Peculiarities of Compensatory Reactions of Hepatic Vessels during Experimental Coarctation of Aorta

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Morphometric and histological methods were employed to study structural changes of hepatic vessels in dogs with compensated coarctation. Simulation of this conditions in animals decreased vascular tone in the inflow and outflow beds of hepatic blood supply and led to the development of atrophy in the media. At the same time, the number of vessels with intimal musculature, elastic muscle sphincters, and polypoid cushions increased in the hepatic arterial bed, while large outflow veins demonstrated thinning of the muscle cushions. All these alterations play an important role in compensation of the disturbed hemodynamics.

Key Words: *aortic coarctation; hepatic vessels; morphology; compensation*

Isolated coarctation of aorta belongs to severe non-cyanotic congenital failures [3,9-11]. This pathology is accompanied by the development of large hyper- or hypotensive areas in the greater circulation [6]. Without surgical intervention, the average lifespan of these patients is about 40 years [4]. The prognosis largely depends on the degree of aortic coarctation and compensatory potencies of the heart. However, not minor role in the development of adaptation to disturbed hemodynamics is given to the liver, which is located in the region of reduced arterial pressure and is actively involved in the control of blood transport [5,7,8].

We found no published data on morphological substrates of circulatory compensation in this organ during aortic coarctation.

Our aim was to reveal the character of morphological alterations in hepatic vascular bed during experimental compensated aortic coarctation.

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MATERIALS AND METHODS

The hemodynamic model of aortic coarctation was reproduced in 16 dog pups according to original method [7,8]. The animals were observed for 6 months to the age of 2 years; thereafter they were sacrificed under ether narcosis. The experiments complied to the "Ethical Guidelines for Investigations with Experimental Animals". The control dogs (n=10) were age-matched. The hepatic specimens were cut in three planes, fixed in 10% neutral formalin, and embedded into paraffin. The histological sections were stained with hematoxylin and eosin, impregnated with silver according to the method Foot, and then they were stained by the methods of Masson, Hart, and Brachet. In some cases, serial sections were prepared. Structural alterations in the liver were examined in the inflow vascular bed (a branch of hepatic artery and portal vein) and in the outflow bed (a branch of hepatic vein). To this end, we used a previously developed method of complex morphometry of hepatic vascular bed [7]. In this approach, all hepatic arteries are subdivided into 4 groups: large (external diametere≥125 μ), middle (124-51 μ), small (50-21 μ), and the arterioles (≤20 μ). The portal veins were classified according to the group of accompanying arteries: veins at the level of large arteries (≥190 μ), veins

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at the level of middle arteries (189-110 μ), veins at the level of small arteries (109-51 μ), and venules (≤50 μ). The hepatic veins were also subdivided into four categories: large, middle, and small veins, and venules. This subdivision is based on the diameter of corresponding portal veins. Morphometry of all vessels found in cross-section of the specimen was carried out under an MOB-1-15^{x} a screw-micrometer eyepiece. The thickness of the tunica media in these vessels was determined. The number of myocytes was counted in the media of small arteries. The size of these cells was assessed by the size of their nuclei [3]. The area and volume of nuclei in leiomyocytes was calculated according to the formulas $S=0.785cd$ and $V=0.523cd^2$, where c and d are longitudinal and transverse axes of a nucleus, respectively. In addition, the number of arteries containing intimal musculature, muscle-elastic sphincters, and polypoid cushions were counted. Thickness of muscle cushions was measured at the level of the collecting hepatic veins. The data were analyzed statistically using Statistica software. Significance was assessed by Student's *t* test at $p<0.05$.

