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Response of Systemic Hemodynamic Parameters to Changes in Blood Viscosity in Spontaneously Hypertensive Rats

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ABSTRACT

Aim. To study the response of systemic hemodynamic parameters to a decrease in blood viscosity in spontaneously hypertensive rats (SHR) compared to normotensive Wistar rats.

Materials and methods. Systemic hemodynamic parameters were recorded using the MP150 system (Biopac Systems, Inc., USA). Blood viscosity was measured using a Brookfield DV–II+Pro rotational viscometer (Brookfield Engineering Labs Inc., USA) at 36°C and a shear rate of 450 s^{-1}. Blood viscosity was reduced using isovolemic hemodilution.

Results. The decrease in the blood viscosity in Wistar rats was not accompanied by significant changes in the parameters of systemic hemodynamics. Only a slight decrease in the mean blood pressire was revealed, probably associated with the experimental conditions and the effect of isoflurane anesthesia. Unlike normotensive animals, in SHR isovolemic hemodilution led to a marked decrease in total peripheral vascular resistance, heart rate, blood pressure, and an increase in stroke volume. At the same time, in SHR rats, the hypotensive reaction of blood pressure in response to a decrease in blood viscosity was 3 times greater than in Wistar rats, which indicates impaired vascular tone regulation in response to a change in shear stress.

Conclusion. Thus, in normotensive animals, a decrease in blood viscosity as a result of isovolemic hemodilution does not cause changes in the main parameters of systemic hemodynamics. In contrast, in spontaneously hypertensive animals, total peripheral vascular resistance and blood pressure decrease alongside with blood viscosity, indicating impaired endothelium-dependent vascular tone regulation in response to changes in shear stress. The results obtained substantiate the use of drugs that reduce blood viscosity as a promising direction in the complex pharmacotherapy of hypertension and its complications.

Keywords: arterial hypertension, blood pressure, blood viscosity, total peripheral resistance, minute blood volume, stroke volume, normotensive Wistar rats, spontaneously hypertensive rats

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Реакция параметров системной гемодинамики на изменение вязкости крови у спонтанно гипертензивных крыс

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РЕЗЮМЕ

Цель: исследование реакции параметров системной гемодинамики в ответ на снижение вязкости крови у спонтанно гипертензивных крыс линии SHR по сравнению с нормотензивными крысами стока Вистар.

Материалы и методы. Параметры системной гемодинамики регистрировали с помощью системы MP150 (Biopac Systems, Inc., США). Вязкость крови измеряли на ротационном вискозиметре Brookfield DV–II+Pro (Brookfield Engineering Labs Inc., США) на скорости сдвига 450 $с^{-1}$. Снижение вязкости крови проводили с помощью изоволемической гемодилюции.

Результаты. Снижение вязкости крови у крыс стока Вистар не сопровождалось значимыми изменениями параметров системной гемодинамики, выявлено лишь небольшое снижение артериального давления, вероятно, связанное с условиями эксперимента и действием изофлуранового наркоза. В отличие от нормотензивных животных у крыс SHR изоволемическая гемодилюция приводила к выраженному снижению общего периферического сопротивления сосудов, частоты сердечных сокращений, артериального давления и увеличению ударного объема. При этом у крыс SHR гипотензивная реакция артериального давления в ответ на снижение вязкости крови была в 3 раза больше, чем у крыс стока Вистар, что свидетельствует о нарушении регуляции тонуса сосудов в ответ на изменение напряжения сдвига.

Заключение. Таким образом, у нормотензивных животных снижение вязкости крови в результате изоволемической гемодилюции не вызывает изменений основных параметров системной гемодинамики. Напротив, у спонтанно гипертензивных животных общее периферическое сопротивление сосудов и артериальное давление пассивно следуют за снижением вязкости крови, что свидетельствует о нарушении эндотелийзависимой регуляции тонуса сосудов в ответ на изменение сдвигового напряжения. Полученные результаты обосновывают применение препаратов, снижающих вязкость крови, в качестве перспективного направления комплексной фармакотерапии артериальной гипертензии и ее осложнений.

Ключевые слова: артериальная гипертензия, артериальное давление, вязкость крови, общее периферическое сопротивление, минутный объем крови, ударный объем, нормотензивные крысы стока Вистар, спонтанно гипертензивные крысы линии SHR

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

Arterial hypertension (AH) is a major risk factor for cardiovascular diseases [1]. Despite the availability of a number of highly effective and well-tolerated drug therapies for AH, blood pressure control parameters leave much to be desired [2]. This justifies the need to search for new therapeutic strategies for the treatment of patients with AH.

