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

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Introduction

- Radiotelemetric approaches recording blood pressure in conscious, freely-moving animals are routinely used for preclinical *in vivo* haemodynamic assessment.[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.

Aim

The objective of the present study was to explore in-depth characterisation of *in vivo* rat blood pressure waveforms using Symmetric Projection Attractor Reconstruction (SPAR), considering changes in **VARIABILITY** and **MORPHOLOGY** after drug administration, in this instance a) sunitinib, a receptor tyrosine kinase inhibitor associated with hypertension and b) vardenafil, a PDE_5 inhibitor associated with hypotension.

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.), vardenafil (10 mg/kg, p.o.) or vehicle control (10 mL/kg, p.o.).

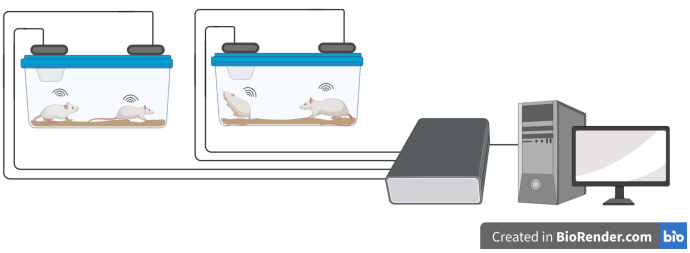

Figure 1: Radiotelemetry. Stellar telemetry implants allow for pair-housing of two instrumented animals and simultaneous, continuous recording of blood pressure, ECG, temperature and activity. (Figure created in Biorender.com)

2. Symmetric Projection Attractor Reconstruction (SPAR)

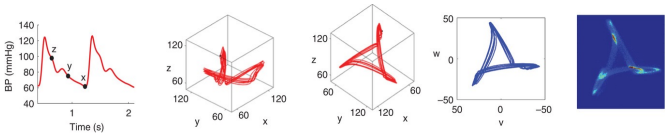

Figure 2: Overview of SPAR model: step-by-step 2D reconstruction of a physiological waveform. Three delay coordinates x, y and z are plotted on the waveform, this set of three delay coordinates corresponds to one value in a 3D space with an x-, y- and z-axis. When the set of x, y and z runs over the 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] Waveform variability is reflected in the color of the attractor. Waveform morphology is reflected in the attractor shape. Attractors were generated in SPARKS from 1-minute blood pressure waveforms, every hour.

Results

1. Circadian rhythm affects waveform variability.

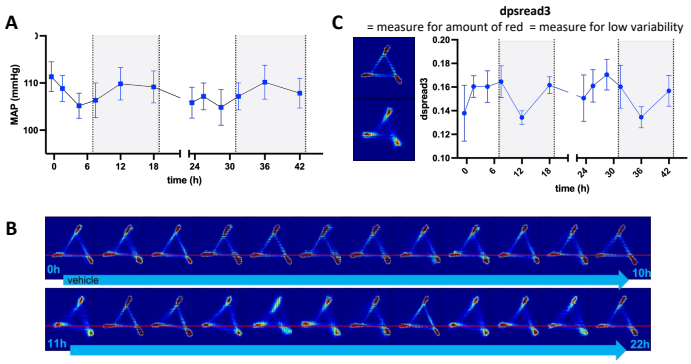

Figure 3: Diurnal haemodynamic changes.
A. MAP of vehicle animals, data presented as mean ± SEM (n=6). **B.** SPAR representations of every hour on day 2, generated from 1-minute recordings from an exemplar vehicle-treated animal. **C.** Example of subsequent quantitative analysis of variability. Dspread3 (measure for low variability) decreases during the dark phase of the day (grey areas), data presented as mean ± SEM (n=6).

2. Drug administration affects waveform morphology.

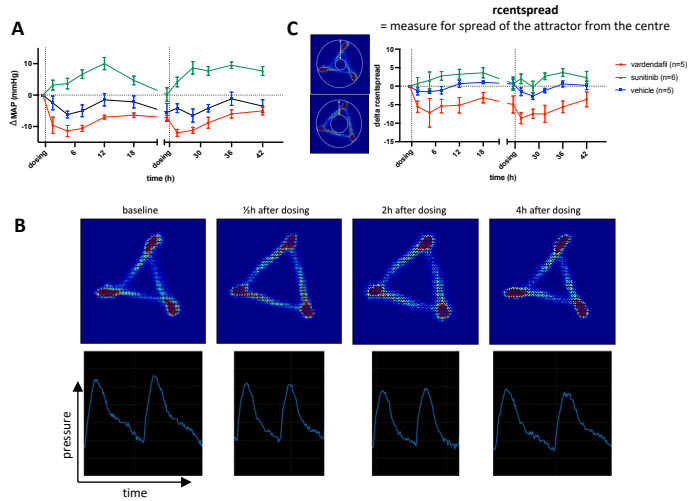

Figure 4: Effects of vardenafil and sunitinib on MAP and attractors.
A. Administration of vardenafil induced a decrease in MAP, sunitinib induced an increase in MAP. Data presented as mean ± SEM **B.** SPAR representations of selected time points, generated from 1-minute recordings from an exemplar vardenafil-treated animal, with corresponding waveforms. **C.** Example of subsequent quantitative analysis of morphology. Rcentspread decreases after vardenafil administration and increases after sunitinib administration.

Conclusion and future directions

- SPAR can detect subtle diurnal changes in variability in vehicle animals and changes in waveform morphology after drug administration.
- 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 possible 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

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