FUNCTIONAL ACTIVITY OF THE VENOUS SYSTEM DURING HYPERTENSION DEVELOPMENT IN RATS

V. V. Barabanova and N. B. Petrova

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Rats of the Okamoto strain (spontaneously hypertensive rats, SHR), in the early stages of development of arterial hypertension, are characterized by a hyperkinetic type of hemodynamics, which changes in the stage of stable hypertension into hypokinetics [9, 12]. It is suggested that the increased venous return of blood to the right heart, followed by hyperfunction of its left portions, makes a definite contribution to this state of affairs [1, 2, 6]. In connection with the development of the mechanisms of formation of the different types of hemodynamics and to elucidate the role of the venous return in the development of hypertension, it is interesting to study functional activity of the venous system and of the right heart.

This paper describes the results of a study of functional activity of the venous system during formation of both hyperkinetic and hypokinetic types of hemodynamics in SHR.

EXPERIMENTAL METHOD

Experiments were carried out on fragments of the portal vein (PV) from the liver of SHR and of normotensive Wistar-Kyoto rats of different ages. PV is an extremely convenient and widely available object for the study of the veins and it objectively characterizes the state of the venous system and, in particular, the inferior vena cava and pulmonary artery [8]. The spontaneous contractile activity of PV is linked with the performance of its function of the reduced "portal" heart of the invertebrates [5]. Contractions of fragments of PV were recorded under near-isometric conditions by means of a 6MKhIS mechanotron in Krebs' solution at 34°C, pH 7.4. Simultaneously with the recording on N-3031-1 graph paper, the signal was recorded in the operative memory of a "Pravets-8" computer, and subsequently recorded on a magnetic disc. Programs of automated analysis of the electromyograms and statistical analysis were developed by R. N. Kiyanov. By computer analysis of the electromyograms it was possible to distinguish phasic and tonic (tetanic tone) components in spontaneous contractile activity of PV (Fig. 1). Contractile activity was assessed as the amplitude of phasic contractions, tetanic tone, and total amplitude (this last parameter was dependent on two independent values), the contribution of phasic and tonic components to contraction, and also the area beneath the curve, which was calculated per minute: S(F + T) and so on (Table 1). Altogether 15 parameters were analyzed. In addition, a method of processing the electromyograms whereby changes in the lumen of the vessels could be characterized at different levels of mechanical tension of its wall, was suggested by V. Ya. Izakov. A hyperbolic relationship (the force—velocity relationship according to A. Hill) exists between the velocity of shortening and mechanical tension. The same relationship is found between the degree of shortening and the load: the smaller the load the greater the degree of shortening. If a load Pn is suspended on the muscle, the degree of shortening will be determined by the difference between the isometric force Pu and Pn. Thus the degree of shortening $X \sim Pu - Pn$. Taking this into consideration, by recording contractions under isometric conditions it is possible to judge the degree of shortening. For this purpose the cross section at any level of force can be taken and the excess of this level of isometric force will determine the degree of shortening. To assess the ability of spontaneously contracting small muscle to

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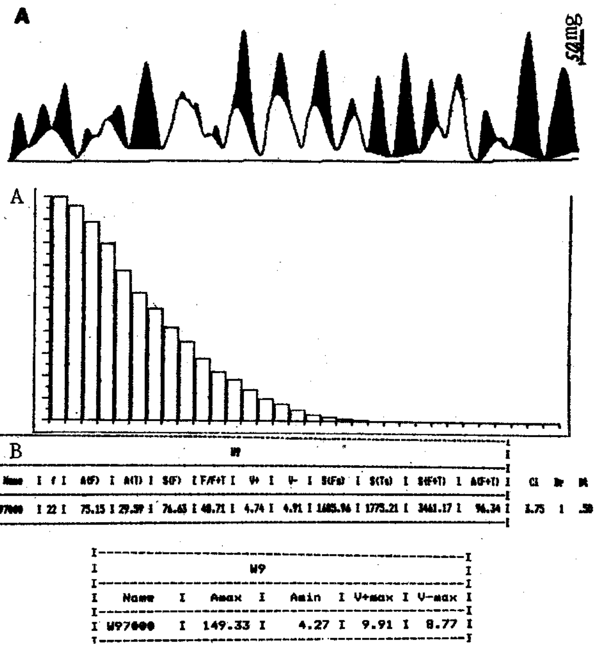

