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A NEW MINIMALLY INVASIVE METHOD FOR MEASURING BLOOD PRESSURE IN THE CAUDAL VENTRAL ARTERY IN RATS — EVALUATION

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Abstract. *Introduction.* Blood pressure is an important hemodynamic indicator characterizing the state of the cardiovascular system, which plays an important role in the experimental modeling of pathological conditions associated with impaired hemodynamics (for example, blood loss or hemorrhagic shock) in biological test systems. In modern practice, invasive and non-invasive blood pressure measurement methods are used in conducting research. However, if the objectives of the study include the registration of blood pressure in modeling pathological conditions associated with impaired hemodynamic processes, such as hemorrhagic shock, then with existing methods of measuring blood pressure, obtaining accurate, reliable data is often difficult. ***The aim of the study*** was to develop a minimally invasive, continuous method for recording blood pressure in the caudal artery in rats, both under anesthesia and without it, including without the use of anticoagulants; comparative analysis of various blood pressure measurement techniques in intact animals, in experimental modeling of hemorrhagic shock. ***Materials and methods.*** 110 male rats, Sprague Dawley, weighing 360±20 g were involved in the work. During the experiment, a minimally invasive method of blood pressure registration was developed, surgical modeling of hemorrhagic shock was performed, and a comparative analysis of various blood pressure measurement methods was carried out. ***The results of the study.*** It was found that the developed method can be considered accurate and low-traumatic, allowing fast, continuous blood pressure measurements in real time, both under general anesthesia and without it, without the use of anticoagulants. The accuracy of measurements does not depend on the nature, complexity of the experimental study and the general hemodynamic picture of the animal.

Keywords: blood pressure, caudal ventral artery, hemorrhagic shock, heparinized saline solution, biological test system

НОВЫЙ МАЛОИНВАЗИВНЫЙ МЕТОД ИЗМЕРЕНИЯ АРТЕРИАЛЬНОГО ДАВЛЕНИЯ В ХВОСТОВОЙ ВЕНТРАЛЬНОЙ АРТЕРИИ У КРЫС — ОЦЕНКА

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Резюме. ***Введение.*** Артериальное давление (АД) — важный гемодинамический показатель, характеризующий состояние сердечно-сосудистой системы, выполняющий важную роль при экспериментальном моделировании патологических состояний, связанных с нарушением гемодинамики (например, кровопотери или геморрагического шока) в биологических тест-системах. В современной практике при проведении исследований применяются инвазивные и неинвазивные методы измерения АД. Однако если в задачи исследования входит регистрация АД при моделировании патологических состояний, связанных с нарушением процессов гемодинамики, таких как геморрагический шок, то с существующими методами измерения АД получение точных, достоверных данных зачастую бывает затруднительно. ***Цель исследования*** — разработка малоинвазивного, непрерывного метода регистрации АД в хвостовой артерии у крыс, как под анестезией, так и без нее, в том числе без использования антикоагулянтов; сравнительный анализ различных методик измерения АД у интактных животных, при экспериментальном моделировании геморрагического шока. ***Материалы и методы.*** К работе привлечено 110 самцов крыс, Sprague Dawley, весом 360±20 г. В процессе эксперимента разработан малоинвазивный метод регистрации АД, выполнено хирургическое моделирование геморрагического шока, проведен сравнительный анализ различных методик измерения АД. ***Результаты исследования.*** Установлено, что разработанный метод можно считать точным и малотравматичным, позволяющим выполнять быстрые, непрерывные измерения АД в режиме реального времени, как под общей анестезией, так и без нее, без использования антикоагулянтов. Точность измерений не зависит от характера, сложности экспериментального исследования и общей гемодинамической картины животного.

Ключевые слова: артериальное давление, хвостовая вентральная артерия, геморрагический шок, гепаринизированный физиологический раствор, биологическая тест-система

INTRODUCTION

According to generally accepted methods, invasive measurement of arterial pressure (AP) in rats is carried out directly in isolated vessels (aorta, femoral or carotid arteries) or in the heart cavity using “liquid” and “non-liquid” methods [2, 3, 4].

