THE EFFECT OF UNILATERAL NEPHRECTOMY
ON ARTERIAL BLOOD PRESSURE VARIABILITY
IN SPONTANEOUSLY HYPERTENSIVE RATS

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Abstract

The aim of the current study was to investigate the effects of unilateral nephrectomy (ULN) on fast oscillation of arterial blood pressure in spontaneously hypertensive rats (SHR). Experiments were carried out on conscious normotensive Wistar rats and SHR divided in groups with intact kidneys: W, $n = 10$; SHR, $n = 9$ and with unilateral nephrectomy: WN, $n = 10$; SHRN, $n = 10$. ULN was performed under general anaesthesia (Nembutal 35 mg/kg b.w. i.p.), eight days before the experiments. Blood pressure variability was investigated by means of spectral analysis of systolic (SAP) diastolic (DAP) and mean (MAP) arterial blood pressure, estimated in directly registered arterial blood pressure wave. In SAP, DAP and MAP spectrograms, derived by Lab View software equipment, the spectral power (P) in low (LF, 20–195 mHz), mid (MF, 195–605 mHz) and high frequency (HF, 605–3000 mHz) bands was calculated. P_{LF} in SAP spectrograms increased after ULN both in Wistar rats and SHR. ULN led to decrease of P_{MF} in SAP, DAP and MAP spectrograms only in SHR. The ULN provokes changes in blood pressure variability in different manner in the normotensive and the spontaneously hypertensive rats. In addition to humorally-mediated low-frequency oscillations, ULN in SHR also affected the spectral characteristics of the arterial pressure in which sympathetic nervous activity operates.

Key words: unilateral nephrectomy, SHR, blood pressure variability

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Introduction. Nephrectomy is a surgical manipulation in which the entire kidney or a part of it is removed following severe kidney trauma, malignant neoplasms, diseases that have caused complete disruption of the kidney with functional and morphological changes or organ-saving operations. Living kidney donors might be subjected to unilateral nephrectomy (UN) as well. The predominant role of the kidney in the long-term regulation of blood pressure through the mechanism of pressure diuresis and natriuresis is undoubtedly proven [1]. Apart from long-term regulation of arterial pressure, the kidney affects mechanisms associated with short-term regulation of the cardiovascular system. Central mechanisms associated with short-term blood pressure regulation can be affected by afferent renal nerves [2]. On the other hand, the efferent renal nerves play a significant role in the regulation of renin secretion. Activation of the renin-angiotensin system affects different levels of regulation in the cardiovascular system [3]. The investigation of fast mechanisms of regulation of the cardiovascular system by spectral analysis is a widely applied approach in research work [4,5]. The blood pressure variability has been identified as independent cardiovascular risk factor [6]. Three prominent peaks from arterial blood pressure spectrograms were established in different frequency bands, namely low, mid and high frequency components. The available experimental data indicated that low frequency blood pressure variations were related to many factors including renin-angiotensin system [7,8], catecholamines [9], myogenic vascular function [10]. Mid frequency variations in arterial blood pressure spectrograms have been associated mostly with sympathetic modulation of vascular tone [5,11]. The variation of arterial blood pressure in high frequency band has been suggested to involve variations in cardiac output of purely mechanical origin secondary to respiratory sinus arrhythmia [12].

Despite the view that nephrectomy has minimal adverse effects on overall health status, available data from studies show an increased risk of developing hypertension and cardiovascular events [13,14]. Particular attention to changes in blood pressure is attributed to patients with essential hypertension after nephrectomy. The available experimental data demonstrated the influence of nephrectomy on the arterial blood pressure and its circadian rhythm [15] but the effect of nephrectomy on the short-term mechanisms of regulation of the cardiovascular system evaluated by spectral analysis in normotensive as well as in hypertensive state has not been established. In the current study we investigate the influence of unilateral nephrectomy on the arterial blood pressure and its fast oscillations in spontaneously hypertensive rats which are a widely used genetic model of essential hypertension compared to normotensive rats.

