



## Changes in linear and nonlinear measures of RR and QT interval series after beer intake

Promene linearnih i nelinearnih mera nizova RR i QT intervala posle uzimanja piva

Mirjana M. Platiša\*, Vera Gal\*, Zorica Nestorović\*, Ida Leskošek-Čukalović†, Saša Despotović†, Mile Veljović†, Aleksandar Petrović†, Jovana Rajković‡, Vladimir Đokić‡, Radmila Novaković‡, Ljiljana Gojković-Bukarica‡

University of Belgrade, Faculty of Medicine, \*Institute of Biophysics, †Institute of Pharmacology, Clinical Pharmacology and Toxicology; Faculty of Agriculture, ‡Department of Food Technology and Biochemistry, Belgrade, Serbia

### Abstract

**Background/Aim.** There are only several studies on the acute effect of alcoholic drinks intake on heart rhythm and this phenomenon is still not well understood. We wanted to examine whether linear and nonlinear measures of RR interval and QT interval series could quantify the effect of beer in healthy subjects. **Methods.** Eighteen young volunteers drank 500 mL of beer (21 g of ethanol). Electrocardiogram (ECG) recordings were taken in supine position: 20 minutes before (relaxation) and 60 minutes after drink intake. The RR interval series and the QT interval series were extracted from ECG and we calculated short-term ( $\alpha_1$ ) and long-term ( $\alpha_2$ ) scaling exponents and sample entropy (SampEn) for both series; low frequency (LF) and high frequency (HF) spectral components from RR interval series and QT variability (QTV). Blood pressure was measured every 10 minutes. **Results.** It was shown that beer induced changes in variability and correlation properties of these series. Immediate effect of beer intake was detected as a transient increase in the QT variability, heart rate and blood pressure. Delayed effects of beer were shortening of the RR and QT intervals and reduction of the HF spectral component. Beer intake also increased short-term scaling exponent ( $\alpha_1$ ) of the RR time series and long-term scaling exponent ( $\alpha_2$ ) of the QT time series. **Conclusion.** Our results suggest that acute effects of beer are reduced parasympathetic control of the heart and changed dynamic complexity of the ventricular repolarization.

**Key words:** alcohol drinking; beer; heart rate; electrocardiography; adult.

### Apstrakt

**Uvod/Cilj.** Akutni efekat uzimanja alkoholnih pića na kardiovaskularne ritmove je fenomen koji još uvek nije dovoljno razjašnjen i u literaturi postoji svega nekoliko radova na tu temu. Cilj rada je bio da se ispita da li se linearnim i nelinearnim merama nizova RR i QT intervala može kvantifikovati akutni efekat male količine piva kod zdravih osoba. **Metode.** Osamnaest mladih zdravih muškaraca je pilo po 500 mL piva (21 g etanola). Elektrokardiogram (EKG) je beležen u ležećem položaju: 20 minuta pre (u relaksaciji) i 60 minuta neposredno posle uzimanja pića. Iz digitalizovanog zapisa EKG-a izdvojeni su nizovi RR i QT intervala. Iz oba niza smo izračunali kratkodometni ( $\alpha_1$ ) i dugo-dometni skalirajući eksponent ( $\alpha_2$ ), kao i entropiju uzorka (SampEn). Iz nizova RR intervala određene su spektralne komponente niskofrekventnih (LF) i visokofrekventnih (HF) opsega, a iz nizova QT intervala varijabilnost QT intervala (QTV). Krvni pritisak je bio meren svakih 10 minuta. **Rezultati.** Pokazali smo da pivo menja varijabilnost i korelacione osobine ovih nizova. Neposredni efekat uzimanja piva ogleda se u prolaznim povećanjima QT varijabilnosti, srčane frekvence i krvnog pritiska, a produženi u skraćanju dužine RR i QT intervala i smanjenju spektralne komponente HF. Uzimanje piva je takođe dovelo do porasta kratkodometnog skalirajućeg eksponenta ( $\alpha_1$ ) RR niza i dugodometnog skalirajućeg eksponenta ( $\alpha_2$ ) QT niza. **Zaključak.** Akutni efekat uzimanja piva je redukovana parasimpatička kontrola srca i izmenjena kompleksnost dinamike ventrikularne repolarizacije.