The “liquid” method of recording blood pressure is based on the placement of a catheter or cannula into a “dedicated” vessel, connected via a liquid line filled with heparinized saline to a pressure recording sensor. This system allows for the most accurate measurement of arterial pressure, however, under certain conditions (catheter flushing), heparinized saline solution can enter the animal’s body, which in some cases is unacceptable or critical for experimental research [1–7].

To measure blood pressure using the “non-liquid” method, a micro pressure sensor is used. It consists of a sensitive sensor part connected to the main unit of the pressure measurement system, which allows for quick measurements without introducing anticoagulants into the animal’s body [2, 3].

When registering blood pressure using invasive methods, surgical isolation of a vessel is required.

In turn, among non-invasive methods of measuring blood pressure, the most widely used is the electroplethysmographic (cuff) method associated with the caudal artery (tail-cuff) of rats. This method is based on the same principle as the measurement of blood pressure in humans by the Riva–Rocci method [1-3]. Compared to invasive methods, the Riva–Rocci method does not require anesthesia for animals, including reuse, although it is less accurate. For example, in the hemorrhagic shock (HS) model, with exfusion of more than 40% of the circulating blood volume (CBV), blood pressure is not recorded by this method).

Thus, in preclinical practice, the task of finding and developing a minimally invasive method for recording arterial pressure in the body of rats remains relevant.

AIM

The aim of our study is to develop a minimally invasive, continuous method for recording blood pressure in the caudal artery in rats, both with and without anesthesia, without use of anticoagulants. To provide a comparative analysis of various methods for measuring blood pressure in intact animals (without anesthesia and with injection anesthesia), including experimental modelling of HS.

MATERIALS AND METHODS

Animals. 110 male rats, Sprague Dawley, weighing 360±20 g, SPF category, obtained from the Scientific and Production Enterprise “Nursery of Laboratory Animals” of the branch of the Institute of Bioorganic Chemistry of the Russian Academy of Sciences, Pushchino, were used as biological test systems in the experiment. The maintenance, care of animals and experimental modelling were carried out in accordance with international European bioethical standards, Russian ethical standards for the maintenance and handling of laboratory animals, and the norms and rules of the "Policy for Working with Animals of JSC GENERIUM".

Equipment. To record arterial pressure in rats, modules and sensors of the MP150WSW electrophysiological research apparatus (BIOPAC Systems Inc., USA) were used:

1) minimally invasive and non-liquid methods — MPMS100 unit and TSD175A micro pressure sensor;
2) cuff method — NIBP200A2 module and RXTCUF-SENSOR pressure sensor;
3) liquid method — DA100C module and TSD104A invasive pressure sensor.

Study design. The experiment consisted of four stages.

Stage I — The development of a minimally invasive method for recording blood pressure in the caudal artery in rats (n=10).

Stage II — A comparative analysis of various methods for recording blood pressure in rats without anesthesia: 1) minimally invasive method (n=10); 2) cuff method (n=10).

Stage III — A comparative analysis of various methods of recording blood pressure in rats with anesthesia (n=40): 1) minimally invasive method (n=10); 2) cuff method (n=10); 3) liquid method (n=10); 4) non-liquid method (n=10).

Stage IV — A comparative analysis of various methods of recording blood pressure in rats in the HS model (n=40): 1) minimally invasive method (n=10); 2) cuff method (n=10); 3) liquid method (n=10); 4) non-liquid method (n=10).