Fig. 1. Contractile activity of PV of WKY rat aged 4 weeks: a) original electromyogram (recording time 1 min, computer graphic). On right — calibration signal; b) hyperbolic relationship reflecting change in lumen of vessels at different levels of mechanical tension of the wall (A = F(t)Δt); c) absolute values (mean values during 1 min) of recorded parameters of phasic-tonic contractions of PV.

shorten, a level of section of force is chosen and the total amplitude of contraction at this level of force is calculated. It is also possible to calculate the total time of contraction above a given section of force. Finally, the relationship between force and amplitude in excess of Pn is constructed: $A = \int F(t)\Delta t$. A characteristic example is given in Fig. 1b. This dependence reflects the change in the lumen of the vessel at different levels of mechanical tension of its wall.

Vessels of animals of three age groups were studied: group 1) 4-6 weeks, group 2) 12-16 weeks, and group 3) 24-28 weeks old. For SHR, age group 1 corresponded to the prehypertensive period, group 2 to the period of early (labile) hypertension, and group 3 to the period of stable hypertension (I, II).

EXPERIMENTAL RESULTS

The basal tone of PV of SHR of all age groups was higher than in WKY rats: 0.41 ± 0.08 and 0.23 ± 0.07 mN respectively. In the SHR in the prehypertensive period, the highest basal tone was observed: 0.60 ± 0.07 mN.

Age differences in spontaneous contractile activity were most marked in SHR and WKY rats of age group 2. In this period of early hypertension in SHR an increase in the amplitude of phasic-tonic contractions of PV was observed by 60-80% compared with rats aged 4-6 weeks. The frequency of spontaneous contractile activity of PV of SHR did not change significantly, whereas in WKY rats in this age period the frequency of contractions rose significantly. During growth of the animals the direction of the changes in contractile activity of PV of SHR and WKY rats differed (Table 1). In WKY rats an increase in the spontaneous contractile activity of PV was recorded. By the 24th-28th week of age the parameters recorded reached values characteristic of the functional activity of PV in SHR aged 4-6 weeks: the total amplitude of contractions of PV of SHR aged 4-6 weeks was 1.13 ± 0.08 mN, whereas the amplitude of contractions of PV of WKY rats aged 24-28 weeks was 1.17 ± 0.21 mN; the same may also be said about the area of contraction (see Table 1) and the change in lumen of the vessels at different levels of mechanical tension of the wall (Fig. 2).

TABLE 1. Parameters of Contractile Activity of PV of Hypertensive and Normotensive Rats of Different Ages (M ± m)

Group of animals	f, per minute	A (F), mN	A (T), mN	A (F+T), mN	S (F+T)
1- (n=12)	23±1	0,84±0,05	0,31±0,03	1,13±0,08	32,2±3,8
WKY (n=21)	22±1	0,74±0,05	0,23±0,01*	0,93±0,05	29,4±2,0*
2-					
SHR (n=15)	24±1	1,39±0,07	0,55±0,06	1,82±0,10	65,7±4,4
WKY (n=15)	28±1	0,86±0,09*	0,29±0,05*	0,98±0,10*	36,8±4,3*
3-					
SHR (n=11)	25±2	0,73±0,07	0,21±0,04	0,91±0,09	28,0±4,1
WKY (n=6)	26±3	0,94±0,17	0,27±0,07	1,17±0,21	38,2±7,3

Legend. f) **Frequency** of spontaneous phasic contractions, A(F) mean amplitude of phasic contractions, A(T) mean amplitude of tetanic tone, A(F + T) total amplitude; S(F + T) total area during 1 min; asterisk indicates significance of differences ($p < 0.05$).