**Ključne reči:** alkohol, pijenje; pivo; srce, frekvencija; elektrokardiografija; odrasle osobe.

## Introduction

In last decade(s) studies appeared that revealed beneficial effect of low doses of alcoholic drink<sup>1, 2</sup>. However, it is still poorly understood in which way social drinking influences cardiovascular system. Spaak et al.<sup>3</sup> showed that acute effect of ethanol on heart rate variability (HRV) was dose-related; one standard alcoholic drink (155 mL) had no influence on heart rate (HR) and HRV measures but two drinks had. Nonlinear measures of HRV have gained recent interest as powerful methods for quantification of integrated cardiac control in various clinical settings<sup>4</sup>. Scaling exponents have been used as relatively simple scale-independent measures which quantified correlations in the output signals of complex biological systems<sup>5</sup>. In the RR interval fluctuations they quantified integrated control of the heart. A breakdown of scaling (changes in scaling exponents) indicated disturbances in the overall control of the heart<sup>6</sup>. The sample entropy (SampEn) is frequently used nonlinear measure which quantifies complexity/regularity of physiological time series<sup>7</sup>. Lorscheid et al.<sup>8</sup> reported that acute ingestion of alcohol in healthy population could induce prolongation of QTc interval (QT interval corrected for HR) and that the mechanism causing the QT prolongation originated from changes in the duration of ventricular repolarization.

Recently, we have reported the analysis of perturbation of HRV by a low dose of red wine using linear and nonlinear measures<sup>9</sup> which has not been done before<sup>9</sup>. We found that nonlinear properties of RR and QT interval series could be used to differentiate effect of wine and ethanol. Changes in the RR and QT interval series induced by a low dose of red wine were more detectable by methods that quantify the structure of the series than methods that quantify their variability.

The same analytical methodology was used in the present study as in the study on the effect of wine. The aim of the study was to assess acute effect of beer intake on linear and nonlinear measures of RR interval and QT interval series. We wanted to estimate whether these methods of time series analysis are sensitive to reveal small changes induced by a small quantity of beer intake.

## Methods

### *Study population*

The study group comprised eighteen men without medical history, aged  $26 \pm 4$  years with body mass index (BMI) =  $24 \pm 2$  kg/m<sup>2</sup>. They were apparently healthy, with no history or symptoms of heart disease, hypertension, or diabetes, with normal findings at clinical checks, and with no alcohol, no smoking or drug related problems. The study was approved by the Ethics Committee of the Faculty of Medicine, University of Belgrade, and each subject signed an informed consent to the study protocol.

### *Study protocol*

Subjects attended one session in the morning at 10.00 AM when after relaxation in supine position for 30 minutes they drunk 500 mL of beer (21 g of ethanol). The drink was taken

within 5 minutes time frame. The subjects were instructed to eat nothing on the study morning and to abstain from caffeine and alcohol since the afternoon of previous day. The beer was made in the Department of Food Technology and Biochemistry at the Faculty of Agriculture, University of Belgrade<sup>10</sup>.

### *Data acquisition and analysis*

Electrocardiogram (ECG) was recorded by two-channel ECG type recorder (Rozinn Electronics Inc, USA) in supine position, for 20 minutes before (relaxation) and 60 minutes after drink intake, but not during actual drinking. ECG recordings were digitized using commercial software Wavelab (Steinberg Media Technologies GmbH, Germany) on a personal computer via an analogue-to-digital converter, with a sampling frequency of 1,000 Hz. The R peaks and the RR intervals were determined by Origin (Microcal Software, Inc., Northampton, MA, USA) software. The QT intervals were determined by our own software based on tangent method estimation<sup>11</sup>. According to this method, the end of the T wave was defined as the point where the line from the peak of the T wave to the steepest point of the descending limb of the T wave intersected the isoelectric baseline. Mean RR, mean QT, HRV indices, and QT variability were calculated from non-overlapping segments of 256 points. The number of these 256 points segments was: 5 in period of relaxation and 15 after drink intake. Presented quantities are mean values calculated from all segments and averaged over all subjects. Power spectrum densities and spectral components were calculated as reported previously<sup>12</sup>. QT variability (QTV) was calculated as square of the QT standard deviation. Blood pressure BP and HR were recorded by automatic wrist blood pressure monitor (Geratherm Medical AG, Germany) at the end of relaxation, immediately after the drink intake, and then every 10 minutes until the end of the recordings.

### *Detrended fluctuation analysis (DFA)*

The DFA, modification of the random walk model analysis was used to quantify the fractal-like scaling properties of time series<sup>5</sup>. The root mean-square fluctuations of the integrated and linearly detrended data were calculated in observation windows of varying sizes and then plotted against the size of window on a log-log scale. The power-law behaviour was quantified as the slope of the linear regression line. The slopes, the short-term scaling exponent  $\alpha_1$  and long-term scaling exponent  $\alpha_2$ , were calculated over the window size  $n < 32$  and  $n > 32$  intervals. The values of scaling exponent indicate type of noise:  $\alpha \sim 0.5$  (uncorrelated white noise),  $\alpha \sim 1$  (correlated 1/f noise) and  $\alpha \sim 1.5$  (strongly correlated noise). The scaling exponents were calculated from the whole time series of RR and QT in relaxation and after the drink intake.

