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Effect of xanthine oxidase inhibition with allopurinol on autonomic regulation of the heart rhythm in normoxia and hypoxia

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Introduction: Xanthine oxidase (XO) which catalyses superoxide formation is among the major sources of reactive oxygen species (ROS) in cardiovascular system. Increased ROS level, particularly to occur during ischemia may negatively affect autonomic nervous system (ANS) control of the heart. Recent data have indicated that XO inhibitor, allopurinol (ALLO) prevents hypoxic injury of the heart.

Aim: We investigated how XO inhibition influences the ANS regulation of heart rhythm in baseline normobaric normoxia and hypobaric hypoxia in rats.

Methods: The study was approved by the Local Ethics Committee. Time-series of 1024-RR-intervals (RRi) were extracted from 4 kHz ECG recorded in conscious unrestrained Wistar rats (N=8, 300 g) in standard atmospheric conditions (normoxia), followed by 1-hour controlled hypobaric hypoxia (-400mmHg). The procedure was performed before and after ALLO administration (5 mg/kg) in two consecutive days. ANS regulation was assessed by heart rate variability (HRV) analysis (Kubios HRV Pro software) performed in time- and frequency-domains. Frequency ranges: 0.27 to 0.75 Hz (low frequency, LF) and 0.75 to 2.5 Hz (high frequency, HF) were selected for spectral powers. Nonlinear dynamics of HRV was also analysed through Sample, Shannon and Approximate entropies (SampEn, ShanEn, ApEn).

Results: Hypoxia resulted in a significant reduction of HR (from 334±9 to 288±11 BPM; p=0.003). The overall HRV, assessed by SDNN or total spectral power (TSP) did not significantly change but indexes of vagal activity were significantly increased: rMSSD (from 3.29±0.42 to 5.39±0.55ms2; p=0.02) and HF (from 3.52±1.12 to 6.37±1.02ms2; p=0.02). SampEn, ShanEn, ApEn remained unchanged. ALLO evoked a significant change of ShanEn (from 3.7±0.13 to 3.93±0.09 p=0.047) and ApEn (from 1.37±0.03 to 1.29±0.05; p=0.029) in normoxic conditions, while in following hypoxia all those changes returned to baseline. In normoxia, ALLO did not significantly changed the time-domain (SDNN, rMSSD) and spectral HRV parameters (LF, HF), but in hypoxia, ALLO evoked an increase of SDNN (from 6.08±1.05 to 11.36±2.14ms; p=0.013), TSP (from 29.94±6.57 to 138.34±36.75ms2;p=0.016) and LF (from 5.75±1.73 to 38.56±12.05ms2; p=0.02) together with parasympathetic drive (rMSSD from 5.39±0.55 to 9.33±1.59ms; p=0.019 and HF from 6.37±1.02 to 20.31±4.67ms2; p=0.014). Summary: The major finding is that XO inhibition influenced autonomic control upon the heart, especially during hypoxia when XO is supposed to increase. Changes in ShanEn and ApEn evoked by ALLO indicate the reduction of complexity of heart rate regulation. What is interesting complexity and predictability was changed without altering the sympato-vagal balance, as shown by linear parameters. In hypoxia allopurinol resulted in a significantly increased overall autonomic control including an increased vagal drive.
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