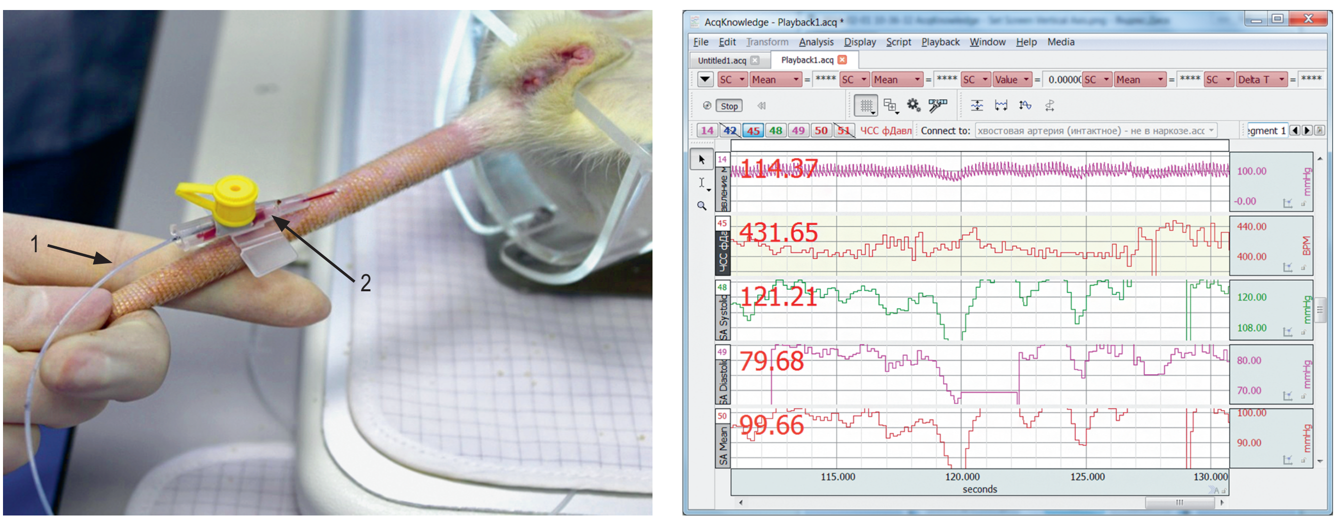
Stage I — the development of a minimally invasive method for recording blood pressure in the caudal artery of rats

The development of this method for recording arterial pressure in rats is based on the technique of catheterization of the caudal artery and placement of a micro pressure sensor in the vessel.

To insert a microsensor, an animal was placed in the spinal position on a heated operating panel (Mediheat V500DVsta (PecoServices LTD, UK)) and the caudal artery was visualized by gently massaging the tail. Next, the caudal artery was catheterized using a peripheral intravenous catheter (G24/26 intravenous catheter (HELMFLON®ptfe, Germany)). The catheter was inserted into the vessel at an acute angle (~10–15°); when inserted correctly, blood appeared in the catheter port. In this case, the artery was clamped proximal to the puncture site to stop bleeding. Then the needle was removed from the catheter, a pressure microsensor was inserted into the lumen of the catheter, after which the clamp was removed from the artery and blood pressure was recorded (Fig. 1).

Stage II — a comparative analysis of various methods for recording blood pressure in rats without anesthesia

Recording of blood pressure in the study without anesthesia was carried out in rats using both a minimally inva-



a/a b/б

Fig. 1. Minimally invasive method of recording blood pressure in the caudal artery in an intact animal without anesthesia: *a* — technique of placing a catheter and a pressure sensor into the caudal artery (1 — intravenous catheter; 2 — micro pressure sensor TSD175A); *b* — schedule of blood pressure registration (1 — systolic blood pressure, mmHg; 2 — diastolic blood pressure, mmHg; 3 — average blood pressure, mmHg)

Рис. 1. Малоинвазивный метод регистрации артериального давления (АД) в хвостовой артерии у интактного животного без анестезии: *а* — техника постановки катетера и микродатчика давления в хвостовую артерию (1 — внутривенный катетер; 2 — микродатчик давления TSD175A); *б* — график регистрации АД (1 — АД систолическое, мм рт.ст.; 2 — АД диастолическое, мм рт.ст.; 3 — АД среднее, мм рт.ст.)

sive method and a cuff method in the caudal artery area of the middle third of a tail.

Stage III — comparative analysis of various methods for recording blood pressure in rats under anesthesia.

Liquid, non-liquid, and minimally invasive methods were used to measure blood pressure in rats under anesthesia.

Injectable zoletil-xylazine anesthesia was used for general anesthesia when preparing an animal for work.

Femoral artery catheterization was performed when recording blood pressure using non-liquid and liquid methods.

Stage IV — comparative analysis of various methods for recording blood pressure in rats in the HS model

When recording blood pressure in rats in a HS model, the researchers performed experimental modelling of hemorrhagic shock using the «fixed volume» method without introducing heparinized saline into the body. To perform exfusion, arteriosection of the femoral artery was performed with subsequent controlled exfusion. The exfusion was 2.8–3.0% of the animal's weight, which corresponded to 40–50% of the total circulating blood volume. Ringer–Locke solution was used for reperfusion. Blood pressure was measured: 1) before exfusion; 2) during exfusion; 3) in the time interval from exfusion to reperfusion; 4) during reperfusion; 5) 10 minutes after reperfusion.