The hyperviscosity syndrome that develops in AH is one of the links in the pathogenesis of this disease [3, 4, 5]. Increased blood viscosity (BV) in AH significantly contributes to an increase in total peripheral resistance, impaired systemic hemodynamics, and microcirculation disorder [3, 4]. However, there are complex relationships between BV and hemodynamic parameters [4, 6]. BV has two opposite effects on total peripheral vascular resistance, which includes effects on hydrodynamic resistance and on vascular tone through mechanotransduction involving the vascular endothelium. On the one hand, an increase in BV in AH leads to an increase in total peripheral resistance [3]. On the other hand, BV determines the shear stress acting on the endothelium of the vascular wall, and with an increase in BV, the shear stress on the vascular endothelium increases, which can lead to a decrease in vascular tone [7].

Experimental studies have been conducted to investigate the relationship between BV and blood pressure [8, 9]. However, these studies contain contradictory data on changes in systemic hemodynamic parameters in response to changes in BV in normotensive animals. Similar studies have not been conducted on spontaneously hypertensive rats (SHR). At the same time, SHR are the most adequate model of essential arterial hypertension.

The aim was to study the reaction of systemic hemodynamic parameters in response to a decrease in blood pressure in SHR compared to normotensive Wistar rats.

MATERIALS AND METHODS

The experiments were conducted on 8 outbred male Wistar rats aged 13–14 weeks, obtained from the Department of Experimental Biological Models of Goldberg Research Institute of Pharmacology and Regenerative Medicine of Tomsk NRMC and 9 spontaneously hypertensive male rats aged 13–14 weeks, obtained from the vivarium of the Institute of Bioorganic Chemistry, Russian Academy of Sciences, Pushchino. In the vivarium of Goldberg Research Institute of Pharmacology and Regenerative Medicine, the animals were kept in a partial barrier system with the following environmental parameters: temperature of 20–24 ºC, relative humidity of 50±20%, air exchange rate of 12–15 room volumes per hour, and light conditions of 12:12 h. The animals were kept and cared for in accordance with the rules of the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (Directive 2010/63/EU). The research protocol (No. 207012023) was approved by the Committee for the Control of the Care and Use of Laboratory Animals of Goldberg Research Institute of Pharmacology and Regenerative Medicine. The experiments were conducted under isoflurane anesthesia. For isoflurane inhalation, an Ugo Basile 21050 anesthesia apparatus (Ugo Basile, Italy) was used. A decrease in BV was achieved using isovolemic hemodilution, which was carried out by equivolume replacement of 10% of the circulating blood volume with plasma obtained from a donor rat. The circulating blood volume was determined for each rat based on 7.5% of the body weight [10]. The isovolemic hemodilution procedure was performed in recipient rats by withdrawing blood from the jugular vein and simultaneously transfusing plasma from a donor rat into the femoral vein using an SN-50C6 infusion syringe pump at a rate of 0.17 ml/min. Blood was collected from donor rats through a catheter from the common carotid artery; heparin was used as an anticoagulant. The blood was centrifuged at 1600 g for 15 min to obtain plasma. The mean arterial pressure (MAP) was recorded in the common carotid artery of the animal. The stroke volume (SV) of the heart was determined using the tetrapolar rheography method. The SV of blood was calculated using the formula:

$$SV = \rho \cdot (L/Z_0)^2 \cdot dz/dt_{max} \cdot LVET$$

where ρ is the specific resistance of the blood; L is the distance between the outer measuring electrodes; Z_0 is the total impedance (resistance); dz/dt_{max} is the amplitude of the first derivative of the rheogram; LVET is left ventricular ejection time. Based on the SV, heart rate (HR) and animal weight, the values of the cardiac index (CI) and total peripheral resistance (TPR) were calculated. The parameters of systemic hemodynamics were recorded using a high-speed data acquisition and analysis system MP150 (Biopac Systems, Inc, USA) with a DA100C MAP recording unit with a TSD104A sensor and an EBI100C impedance recording unit

with the AcqKnowledge 4.2 for MP150 software. BV was assessed on a Brookfield DV–II+Pro rotational viscometer (Brookfield Engineering Labs Inc., USA) at a shear rate of 450 s^{-1} at a temperature of 36 °C.

Registration of systemic hemodynamic parameters and BV was performed before isovolemic hemodilution and 30 minutes after.