RESULTS

During compensated coarctation of the aorta blood supply to the liver and arterial tone decreased, which was manifested by widening of arteries, reduced rugosity and disintegration of internal elastic lamina (Fig. 1, *a*, *b*). Morphometry revealed that thickness of the tunica media in large and middle arteries decreased 1.4-fold, while in small arteries and in arterioles it decreased by 1.5 times (Table 1). In the wall of small arteries, the longitudinal axes of myocyte nuclei decreased by 1.4 times, while their transverse axis, area, and volume decreased by 1.5, 2.1, and 3.2 times, respectively, in comparison with the control data (Table 2). The number of these cells decreased by 1.9 times. The hepatic sinusoids were somewhat widened, but little differed from the control. The number of arterial vessels with oblique-longitudinal musculature, muscular elastic sphincters, and polypoid cushions increased. The oblique-longitudinal musculature in the intima was presented as individual cells or fascicles (Fig. 1, *c*) and as layers of myocytes that encompassed the entire perimeter of vascular lumen. In these sites, the internal elastic membrane was split into two plates and formed a duplicate structure. The number of vessels with oblique-longitudinal musculature at the level of arterioles and middle and large arteries increased 3-fold and at the level of small arteries by 18 times. The muscular elastic sphincters encompassed the openings of the side branches of arteries along the entire perimeter; in the cross-section they looked like cushions projecting into the lumen of the major arterial trunk (Fig. 1, *d*). The cushions consisted of clusters composed of smooth muscle cells enclosed between two leaves of internal elastic membrane. In the region of arteriole branching and at the level of middle and large arteries, the number of vessels with sphincters increased 2-fold, while at the level of small arteries the number of vessels with sphincters increased by

TABLE 1. Thickness of Tunica Media in Hepatic Vessels in Control and during Compensated Aortic Coarctation (μm, *M*±*m*)

Vessels			Control	Compensated coarctation of aorta
Hepatic blood inflow bed	arteries	large	24.0±1.1	17.0±0.9*
		middle	13.2±0.8	9.3±0.3*
		small	6.5±0.1	4.3±0.1*
		arterioles	3.80±0.09	2.60±0.05*
	portal vein, the level of:	large	6.0±0.2	3.6±0.1*
		middle	5.1±0.3	3.1±0.1*
		small	4.1±0.2	2.5±0.1*
		arterioles	2.8±0.1	2.1±0.1*
Hepatic blood outflow bed	hepatic veins	large	6.2±0.3	4.0±0.2*
		middle	4.4±0.1	3.0±0.1*
		small	3.2±0.1	2.4±0.1*
		venule	2.7±0.1	2.1±0.1*

Note. *$p<0.001$ compared to the control.

