ANALYSIS OF FACTORS DETERMINING CHANGES IN CARDIAC OUTPUT IN REPONSE TO CATECHOLAMINES

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Stress factors cause excitation of the sympathicoadrenal system, followed by elevation of the blood catechoalmine levels [9], and this is accompanied by a generalized reaction of the cardiovascular system and, in particular, by changes in the cardiac output (CO). The action of catechoalmines has been studied on CO [1, 2] or on individual parameters of the hemodynamics that may be involved in the formation of these changes in CO: the venous return (VR) to the heart [3, 5, 8, 11, 13], the heart rate [1, 13], and the coronary blood flow [4]. However, there are no data in the literature on the effect of pressure loading in the aorta, which may change significantly even in response to small doses of catecholamines [2], in the aorta. Most investigations into the role of VR have been undertaken on an open circulation [3, 5, 11, 13]. It was therefore decided to study factors determining changes in CO under closed circulation conditions, maintaining interaction between the heart and vessels of systemic circulation. It was also necessary to study the relative roles of the direct effect of catecholamines on the myocardium and their indirect action on the heat mediated through accompanying changes in the arterial and venous hemodynamics

The effect of changes arising in the systemic hemodynamics in response to intravascular injection of noradrenalin (NA) and adrenalin on the development of changes in CO was studied.

EXPERIMENTAL METHOD

Experiments were carrried out on 17 cats anesthetized with thiopental sodium (50 mg/mg). Vascular transducers of an RKÉ-2 electromagnetic flowmeter were used to measure CO (minus the coronary blood flow) in the ascending aorta, and the blood flow in the posterior and anterior venae cavae (diameters of the transducers were 7.6 and 3 mm respectively). VR was measured by summation of the blood flow along the anterior and posterior venae cavae, by means of an MN-7N analog computer. The mean arterial pressure (AP) was measured in the femoral artery by means of an electromanometer. Drugs were injected into the femoral vein: NA in a dose of 20 μg, adrenalin 10 μg, atropine 0.2 mg/kg body weight, and the β-blocker propranolol 1 mg/kg.

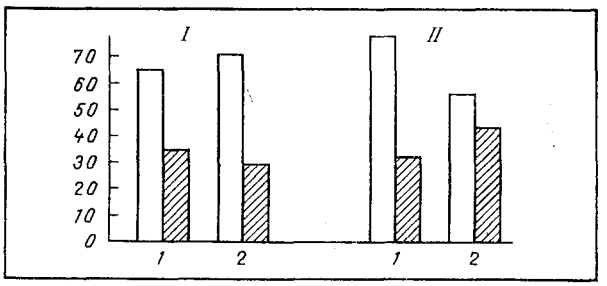

Fig. 1. Correlation between changes in CO in response to injection of catecholamines (in % of total number of observations). 1) Before injection of atropine and propranolol, 2) after injection of atropine and propranolol. Unshaded columns — increase or increase followed by decrease, shaded columns — in CO. I) NA, II) adrenalin.

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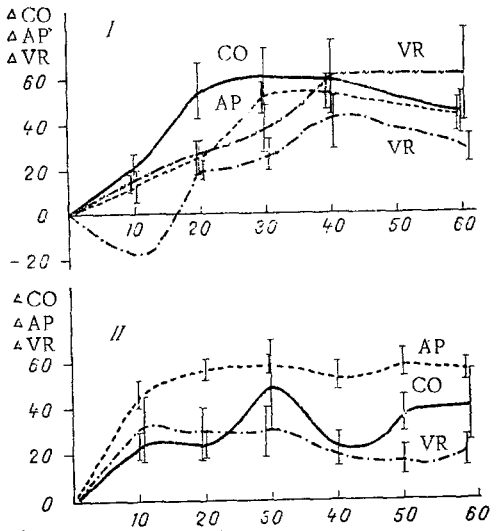

Fig. 2. Relations between AP and VR in group of patients with an increase in CO in response to injection of NA. Ordinate, changes in AP (in mm Hg), CO (in ml/min), and VR (in ml/min); abscissa, time after beginning of injection of NA. I) Before, II) after injection of atropine and propranolol.