Statistical processing of the obtained results was performed using the Statistica 8.0 statistical software package. The data are presented as M±SE, where M is the mean value, SE is the standard error of the mean. The nonparametric Mann–Whitney *U*-test was used to assess the statistical significance of intergroup differences. The differences were considered statistically significant at $p < 0.05$.

RESULTS

The baseline of the BV in Wistar rats was 3.64±0.07 mPa·s (Fig. 1a). After isovolemic hemodilution, the BV in Wistar rats significantly decreased by 16% compared to the baseline. The HR, SV, CI, and TPR indices in Wistar rats after isovolemic hemodilution did not differ from the baseline (Fig. 1c, Fig. 1d, Fig. 1e, Fig. 1f). A slight decrease in MAP was revealed after isovolemic hemodilution in Wistar rats (by 7±2%) (Fig. 1b).

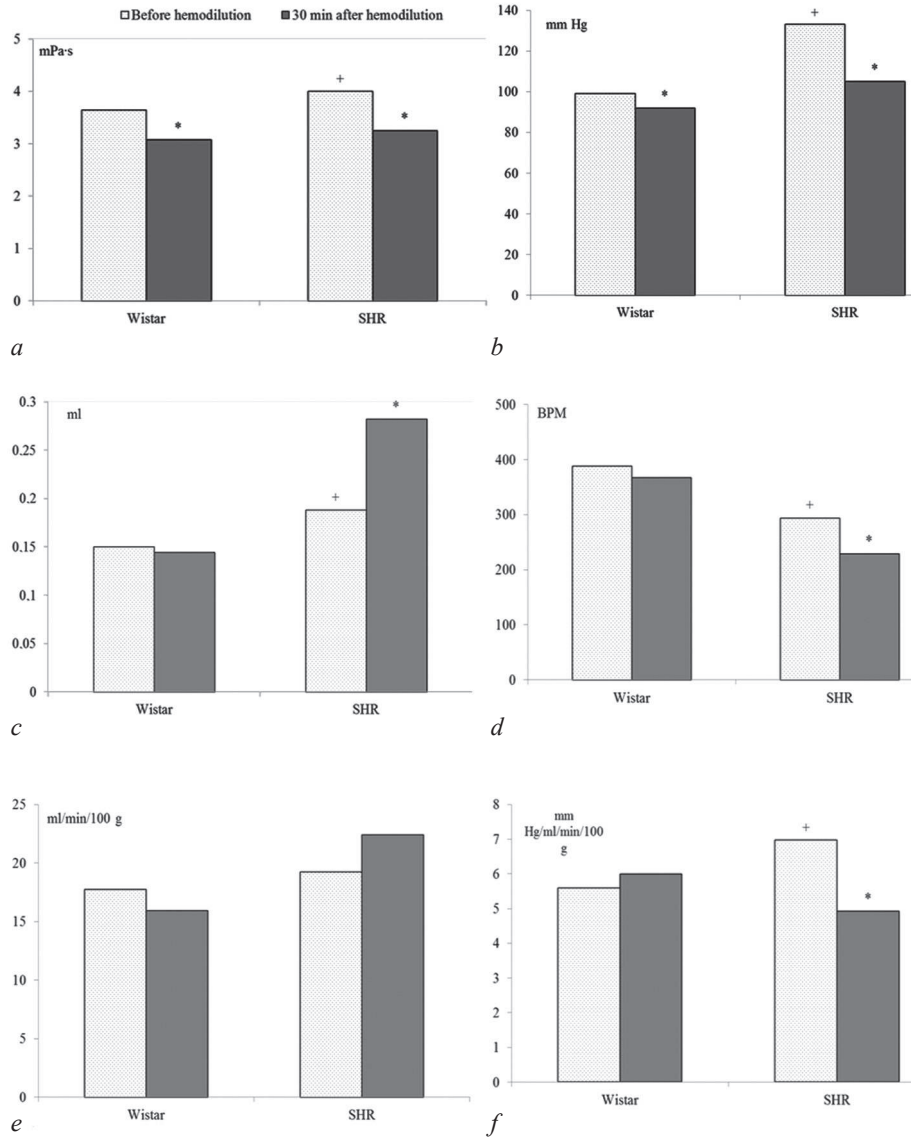

Fig. 1 Changes in blood viscosity (*a*), mean arterial pressure (*b*), stroke volume (*c*), heart rate (*d*), cardiac index (*e*) and total peripheral resistance (*f*) in normotensive Wistar rats and SHR after isovolemic hemodilution. $^{+}$ – statistically significant difference ($p < 0.05$) compared to values in Wistar rats; * – statistically significant difference ($p < 0.05$) compared to values before hemodilution.