### *Sample entropy*

Sample entropy (SampEn) was computed according to the procedure published by Richman and Moorman<sup>7</sup>. The

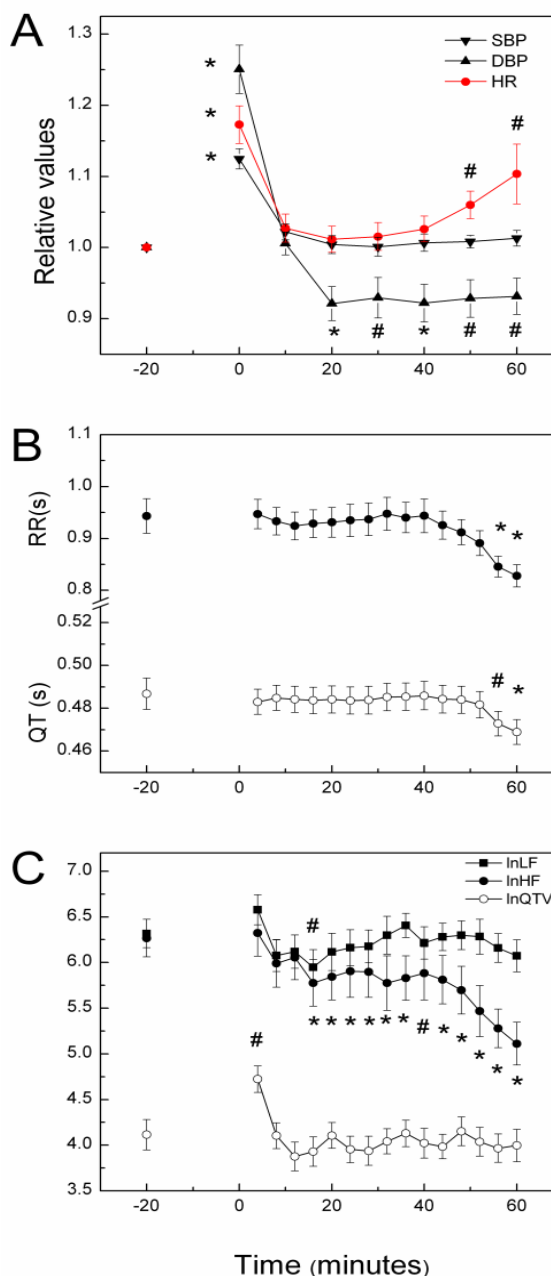
SampEn quantifies the irregularity of a time series and estimates the conditional probability that two sequences of  $m$  consecutive data points, which are similar to each other (within given tolerance  $r$ ), will remain similar when one consecutive point is included. The SampEn algorithm considers two parameters: tolerance level ( $r$ ) and pattern length ( $m$ ). According to the authors' recommendation, we chose a tolerance level of  $r = 0.15$  times standard deviation of the time series and  $m = 2$ . SampEn was also calculated from the whole time series of RR and QT in relaxation and after the drink intake.

*Statistics*

Data are presented as mean  $\pm$  standard error (SE). Due to their skewed distributions, spectral components of RR intervals and variability of the QT intervals were analyzed after natural logarithmic transformation. Scaling exponents and SampEn values were averaged over subjects for relaxation and over subjects and time after beer intake. Paired samples  $t$ -test was used for all comparisons. A  $p < 0.05$  was considered statistically significant. Analyses were performed using the SPSS (Statistical Package for the Social Sciences, Chicago, IL) software release 15.0.

**Results**

Immediately after the intake, beer induced simultaneous significant peaks of HR and systolic and diastolic blood pressures (SBP and DBP, respectively) (Figure 1A). However, after 10 minutes these quantities returned to initial values or below them. Compared to baseline values, beer induced decrease of DBP and increase of HR in the last 10 minutes of recordings. In addition, in the last 10 minutes there was a steady decrease in the QT intervals (Figure 1B). However, beer induced different behavior of the QT and RR variability (QTV and spectral components LF and HF). QTV had a transient peak after the intake, while HF was reduced significantly (Figure 1C). Beer intake increased short-term scaling exponent ( $\alpha_1$ ) of the RR time series and long-term scaling exponent ( $\alpha_2$ ) of the QT time series (Table 1). We examined above results by determining sample entropy as an independent measure, also derived from nonlinear dynamics. Beer intake decreased SampEn of both, the RR and QT time series compared with relaxation value but not significantly (Table 1).