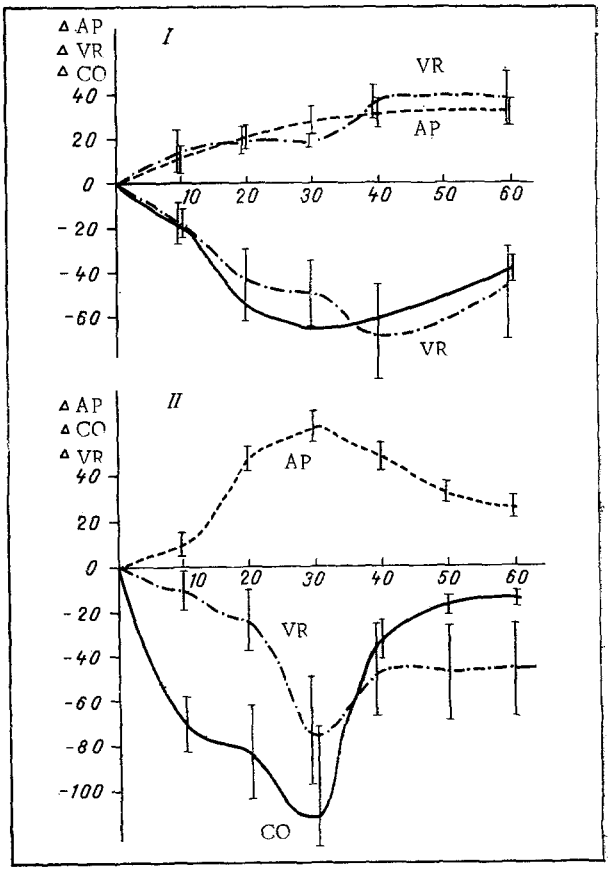

Fig. 3. Interrelations between AP and VR in group of cases with reduction of CO in response to injection of NA. Legend as to Fig. 2.

The dose of adrenalin (10 μg) was close to the physiological level found in the blood of cats in response to stimulation of the splanchnic nerve [12].

EXPERIMENTAL RESULTS

Intravenous injection of NA in a dose of 20 μg caused an increase in AP (on average by 49 ± 8 mm Hg) and an increase in CO or an increase followed by a decrease in 65% of tests, and a decrease in CO in 35% of tests (Fig. 1). In the group of cases in which CO increased

TABLE 1. Changes in CO (in ml/min), AP (in mm Hg), and VR (in ml/min) in Response to Injection of Catecholamines

Catecholamine	Intact animals			After blockade of β-adrenoreceptors and muscarinic acetylcholine receptors of the heart		
	CO	AP	VR	CO	AP	VR
Noradrenalin	+78±12	+57±7	+87±25 —17±6 +43±14	+50±20	+59±4	+32±15
	+31±14 —59±9	+56±11	—96±31 —64±20 +61±9 +27 13 —150 63	+26±9 —62±18* +22±6	+40±6	+35±6 —24±9
	—73±12	+36±6	+34±7 —67±21 +18±9 —84±40	—116±40	+62±6	—73±24
Adrenalin	+99±22	+34±3	+86±18 —39±7	+43±13	+34±6	+92±18
	+20±3 —83±6* +41±9	+34±6	+20±5 —28±12 —42±10 +54±9 +35±9	+16±1 —12±4* +64±8	+52±2	+24±2 —35±9
	—43+23 +61±19	+18±7	—24±15 +39±7	—132±28 +40±32	+64±5	—98±8
	—64±14	+39±12	+38±9 —21±8	—154±30	+59±11	—69±7

Legend. 1) Numerator — first phase of response; denominator — second phase of response. 2) Asterisk denotes triphasic reactions.

or increased and then decreased, the increase occurred during the first 5 sec from the beginning of injection of the drug. The increase in AP in these groups of experiments, incidentally, was 57 ± 7 mm Hg, whereas in the group of tests in which CO decreased, AP increased by 35 ± 6 mm Hg ($P < 0.01$; Figs. 2, I and 3, I). In addition, analysis of dependence of the changes in CO on the changes in AP in two groups of tests with an increase in AP (from 10 to 30 mm Hg and above 50 mm Hg) showed that an increase in CO appeared leass frequently (in 50% of tests) in association with a weaker response of AP than with a stronger response, when CO was increased in 74% of cases. Data on changes in CO, AP, and VR in response to injection of NA are given in Table 1. The appearance of positive changes in CO and the high frequency of these manifestations during changes in AP of over 50 mm Hg may perhaps be due to the positive coronary inotropic effect caused by the rise of pressure in the aorta [5] or by an increase in the coronary blood flow under the influence of NA [4].