The baseline of BV MAP, SV, and TPR in SHR was significantly higher, and HR was lower than in Wistar rats (Fig. 1a, Fig. 1b, Fig. 1c, Fig. 1d, Fig. 1f). Isovolemic hemodilution in SHR resulted in a 19% decrease in BV compared to the baseline. In SHR, isovolemic hemodilution resulted in a statistically significant decrease in HR (by 22%) and TPR (by 29%), while SV increased (by 50%). After isovolemic hemodilution, a statistically significant decrease in MAP by 21±2% was observed in SHR. Moreover, the hypotensive reaction of arterial pressure in response to a decrease in BV in SHR was 3 times greater than in Wistar rats.

DISCUSSION

To correct the syndrome of increased BV and microcirculation disorders in hypertension, the use of pharmacological agents that reduce BV seems to be a theoretically sound approach. However, the ambiguous effect of BV on TPR requires further study of this phenomenon.

Data on changes in hemodynamic parameters after a decrease in hematocrit and, consequently, in BV were obtained in normotensive animals. The experiments of Bonnin et al. demonstrated that in Wistar rats, with a change in hematocrit in the range of 35–46%, arterial pressure, CI, and blood flow in the renal artery remain stable [8]. A decrease in hematocrit in awake Syrian hamsters by 8.4% caused an increase in arterial pressure and CI, while vascular resistance remained stable [9]. In our study, a decrease in BV in normotensive animals did not lead to significant changes in the parameters of central hemodynamics. A slight decrease in arterial pressure after isovolemic hemodilution in Wistar rats was probably associated with the experimental conditions, in particular, the effect of isoflurane anesthesia [11]. The absence of changes in central hemodynamic parameters after a decrease in BV in Wistar rats is associated with the involvement of endothelium-dependent mechanotransduction in the regulation of vascular tone.

In SHR, unlike normotensive animals, isovolemic hemodilution resulted in significant changes in central hemodynamic parameters. A decrease in BV in SHR resulted in a decrease in TPR, indicating a disturbance in the regulation of vascular tone in response to a change in shear stress. A decrease in TPR and HR with a decrease in SV in SHR after isovolemic hemodilution could lead to an increase in SV. A decrease in MAP in SHR after hemodilution was more pronounced than in Wistar rats and is probably associated, in addition to the effect of anesthesia, with a decrease in TPR due to a decrease in BV. A previous study showed that in normotensive animals, before and after hemodilution, there are no correlations between BV and arterial pressure. Whereas in SHR, there is a positive correlation of medium strength between BV and arterial pressure, which persists after isovolemic hemodilution [12].

The involvement of endothelial cells in the regulation of vascular tone with changes in shear stress has been proven in a number of studies. Thus, inhibition of eNOS and NO production in normotensive animals resulted in a direct relationship between changes in BV and peripheral resistance [8, 13]. Violation of the relationship between blood flow velocity and tail artery diameter was demonstrated in normotensive Wistar rats with endothelium damaged by the CHAPS detergent, as well as in SHR [14]. Endothelial cells play a key role in the regulation of vascular tone due to their ability to respond to increased shear stress with increased NO production. In hypertension, elevated blood pressure adversely affects the vascular endothelium [15], which leads to a decrease in its vasodilating activity in response to humoral stimuli [15, 16, 17] with the development of endothelial dysfunction [18, 19]. In addition, patients with hypertension develop a syndrome of increased BV [3, 4, 5], and increased viscosity negatively affects endothelial function [20].

CONCLUSION

Thus, in normotensive animals, a decrease in BV as a result of isovolemic hemodilution does not cause significant changes in the parameters of central hemodynamics. Conversely, in spontaneously hypertensive animals, TPR and arterial pressure passively follow a decrease in BV, which indicates a violation of the regulation of vascular tone in response to a change in shear stress. The obtained results substantiate the use of drugs that reduce BV as a promising direction in the pharmacotherapy of AH and its complications.

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Author contribution

Sidekhmenova A.V., Anishchenko A.M., Plotnikov M.B., Aliev O.I. – conception and design. Sidekhmenova A.V., Anishchenko A.M., Ulyakhina O.A., Poleshchuk O.I. – conducting the experiments, discussion of the results. Sidekhmenova A.V., Anishchenko A.M., Plotnikov M.B., Aliev O.I., Ulyakhina O.A., Poleshchuk O.I. – analysis and interpretation of the data, drafting and editing of the manuscript.

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