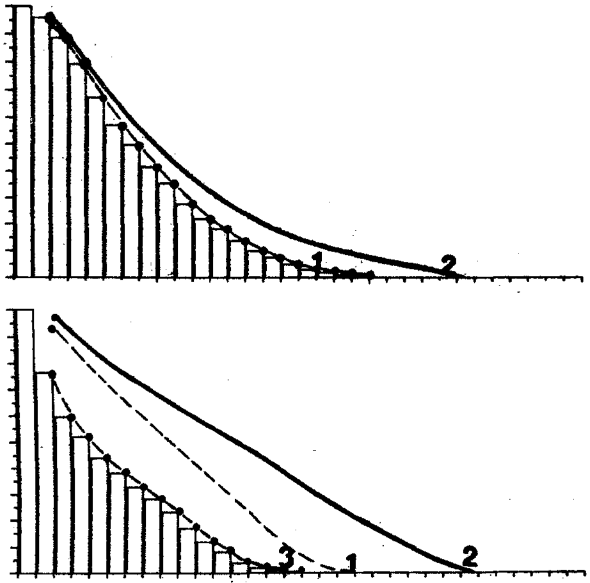

Fig. 2. Hyperbolic relationship reflecting change in lumen of vessels at different levels of mechanical tension of the wall: a) WKY rats: 4 weeks (1) and 24 weeks (2); b) SHR: 4 weeks (1), 12 weeks (2), and 28 weeks (3).

The functional activity of PV of SHR in the period between the ages of 4-6 weeks and 24-28 weeks changed twice, and the sharp increase in contractile activity observed toward the 12th-16th week of age (the period of early hypertension) was followed by a decrease in all the parameters of contraction (Table 1, Fig. 3) toward the 24th-28th weeks of age of the animals. Since increased functional activity of PV is an indicator of increased venous return, the venous return reaches maximal values in the early hypertensive period, when adrenoreactivity of PV is increased and the hyperkinetic type of hemodynamics is most marked [9, 12].

Age differences in functional activity of the venous system and, in particular, of PV, correlated with the patterns of distribution of electrical potentials on the body surface of SHR and WKY rats discovered by the writers previously by the method of electrocardiotopography.

The direction of movements of the positive and negative extrema in SHR rats aged 4-6 weeks and adult WKY rats was the same, indicating predominance of the right half, which is found in newborn infants and also in adults with right ventricular hypertrophy [4]. In our view, the features of the electric field of the heart (EFH) of SHR rats aged 4-6 weeks and of adult WKY rats are determined by the high functional activity of the venous system in these animals, leading to an

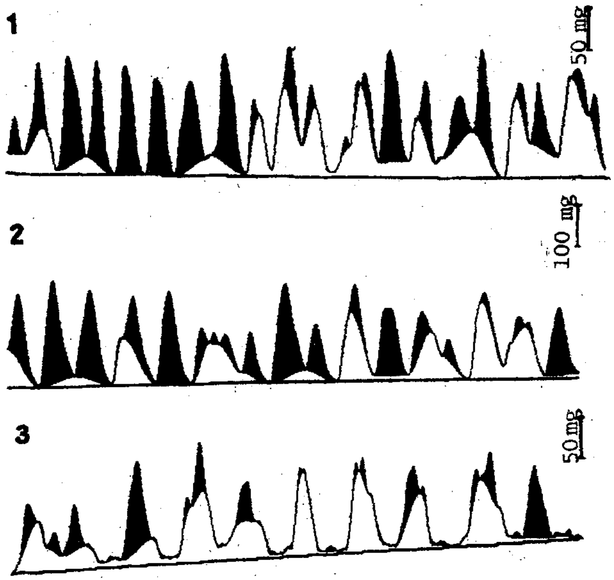

Fig. 3. Original electromyograms of PV of SHR aged 5, 12, and 28 weeks (1, 2, and 3 respectively). Electromyogram of PV of rat aged 12 weeks (2) recorded with degree of amplification reduced by half. Calibration signal on right.