Minimally invasive, cuff, non-liquid and liquid methods were used to record blood pressure.

In the HS model, exfusion and measurement of blood pressure by non-liquid and liquid methods were performed in one femoral artery, since additional isolation of the second femoral artery resulted in trauma to the animal and significantly increased labor costs and time.

Thus, in these variants of blood pressure measurement, its monitoring was possible only during the periods: 1) during exfusion (in our case, at 5, 10, 15 and 20 minutes, which corresponded to 40, 70, 90 and 100% of the calculated exfusion volume); 2) in the time interval from exfusion to reperfusion; 3) during and after reperfusion.

Blood pressure recording using the minimally invasive and cuff method during the HS modeling was performed continuously.

Statistical processing. The data obtained during the work were checked for normal distribution. Statistical analysis included calculation of the mean value, standard deviation. To compare values, a parametric indicator was used — Student's t-test, since the sample corresponded to the law of normal distribution. Differences were considered statistically significant at $p < 0.05$. Statistical data processing was performed using IBM SPSS Statistics (23 v (IBM SPSS Statistics 23) (IBM Corp., USA)).

RESULTS AND DISCUSSION

During the experiment, a minimally invasive method for recording arterial pressure in the caudal artery of rats was developed, and a comparative analysis of blood pressure with existing methods for recording arterial pressure in intact animals without anesthesia, with anesthesia, and in the HS model was conducted.

Comparative analysis of various methods of recording blood pressure in rats with and without anesthesia. No statistically significant differences were found when recording blood pressure in animals with and without anesthesia (Table 1).

Comparative analysis of various methods of recording blood pressure in dynamics during experimental modelling of HS. The use of the cuff method in the HS model was difficult, since when exfoliating more than 40% of the calculated volume, the equipment did not record blood pressure.

The use of the non-liquid method allowed reliable and accurate measurement of BP throughout the experiment, but at certain periods: 1) during exfusion (in our case, at 5, 10, 15 and 20 minutes, which corresponded to 40, 70, 90 and 100% of the calculated exfusion volume); 2) in the time interval from exfusion to reperfusion; 3) during and after reperfusion. To conduct continuous recording of BP

Table 1

Indicators of average blood pressure in animals without anesthesia and under anesthesia

Таблица 1

Показатели среднего артериального давления у животных без анестезии и под анестезией

Методы регистрации артериального давления / Blood pressure registration methods	Среднее артериальное давление, мм рт.ст., x±ст. откл. / Average blood pressure, mmHg, x±standard deviation	
	без анестезии / without anesthesia	с анестезией / under anesthesia
Малоинвазивный метод / Minimally invasive method	92,0±7,1	76,5±2,7
Манжеточный метод / The cuff method	91,3±6,7	72,0±2,7
Жидкостный метод / The liquid method	–	76,3±2,0
Безжидкостный метод / The non-liquid method	–	81,5±2,2