The most important problem is that of correlation between the direct inotropic action of NA on the myocardium and the effect of the intra-aortic pressure and venous return, modified as a result of the action of NA on the blood vessels, on CO. We know that the circulation time from the femoral vein to the carotid artery (and, consequently, to the coronary system) in cats in 3-5 sec [14], in agreement with the time of the positive changes in CO (5 sec). Experiments with pharmacologic denervation of the heart (injection of atropine and propranolol), aimed at blocking the direct action of NA on the heart, showed the frequency of cases of an increase or increase followed by a decrease in CO showed no significant change, at 71% of the total number of tests (Fig. 1). The beginning of the positive changes in CO took place within the same time interval as before blockade (Fig. 2, II). As will be clear from Table 1, no significant differences were found between the changes in CO before and during blockade. Consequently, the direction action of NA on the heart was not signifciant in these experiments, and a change in the hemodynamics in the systemic circulation and, in particular, the intra-aortic pressure, had the main effect. During blockade the increase in AP in response to injection of NA was 59 ± 4 mm Hg, i.e., within the same pressure range as that in which positive shifts of CO appeared more often before blockade.

In each group of changes in CO the changes in VR differed in value (Figs. 2 qnd 3; Table 1). Both in the group with an increase in CO and in the group with a decrease, an increase in VR was observed more often (in 75% of tests). The change in VR was greater in magnitude if it coincided in direction with the changes in CO. The increase in CO may perhaps have been due to an increase in VR as the result of the direct constrictor action of NA on the veins, leading to expression of blood from them [5, 10], or as a result of a decrease in the venous resistance [13].

Injection of adrenalin caused changes of different magnitude in CO (Fig. 1). Comparison of changes in CO in cases when the response of AP was between 10 and 30 mm Hg and over 50 mm Hg revealed no significnat differences. In both cases either an increase in CO appeared most frequently, or an increase, followed by a decrease, followed by a second increase. The absence of dependence of changes in CO on the value of AP in response to injection of adrenalin, which was observed to NA, was probably due to differences in the effects of adrenalin and NA on the coronary vessels [15], which masked manifestation of the positive inotropic effects of an increase in AP.

To study the role of the direct action of adrenalin in the character of changes in CO, these changes were studied after pharmacologic denervation of the heart. Under these conditions the number of negative changes in CO increased and the number of positive changes decreased (Fig. 1), but the degree of increase and the degree of decrease in CO differed significantly ($0.5 > P > 0.01$) in the presence of the blockade from the original data (Table 1). Unlike NA, adrenalin thus has a direct action on myocardial contractility.

Changes in VR under the influence of adrenalin also differed in magnitude. In the groups with an increase in CO, an increase in VR was observed in 53% of tests and a decrease in only 15%, whereas in 31% of tests VR was unchanged. In the group with a decrease in CO, either a decrease in VR or a decrease followed by an increase was observed in 56% of tests, and an increase in VR in 44%. Consequently, changes in VR often are identical in direction with changes in CO, so that the cardiac effect can be explained by a Frank–Starling mechanism.

In response to injection of catecholamines under closed circulation conditions, the main role is therefore played by changes in VR, and also by the effect of pressure changes in the aorta (following injection of NA) and by direct action of the myocardium (after injection of adrenalin). The dissimilar changes in CO in response to injection of catecholamines can be attributed to differences in their action on the coronary vessels, which in turn give rise to positive and negative coronary inotropic effects [6]. The absence of a marked direct action of NA on CO can be explained on the grounds that these experiments were conducted on an intact animal, whereas the main evidence for the effect of NA on the myocardium has been obtained on the isolated heart [2, 7].

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