o.).

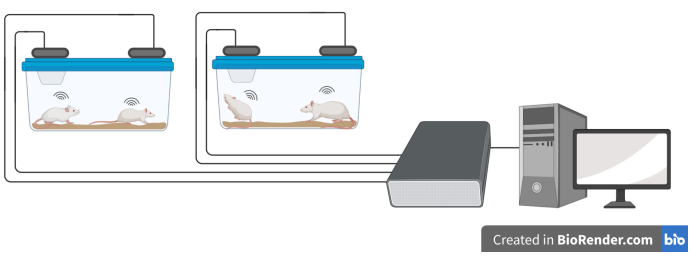

Figure 1: Radiotelemetry. Stellar telemetry implants allow for pair-housing of two instrumented animals and simultaneous, continuous recording of blood pressure, ECG, temperature and activity. (Figure created in Biorender.com)

2. Symmetric Projection Attractor Reconstruction (SPAR)

Attractors were generated in SPARKS from 1 min blood pressure waveforms every hour.

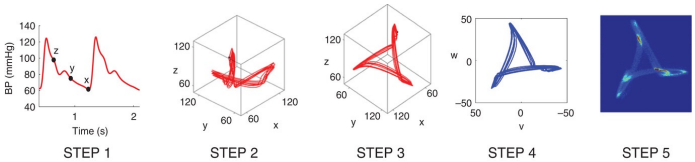

Figure 2: Overview of SPAR model: step-by-step 2D reconstruction of a physiological waveform. Three delay coordinates x, y and z are plotted on the waveform, separated by a time delay that equals one third of the average duration of a waveform cycle. This set of three delay coordinates corresponds to one value in a 3D space with a x-, y- and z-axis. When the set of x, y and z runs over the entire waveform, a 3D presentation of the recorded time trace is obtained, as shown in step 2. This set of loops is rotated and a triangle-like shape is achieved, shown in step 3. This 3D image is projected into a symmetrical 2D image, an attractor, (step 4) and a heat map is added, showing the overlap of the individual loops. (Nandi & Aston, 2020)[3]

Results

1. Effect of circadian changes on MAP and attractors.

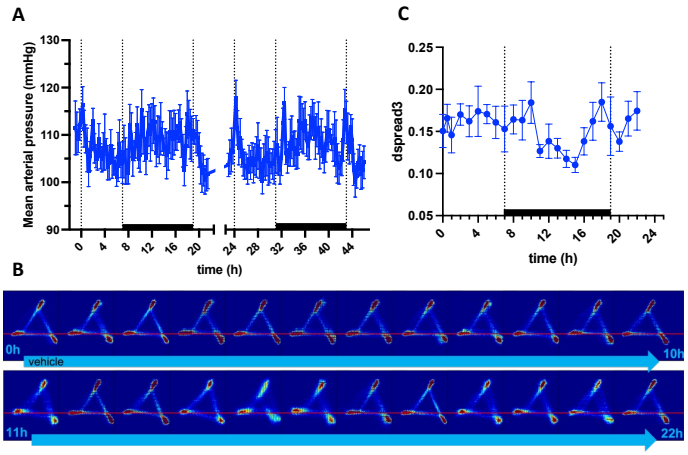

Figure 3: Diurnal haemodynamic changes.
A. 15 min averages of MAP of vehicle-treated control animals, data presented as mean ± SEM from n=6. **B.** SPAR representations of every hour on day 2, generated from 1-min recordings from an exemplar vehicle-treated animal. **C.** Subsequent analysis of attractor features. Changes in dspread3 (measure for low variability), during day 2, data presented as mean ± SEM from n=6.

2. Effects of sunitinib on MAP and attractors.

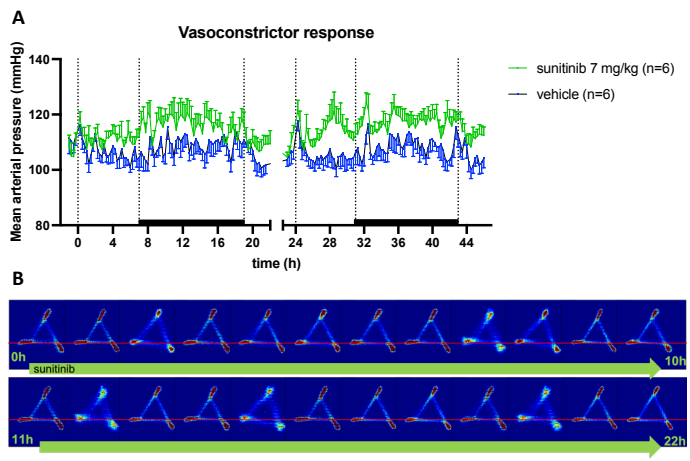

Figure 4: Effects of daily administration of sunitinib on MAP and attractors.
A. 15 min averages of MAP, data presented as mean ± SEM from n=6. Administration of sunitinib induced an increase in MAP, with a larger effect observed on day 2. **B.** SPAR representations of every hour on day 2, generated from 1-min recordings from an exemplar sunitinib-treated animal.

Conclusion and future directions

- SPAR can detect subtle diurnal changes in variability and morphology of attractors in vehicle control animals.
- Preliminary SPAR analysis of one exemplar animal suggests attractors change after sunitinib administration, further quantification is needed to confirm.
- SPAR could serve as a method for waveform analysis to enhance understanding of cardiovascular safety liabilities in early stages of drug development.
- Further quantitative SPAR analysis after administration of vasoactive compounds is needed to validate this method for use in preclinical models.

References

[1]Kramer K and Kinter LB. (2003). Physiol Genomics; 13: 197–205
[2]Mynard JJ et al. (2020). Frontiers in Physiology; 11: 1–26
[3]Nandi, M. & Aston, P. J. (2020) Exp. Physiol.; 105: 1444–1451

This work is funded by the European Union's H2020 Research & Innovation Program (GA 858070).