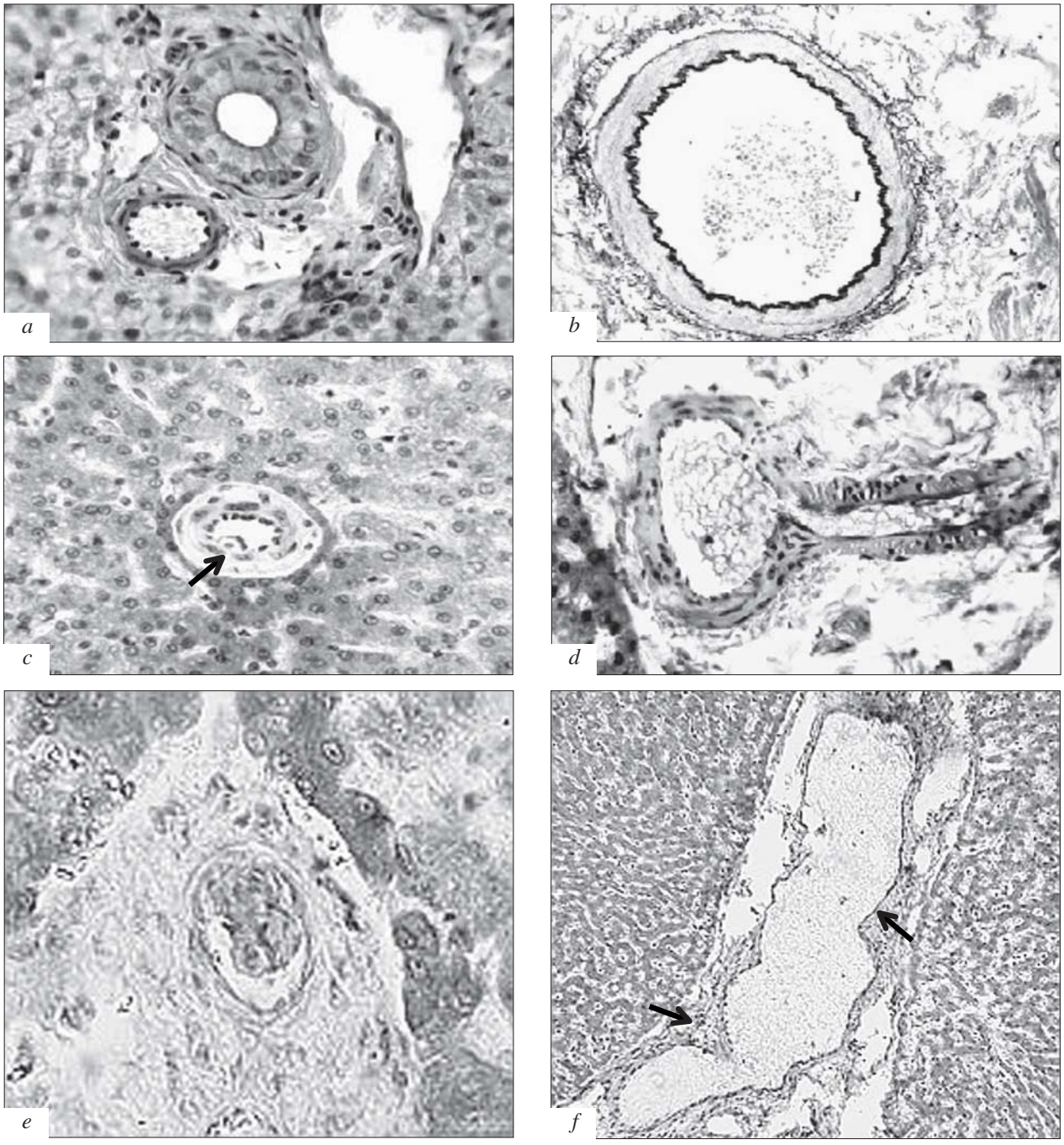

Fig. 1. Histological picture of hepatic vessels during compensated coarctation of aorta. *a*) widening of the lumen and thinning of the wall of a small artery (×200); *b*) slackening of the folded structure of the internal elastic membrane of a middle artery (×200); *c*) a fascicle of intimal musculature of a small artery (arrow, ×200); *d*) muscular-elastic sphincter in the orifice of middle artery (×200); *e*) polypoid cushion of a middle artery against the background atrophy of its wall (×100); *f*) sawtooth contours of a collecting hepatic vein and atrophy of its muscular cushions (arrows, ×100); *a*) Hill staining; *c*, *d*, *f*) hemotoxilin and eosin staining; *e*) Brachet staining.

4 times compared to the control. The polypoid cushions looked like the rounded structures located in the vascular lumens (Fig. 1, *e*). The serial sections showed that the cushions were connected to the vascular wall with a thin stalk. The basis of these cushions was formed by smooth muscle fascicles passing in different directions and alternating with collagen and elastic fibers. In morphological papers, such structures are referred to as Conti cushions [8]. They were often seen at the level of the large hepatic arteries in experimental dogs, but were absent in the control.

Essential morphological rearrangement induced by aortic coarctation took place not only in the

TABLE 2. Parameters of Smooth Muscle Cells in Tunica Media of Hepatic Small Arteries in Control and during Compensated Coarctation of Aorta (*M*±*m*)

Parameters	Control	Compensated coarctation of aorta
Longitudinal axis of the nuclei, μ	7.6±0.1	5.60±0.09*
Transversal axis of the nuclei, μ	4.1±0.6	2.70±0.02*
Nuclear area, μ^2	24.6±0.6	11.9±0.2*
Nuclear volume, μ^3	72.4±3.3	22.6±1.0*
Number of cells	9.7±0.8	5.1±0.1*

Note. *$p<0.001$ compared to the control.

hepatic arteries, but also in other inflow vessels, branches of the portal vein. Tortuosity of elastic membranes in these vessels was less pronounced indicating a decrease in vascular tone. The wall of portal veins of various calibers thinned: at the level of large arteries, it decreased by 1.7 times; it dropped 1.6-fold at the level of middle and small arteries, and by 1.3 times at the arteriole level (Table 1). Moreover, examination revealed the sphincters at the sites of vein branching.