**Fig. 1 – Time course of relative values: A) of heart rate (HR) and systolic and diastolic blood pressures (SBP and DBP); B) RR and QT; C) logarithm of spectral components of low frequency (LF) and high frequency (HF) and QT variability (QTV) in  $ms^2$ . Mean values  $\pm$  standard error (SE); \* $p < 0.01$ , # $p < 0.05$  post drink period vs relaxation (-20 minutes).**

**Nonlinear measures of RR and QT interval time series**

**Table 1**

Variable	RR		<i>p</i>	QT		<i>p</i>
	Relaxation	Beer		Relaxation	Beer	
$\alpha_1$	0.76 $\pm$ 0.04	0.85 $\pm$ 0.04	0.01	0.62 $\pm$ 0.02	0.60 $\pm$ 0.02	0.38
$\alpha_2$	0.84 $\pm$ 0.03	0.88 $\pm$ 0.03	0.19	0.88 $\pm$ 0.04	0.95 $\pm$ 0.03	0.04
SampEn	1.5 $\pm$ 0.1	1.4 $\pm$ 0.1	0.54	2.20 $\pm$ 0.08	2.13 $\pm$ 0.06	0.47

Values are expressed as mean  $\pm$  standard error (SE).

*p* – significance of statistical comparison of post drink period with relaxation.  $\alpha_1$  – short term scaling exponent;  $\alpha_2$  – long-term scaling exponent; SampEn – sample entropy.

## Discussion

In this study, the acute effect of beer was quantified for the first time by linear and nonlinear measures of RR and QT interval series. We found a similar shortening of RR and QT intervals between 50 and 60 minutes after beer intake. However, beer had different effect on variability and structure properties of these series.

Increase of HR immediately and about 50 minutes after drinking beer probably had origin in different physiological mechanisms. The first increase is well known as direct pressor effect due to direct acute vasoconstrictor effect of alcohol induced by shift in intracellular calcium<sup>13,14</sup>. We also observed this effect as increase in blood pressure. The latter one corresponds to reduced HF, i.e. reduction of parasympathetic control of the heart, which has been found after intake of ethanol and red wine<sup>3</sup>.

QT variability was significantly increased after beer intake and returned to initial values. Exact mechanisms which generate and modulate QTV are unknown. It is probably influenced by both, the intrinsic adaptation of the action potential duration and the autonomic nervous system activity. Cardiac norepinephrine spillover, the direct index of cardiac sympathetic activity, is related to QTV in patients with hypertension<sup>15</sup>, but not in patients with panic disorder and depression<sup>16</sup>, or in normal conditions<sup>17</sup>. Our results point out that the structure of the QT interval series was different from that of the RR series in relaxation and that beer intake had different effects on these two series. Values of scaling exponents were lower and sample entropy was higher for the QT series during resting state. Lewis and Short<sup>18</sup> suggested that the greater complexity in the modulation of the QT interval compared with the RR interval might be explained with regard to differential autonomic nervous system (ANS) modulation of the atrial and ventricular myocardium. SampEn of QT reflects the ANS modulation of both the atrial and ventricular myocardium<sup>18</sup>. We found that beer induced a significant increase in short-term scaling,  $\alpha_1$ , exponent of RR

series, and long-term scaling exponent,  $\alpha_2$ , of QT series. It seems that beer induced changes in short-term regulatory mechanisms of RR series and long-term regulatory mechanisms of more complex QT series (higher SampEn). Both changes, are probably caused by transient reduction of several control mechanisms of the heart or transient domination of vasomotor control.

Immediate effect of beer on the BP is a significant jump and return to the baseline values. However, in the interval 20-60 minutes after beer intake the DBP was significantly reduced. As diastolic pressure is determined mainly by cardiac output and peripheral vascular resistance, it might be that they both are influenced by beer.

The major limitation of our study is relatively low number of subjects introduced in the study. However, according to our knowledge this is the first study that investigated the interaction of beer intake and changes in linear and nonlinear measures of RR and QT interval series in humans. Having in mind that population which consume beer every day is very big, the investigation of proarrhythmic effect of this beverage is very important for cardiovascular science.

## Conclusion

The beer has immediate and delayed effect on the whole cardiovascular system which can be followed directly through changes of BP and HR. However, our study shows that delayed, fine and complex effect of beer could be quantified by properties of the RR and QT interval series. The results indicate reduction of parasympathetic control of the heart and changed dynamic of QT intervals.

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