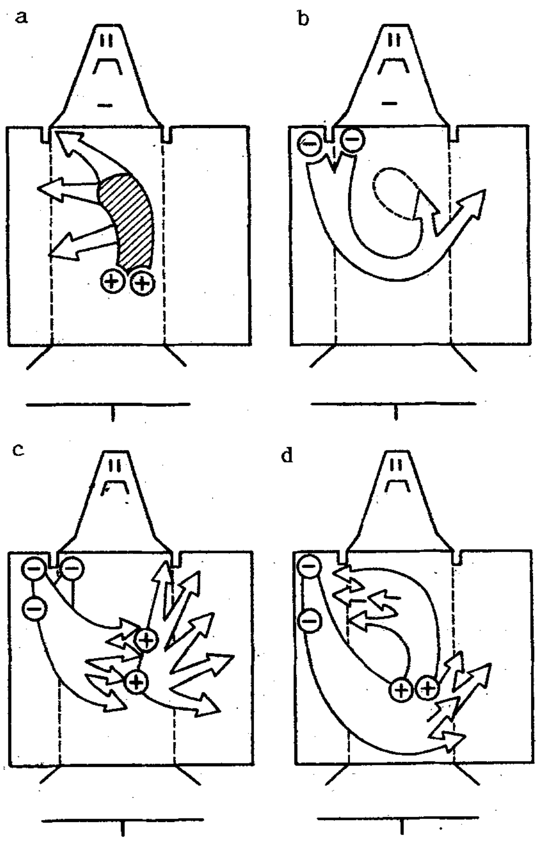

Fig. 4. Basic directions of movement of maximum and minimum of voltage on body surface of SHR and WKY rats: a) trajectory of movement of positive potentials (+) in SHR rats aged 4 weeks; b) trajectory of movement of negative potentials (—) in the same rats (n = 9); c) trajectory of movement of + — potentials in SHR rats aged 28 weeks (n = 7); d) trajectory of movement of + — potentials on body surface of WKY rats aged 28 weeks.

increased venous return. The increase in functional activity of PV in WKY rats observed between the ages of 4-6 weeks and 24-28 weeks leads to an increase in the venous return, hyperfunction of the right heart, and a characteristic distribution of potentials on the body surface of adult rats. By the age of 4-6 weeks (the prehypertensive period) SHR rats are characterized by the same high level of functional activity of the venous system as is achieved in WKY rats at the age of 24-28 weeks.

In the early hypertensive period, when the greatest functional activity of PV, a hyperkinetic type of hemodynamics, and a raised arterial blood pressure are recorded, EFH indicates the formation of left ventricular hypertrophy [3].

In the period of stable hypertension, when the trajectory of movement of the voltage peak on the body surface of SHR rats reflects hypertrophy of the left ventricle, functional activity of the venous system is depressed, and, consequently, the venous return is reduced.

In our view, the character of EFH, as we observed previously [3] during a cardiotopographic study of WKY and SHR rats of different ages, is due primarily to functional activity of the venous system, and, consequently, to an increase or decrease in the venous return.

Thus during the formation and development of hypertension in SHR rats a biphasic change takes place in functional activity of the venous system, accompanied by alternation of the types of hemodynamics and a switch from hyperkinetic to normo- or hypokinetic.

High functional activity of the venous system and the increased venous return in the pre hypertensive and early hypertensive periods lead to an increase in volume preloading of the right heart and to stretching of the atria or an increase of pressure [13]. The last of these phenomena triggers several mechanisms of autoregulation, giving rise to compensatory and adaptive reactions of the cardiovascular system. Hormonal control by hormone-like peptides, formed in cells of the right atrium and entering the blood stream in response to its stretching, namely the atrial natriuretic peptide [10, 13], calcitonin-gene-related peptide [7], and a hypothetical factor with mol. wt. of 8500 [11], is particularly interesting.

These observations suggest that functional activity of the venous system is a determining factor in the formation of types of the hemodynamics, and that the right atrium is an extremely important structure with respect to maintaining the adaptive reactions of the cardiovascular system, namely hypertension and hypertrophy.

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