Similar structural alternations were seen in the vessels belonging to hepatic outflow bed (in the hepatic veins). The thickness of the wall in large hepatic veins decreased by 1.6 times; the corresponding decrements for middle and small veins were 1.5 and 1.3 times, while the wall of venules thinned 1.3-fold (Table 1). The longitudinal section of the collecting hepatic vein looked saw-like due to projections of peculiar muscle structures into the vascular lumen (Fig. 1, *f*). Visual assessment revealed that these cushions thinned during coarctation. This was also corroborated by the morphometric data. Specifically, their mean thickness decreased by 1.8 times ($p<0.001$).

Thus, experimental coarctation of aorta induced the development of a complex of adaptive alterations in the inflow and outflow hepatic blood beds. Under the conditions of modeled cardiac disease, the blood inflow to the liver propelled by a decreased pressure induced hypotony and dilation of the tribute vessels. The drop in hemodynamic load resulted in thinning of the walls of arterial branches and portal veins underlain by decrease in size and number of medial leiomyocytes. As a kind of adaptive response to disturbed circulation, the number of arteries increased in the hepatic inflow bed. These arteries were characterized with oblique- and longitudinally oriented fascicles of leiomyocytes in the tunica intima, muscular-elastic sphincters, and polypoid cushions together with sphincter-supplied vein. According to literature and our data, these structures were observed in vascular bed of dogs that were not subjected to experimental pathology [6,8]. They were formed in hepatic arteries from the medial myocytes that migrated into the tunica intima through the "pores" in the internal elastic membrane [7-9]. By contracting, these muscular structures control the filling of hepatic arterial bed thereby providing the optimal supply for hepatic parenchyma during chronic ischemia. Thus, the nature of these morphological structures seems to be adaptive. During experimental aortic coarctation, hypotony appeared not only in the inflow vessels, but also in the outflow bed leading to thinning of the walls of the hepatic veins. Similar to hepatic arteries and portal veins, these veins possessed the structures (muscular cushions) involved in the control of hemodynamics. Contraction of these cushions promoted accumulation of the blood in the hepatic vascular bed, which released into circulation during relaxation of the cushions [7]. We found that in contrast to the vessels transporting blood to the liver, where coarctation promoted the development of the adaptive structures, the muscular cushions became less pronounced in the collecting hepatic veins. These alterations moderated the blood-storing function of the liver and promoted a rapid return of the blood to the heart and then to the arteries of the greater circulation, where coarctation provoked persistent hypotension. Therefore, the functions of the control structures situated at the opposite sides by the sinusoids (the fascicles of intimal musculature, muscular sphincters, arterial polypoid cushions, and the sphincters of the portal veins in the inflow bed, on the one hand, and the muscular cushions of the hepatic veins, on the other hand) are principally different. In the inflow vessels, they supply the blood to the actively working hepatic lobes and affect the local hemodynamics. In the outflow vessels, they control the blood volume in the common vascular bed, which is echoed in hemodynamics in the greater circulation.

REFERENCES

1. L. A. Bokeriya and R. G. Gudkova, *Grud. Serd. Sosud. Khir.*, No. 6, 9-23 (2000).
2. O. Ya. Kaufman, *Hypertrophy and Smooth Muscle Regeneration* [in Russian], Ìoscow (1979).
3. V. N. Medvedev, Sh. M. Kurmaev, and G. I. Kharitonov, *Kaz. Med. Zh.*, No. 3, 161-164 (2001).
4. O. A. Mutaf'yan, *Congenital Heart Diseases in Children* [in Russian], St. Petersburg (2002).
5. A. S. Sharykin, *Congenital Heart Diseases* [in Russian], Moscow (2005).

6. I. S. Shormanov, *Byull. Eksp. Biol. Med.,* **137**, No. 3, 332-375 (2004).
7. S. V. Shormanov and S. V. Kulikov, *Morfologiya*, **124**, No. 4, 61-66 (2003).
8. S. V. Shormanov and A. V. Yal'tsev, *Arkh. Pat*., **58**, No. 1, 37-41 (1996).
9. P. S. Rao, *Semin.-Nephrol*., **15**, No. 2, 87-105 (1995).
10. S. S. Stephensen, G. Sigfusson, H. Eiriksson, *et al., Laeknabladid*, **88**, No. 4, 281-287 (2002).
11. C. D. Sudarshan, A. D. Cochrane, and Z. H. Jun, *Ann. Thorac. Surg*., **82**, No. 1, 158-163 (2006).