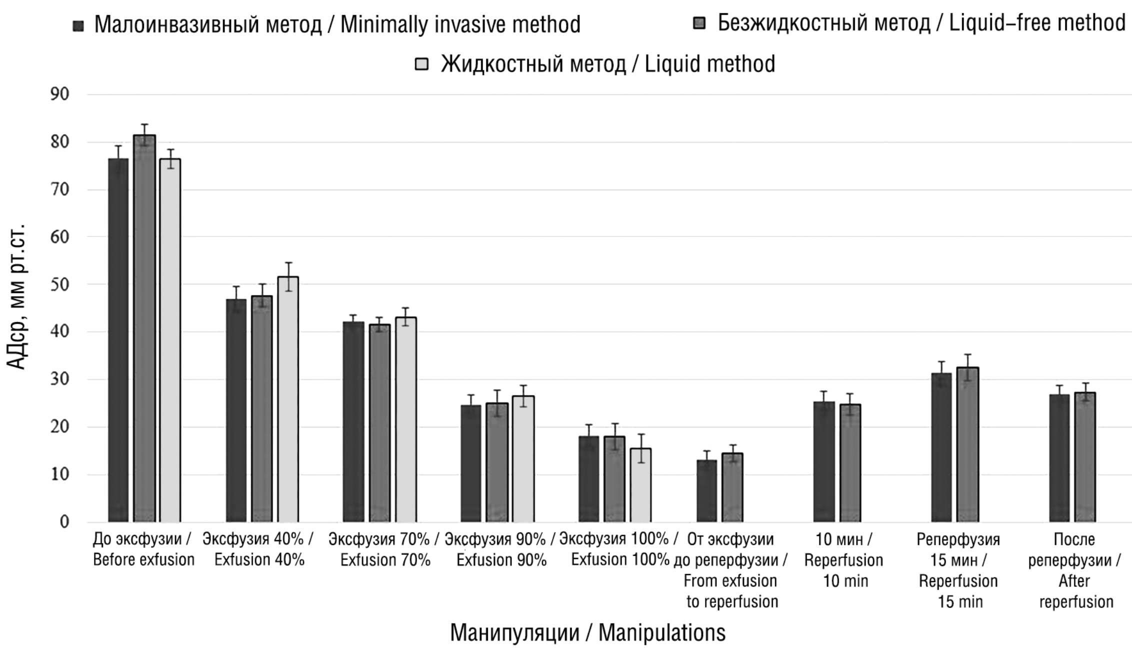


Fig. 2. Parameters of the mean pressure in rats in the CS model during registration by various method

Рис. 2. Параметры АДср у крыс в модели ГШ при регистрации различными методами

Table 2

Parameters of mean blood pressure in rats in a hemorrhagic shock model

Таблица 2

Параметры среднего артериального давления у крыс в модели геморрагического шока

Манипуляции / Manipulations	Время, мин / Time, min	%	АДср, мм рт.ст., x±ст. откл. Методы измерения АД / Average blood pressure, mmHg, x±standard deviation. Blood pressure measurement methods		
			малоинвазивный метод / minimally invasive method	жидкостный метод / the liquid method	безжидкостный метод / the non-liquid method
До эксфузии / Before exfusion	–	–	76,5±2,7	76,3±2,0	81,5±2,2
Эксфузия / Exfusion	5	40	46,9±2,6	51,6±2,9	47,7±2,4
	10	70	42,3±1,3	43,1±1,9	41,6±1,5
	15	90	24,7±2,1	26,5±2,2	25,1±2,8
	20	100	18,0±2,4	18,5±2,9	18,0±2,7
От эксфузии до реперфузии / From exfusion to reperfusion	30	–	13,2±1,7	–	14,5±1,7
Реперфузия / Reperfusion	10	–	25,3±2,3	–	24,8±2,2
	15		31,2±2,4	–	32,5±2,7
После реперфузии / After reperfusion	10	–	26,9±1,8	–	27,4±1,9

Примечание: % — процент от расчетного объема эксфузии.

Note: % is a percentage of the estimated volume of exfusion.

using this method, additional surgical intervention was required to isolate another femoral artery.

Recording of blood pressure using the liquid method was only possible during the exfusion period, since as the volume of exfusion increased and blood viscosity increased, thrombosis of the catheter occurred, which led to data distortion.

When recording BP using a minimally invasive method, continuous monitoring of BP parameters was performed during the experiment, and correct data were obtained throughout all stages of the work on the HS model.

The parameters of middle BP in rats in the HS model when recorded using various methods are shown in Figure 2 and Table 2.

CONCLUSION

Thus, the developed minimally invasive method of recording blood pressure, in comparison with generally accepted methods, has the following characteristics.

1. It is minimally invasive, continuous, does not require surgical intervention;
2. It allows measurements to be taken on animals, both with and without general anesthesia;
3. It allows recording blood pressure without the use of anticoagulants;
4. It allows real-time blood pressure measurements, regardless of the animal's overall hemodynamic picture.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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Experiments with animals were carried out in accordance with international rules (Directive 2010/63/EU of the European Parliament and of the Council of the European Union of September 22, 2010 on the protection of animals used for scientific purposes).

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

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

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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