Materials and methods. The experiments were carried out on conscious, male normotensive Wistar rats and spontaneously hypertensive rats SHR at age: 12–14 weeks. The animals were housed under standard conditions: constant temperature 22 °C; 12/12 h light/dark cycle; free access to standard rat chow and tap water. The experiments were conducted in accordance with guidelines for

the care and use of laboratory animals of the ethical commission at the Medical University – Sofia based on the Convention on Animal Protection. The rats were divided in the following experimental groups: Wistar rats (W, $n = 10$) and SHR (SHR, $n = 9$) with intact kidneys; Wistar rats (WN, $n = 10$) and SHR (SHRN, $n = 10$) with unilateral nephrectomy (ULN). The surgical manipulations: UNL as well as arterial catheter implantation were performed under general anaesthesia with pentobarbital sodium (Nembutal, Sigma) in dose 35 mg/kg b.w., applied intraperitoneally. Access to the right kidney was performed by abdominal incision. Close to the hilum renale, a ligature was placed covering the ureter, renal vein and artery, and then the kidney was removed. Unilaterally nephrectomized rats were allowed to recover for 7 days. The femoral artery was catheterized by polyethylene catheter, tunneled to the back of the neck and exteriorized. In order to avoid clotting the catheter was preliminarily flushed by 200 IU/ml heparin in sterile saline solution. The experiments were performed 24 h after catheterization on conscious freely moving rats. The arterial blood pressure wave was registered directly in femoral artery by using blood pressure transducer Gould Statham P23ID, connected to computerized data acquisition system Biopac MP150WS. After analogue to digital conversion by peak and rate detector of the AcqKnowledge 3.8 software the values of systolic (SAP), diastolic (DAP) and mean (MAP) arterial blood pressure for each heart beat in 5 min long intervals was determined. The obtained row data of investigated parameters was simultaneously resampled for 10 Hz. The SAP, DAP and MAP spectrograms were derived from 512 successive values overlapping by half, using custom written software in graphical programming environment Lab View 3.1.1, through Fast Fourier Transform (FFT) algorithm. In the spectrograms, the spectral power (P) in the low (LF), mid (MF) and high (HF) frequency band typical of rats (20–195; 195–605; 605–3000 mHz, respectively) were studied.

T a b l e 1

Systolic (SAP), diastolic (DAP) and mean (MAP) arterial blood pressure in normotensive Wistar rats (W) and spontaneously hypertensive rats (SHR) with intact kidneys as well as in Wistar rats (WN) and SHR (SHRN), 8 days after unilateral nephrectomy. $^{##}p < 0.01$ – statistically significant differences between normotensive Wistar rats and spontaneously hypertensive rats SHR. $^{*}p < 0.05$ – statistically significant differences after unilateral nephrectomy

	SAP mmHg	DAP mmHg	MAP mmHg
W	134.64 $\pm$ 1.14	82.80 $\pm$ 1.42	103.55 $\pm$ 1.44
SHR	179.04 $\pm$ 2.14 $^{##}$	106.10 $\pm$ 3.03 $^{##}$	132.95 $\pm$ 2.80 $^{##}$
WN	142.04 $\pm$ 4.32	75.52 $\pm$ 3.52	98.02 $\pm$ 4.112
SHRN	169.72 $\pm$ 2.14 *	105.38 $\pm$ 4.13	129.91 $\pm$ 3.89

All results were presented as mean $\pm$ SEM. Student's *t*-test was used for comparison between two means. Differences at a probability level of $p < 0.05$ were considered significant.

Results. The mean values of SAP, DAP and MAP were higher in SHR in comparison to normotensive Wistar rats, $p < 0.01$, (Table 1). In SHR we observed reduced spectral power in LF and MF spectral bands of SAP, DAP and MAP spectrograms in comparison to Wistar rats, (Fig. 1). Mean values of SAP, DAP and MAP in Wistar rats did not alter after ULN. The ULN in SHR led to a small but statistically significant decrease of SAP, $p < 0.05$, (Table 1).

