Cardiovascular and Cardiorespiratory Interactions – From Physiological Mechanisms to Clinical Applications
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Respiratory Instability in Heart Failure and Hypertension: A Cross-Species Mathematical Model and Direct Observation of Intermittency in Anaesthetized SHR Rats

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Introduction. Respiratory instability is a common problem in congestive heart failure (CHF), as well as in primary hypertension (HT). Although certain attempts to mathematical modelling have been made [1], still a substantial effort is required, as both of these therapeutic targets represent a huge population. For V4 countries it reaches 2 million CHF patients, and at least 17 million of HT patients. We are still missing good methods that would provide an early diagnosis of HT and early symptoms of decompensation in already diagnosed patients. A common handler for both these conditions is, quite surprisingly, the respiratory rhythm. The CHF patients are known to develop respiratory disorders such as Cheyne–Stokes respiration (CSR). Observations of instabilities in the HT patients are less frequent, however an increased chemoreflex sensitivity is reported as an important adverse biomarker [2]. A better understanding of the mechanisms underlying respiratory rhythm instability may contribute to the development of improved monitoring techniques and a more precise assessment of breathing

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pattern alterations accompanying the progression of primary hypertension in humans.

In this translational work we have started from an animal model: spontaneously hypertensive rats (SHR), that constitute a well-established model of primary hypertension, to obtain experimental data. Numerous pathophysiological alterations associated with the development of hypertension and its complications have been described in this strain. However, disturbances of respiratory rhythm are rarely investigated in this context.

Aim. To assess the occurrence of Cheyne–Stokes-like breathing in SHR rats and to propose a cross-species mathematical model describing this phenomenon, that can be applied to human subjects.

Methods. Male and female SHR and Wistar-Kyoto (WKY) rats were studied at the ages of 1, 3, 6, 12, and 16 months. Following anaesthesia with ketamine, animals were connected to a pressure sensor (Pressure Pad/Respiration Transducer; Biopac Systems, Inc.; Interlab), which recorded respiratory activity both during anaesthesia and after recovery. Inspiratory peaks were subsequently identified and visualized using carpet plot analysis [3], enabling the evaluation of signal dynamics and periodicity, as well as Argand diagrams.

Results. A long-short type respiratory rhythm instability was observed exclusively in the SHR group and only under anaesthesia.

An example recording is shown, where each horizontal strip corresponds to a segment of respiratory activity encoded by color. The underlying time series is displayed beneath each carpet plot. In the WKY group, occasional sighs are visible as horizontal lines. In contrast, SHR rats exhibited increased variability of the respiratory cycle, and from 3 months of age onward a short-long sequence became apparent, likely resulting from loss of stability through a bifurcation mechanism. Intermittency was also observed, characterized by irregular switching between stable breathing and the short-long oscillatory pattern.

The proposed cross-species mathematical model of CO_2 balance, based on [1], identifies increased chemoreceptor sensitivity (typical to HT) and prolonged circulation time (typical to CHF) as the principal causes of respiratory instability. These factors generate a delay between sensor and effector, thereby destabilizing the feedback control loop. Anaesthesia prolongs reflex-loop latency, unmasking the instability substrate. A similar mechanism may operate during sleep in humans, for example in heart failure or at high altitude. Rebreathing into a bag was found to regularize the respiratory rhythm, consistent with the predictions of the mathematical model.The model may be applied to both rats and humans, as the general mechanisms are common to all mammals, and intra-species differences may be introduced by suitable parametrization.

Conclusions. Respiratory instability was observed in anaesthetized SHR rats, and the data obtained were used to calibrate a cross-species

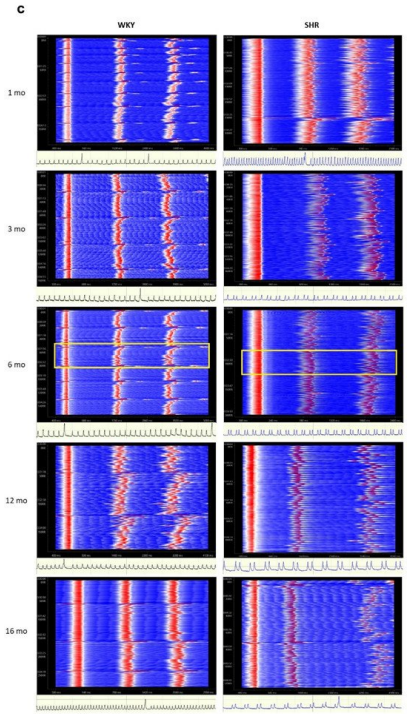


Figure 1: Representative respiratory recordings obtained during anesthesia, presented as carpet plots with corresponding segments of the raw respiratory signal shown below each carpet plot, illustrating strain-specific breathing patterns in WKY and SHR rats. Yellow boxes indicate example carpet plot segments corresponding to the raw traces.

mathematical model. These findings may contribute to the development of methods for monitoring breathing pattern alterations associated with cardiovascular diseases in humans. The cross-species mathematical model may be helpful for early symptoms of primary hypertension and cardiac decompensation in heart failure in V4 population.

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