The ULN in Wistar rats provoked an increase of P_{LF} only in SAP spectrograms from 2.42 ± 0.28 to 3.96 ± 0.66 mmHg², $p < 0.05$ (Fig. 1A). In SHR, the UNL caused also an increase of P_{LF} in SAP spectrograms from 1.68 ± 0.19 to 2.63 ± 0.40 , $p < 0.05$, but unlike in Wistar rats it further affected the P_{MF} in SAP, DAP and MAP spectrograms (Fig. 1B). P_{MF} in SAP DAP and MAP spec-

Fig. 1. Spectral power (P) distribution in low (LF), mid (MF) and high (HF) frequency band in spectrograms of systolic (SAP), diastolic (DAP) and mean (MAP) arterial blood pressure in normotensive Wistar rats (W) with intact kidneys and 8 days after unilateral nephrectomy (WN), panel A, as well as in spontaneously hypertensive rats (SHR) with intact kidneys and 8 days after unilateral nephrectomy (SHRN), panel B. ## $p < 0.01$ – statistically significant differences between normotensive Wistar rats and spontaneously hypertensive rats SHR. * $p < 0.05$ – statistically significant differences after unilateral nephrectomy

trograms decreased from 1.23 ± 0.21 ; 0.95 ± 0.13 and 1.40 ± 0.20 to 0.49 ± 0.09 ; 0.41 ± 0.07 and 0.42 ± 0.08 mmHg², respectively, $p < 0.01$.

Discussion. In the present study, after unilateral nephrectomy, we found an increase of low frequency oscillations P_{LF} in systolic arterial pressure spectrograms in both normotensive and spontaneously hypertensive rats. The available experimental data suggested modulation action of different humoral factors on low frequency variations of arterial blood pressure [7–10]. On the other hand, participation of several endocrine, biochemical and molecular mechanisms in compensation of renal function after renal mass reduction was established. Activation of renin-angiotensin system (RAS) is one of the most important earliest steps in the response to nephron loss [16,17]. It is possible that the established in the current study changes of low frequency spectral power in both normotensive rats and SHR are due to effect of unilateral nephrectomy on the activity of RAS system. In our previous studies, we did not detect differences in PRA between normotensive and spontaneously hypertensive rats [18]. However, we established the lower P_{LF} in SHR spectrograms of SAP, DAP and MAP in comparison to normotensive rats in control condition. The same levels of plasma renin activity as found in the normotensive and spontaneously hypertensive rats as well as lower P_{LF} in arterial blood pressure spectrograms in SHR can be explained by the established specificities of renin-angiotensin system in SHR. In SHR high blood pressure level is associated with a modest increase of baseline levels of Ang II and Ang II generating activity, in the absence of an increase of PRA [19]. We assume the possibility that the specificity of RAS in SHR reflects on the established lower P_{LF} in spectrograms of SAP, DAP and MAP in control condition. Interestingly, ULN does not affect P_{LF} in DAP and MAP spectrogram in both normotensive and spontaneously hypertensive rats. Activation of renin-angiotensin system after nephrectomy should mainly affect diastolic arterial pressure or its fluctuations. The major physiological function of Ang II is vascular smooth muscle cells contraction and maintaining vascular tone [20]. The increase of low frequency spectral power only in SAP spectrograms in Wistar rats as well as in SHR indicated involvement of other factors responsible for regulation mainly of cardiac function. We do not exclude the influence of RAS on the formation of fast fluctuations in blood pressure in SHR, as our previous results indicate a decrease in PRA in the SHP after nephrectomy [18], but the results obtained in the current study give us a reason to suppose the involvement of another factor in the regulation of the low frequency fluctuations of SAP. Unlike in Wistar rats in SHR, the sympathetic mediated spectral power P_{MF} in SAP, DAP and MAP spectrograms decreased after unilateral nephrectomy. It is well accepted that sympathetic nerve activity is elevated in SHR compared to normotensive rats, as well as that increased renal sympathetic nerve activity contributes to the development of hypertension [5]. The established decrease in control condition of P_{MF} in SHR spectrograms displays the limited ability to oscillations of blood pressure, as a result of increased sympathetic tone [5,12]. The

removal of one kidney is accompanied by interruption of part of afferent signal to central autonomic nuclei responsible for the regulation of arterial pressure. We assume that the decrease in the power of sympathetically mediated mid frequency fluctuations in blood pressure spectrograms in SHR is the result of the inability of control mechanisms to balance sympathetic outflow in the absence of afferent signals from the extracted kidney.

Conclusion. The unilateral nephrectomy affected the humoral as well as sympathetic mediated variations of arterial blood pressure in spontaneously hypertensive rats.

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