Restoration of Circulating Plasma Volume After Blood Loss in Newborn and Adult Mammals: a Comparative Analysis

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The rate of spontaneous restoration of the volume of circulating plasma after blood loss (2% of body weight) is different in anesthetized newborn piglets and adult cats. The ability to restore circulating plasma volume is lost within the first weeks after birth, correlating with the interstitial glycosaminoglycan content. Newborn piglets (1-21-day-old) restore circulating plasma volume within several hours after blood loss, their aortic glycosaminoglycan content being almost two-fold lower than that in 22-30-day-old piglets that cannot rapidly restore the circulating plasma volume. The role of the interstitial gel in the replacement of circulating plasma volume is discussed.

Key Words: *ontogenesis; blood loss; plasma volume; interstitium*

Mammalian fetuses, neonates, and adults respond to blood loss, hypoxia, and hypoxemia by reduction in blood supply to skeletal muscles and skin [12-14], where the content of extravascular fluid is greater than in other parts of the body. As a result of blood loss, both the total amount of proteins and the colloid-osmotic pressure of blood plasma decrease [8], which hinders spontaneous replacement of circulating plasma volume (CPV). Nevertheless, in contrast to adult mammals, newborns rapidly restore their CPV after a massive blood loss. The present study is an attempt to elucidate the cause of different rate of CPV replacement by extravascular fluid at different stages of ontogenesis.

MATERIALS AND METHODS

Experiments were performed during the autumn-winter season on 45 newborn piglets aging 1-30 days and 15 adult cats anesthetized with Nembutal (30-40 mg/kg intraperitoneally). Circulating plasma volume was measured using the dye T-1824. Circulating blood volume (CBV) was calculated from hematocrit. The content of glycosaminoglycans (GAG) in the aorta of newborn piglets was determined as described elsewhere [6]. Blood loss was modeled by drawing blood for 8-10 min from the femoral artery (a volume equivalent to 2% body weight). Surviving animals were killed by ether overdosage. The significance of differences between the mean values was evaluated by the difference method [5] and by the nonparametric Wilcoxon—Mann—Whitney U test [3]. The contingency of variates was determined by correlation analysis [4].

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RESULTS

The results obtained indicate that the capacity for rapid spontaneous restoration of CPV is lost in the first few weeks after birth. In 29 piglets aging 1-21 days (mean age 14.5±1.5 days), CPV was restored to 92% of the original value by the 6th h after blood loss and was 16% above the original level after 12 h (Table 1). By contrast, in 22-30-day-old piglets (mean age, 28.0±0.9 days, n=16) CPV was not

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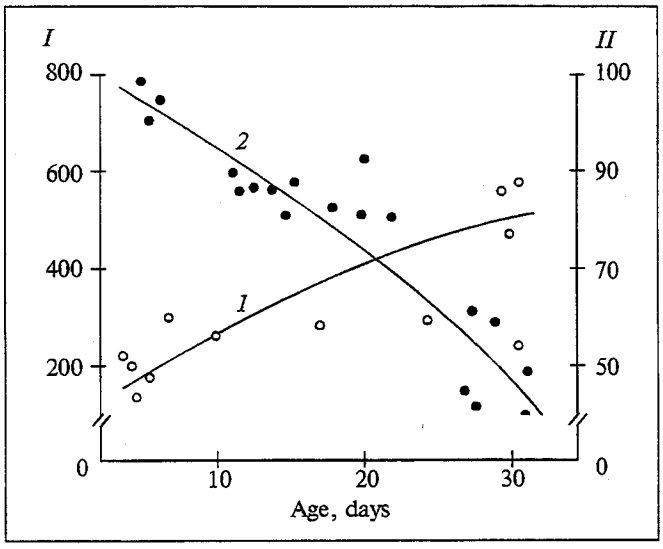

Fig. 1. Changes in the aortic content of glycosaminoglycans (GAG) and the efficiency of restoration of circulating plasma volume (CPV) in piglets of different age after blood loss. Ordinate: *I*) GAG concentration, mg/dl (*1*); *II*) CPV 6 h after blood loss, percent of original volume (*2*).

restored, and hypovolemia was increased, i.e., the dynamics of CPV in these piglets was similar to that in adult cats. Rapid elimination of hypovolemia provided 100% survival of 1-21-day-old piglets. All 22-30-day-old piglets died (the mean survival time was 3.7±0.8 h), and only 3 out of 15 cats survived.

We believe that the major factor of the age-related decrease in the efficiency of CPV restoration in mammals is an intense development of the connective tissue during the first postnatal weeks [1]. In growing connective tissue the distances between capillaries and cells increase, the density of capillaries decreases, and the content of highly hydrophilic GAG increases. Glycosaminoglycans typical of adult mammalian connective tissue (hyaluronic acid and chondroitin sulfates) are formed in the tissues of lower vertebrates [2]. It was demonstrated that the capacity of lower vertebrates to rapidly restore the CPV (similar to that of newborn mammals) [17] declines during phylogenesis.

From these data it can be hypothesized that modifications occurring in the interstitium (for example, an increase in the content of hydrophilic GAG) are the main cause of the age-related decrease in the rate of CPV replacement in mammals. To test this hypothesis we measured the GAG content in the aorta of newborn piglets. The aorta was chosen because blood flow and GAG metabolism in it are not affected by shock as strongly as in the skeletal muscles and skin [16]. The GAG content in the aorta of 1-21-day-old piglets was almost 2-fold lower than that in the aorta of 22-30-day-old piglets (262±24 mg/dl and 479±60 mg/dl, respectively, $p<0.02$; Fig. 1). The tissue GAG content increased with age ($r=0.70$, $p<0.05$), while the efficiency of spontaneous restoration of CPV decreased ($r=0.69$, $p<0.01$). The rise of GAG concentration in the interstitium correlated with a decrease in the rate of CPV recovery ($r=-0.81$, $p<0.05$).

The tendency of the interstitial gel to be saturated with fluid, which leads to fluid extravasation and a considerable increase in gel volume, is counterbalanced by the properties of collagen, elastic fibers, and GAG. This determines the effectiveness of infusion therapy immediately after a massive blood loss. However, prolonged hypovolemia is accompanied by the development of hypoxia and metabolic

TABLE 1. Variations of Circulating Blood (CBV) and Plasma (CPV) Volumes in Newborn Piglets and Adult Cats After Blood Loss

Animals	Parameter, ml/kg	Initial value	Time after blood loss, h			
			0.1	6	12	24
1-21-day-old piglets						
	CBV	80±2.1	60±1.9	69±1.8*	73±1.6*	84±1.8*
	CPV	51±1.9	39±2.1	47±1.4*	51±1.8*	59±1.2*
				n=29		
22-30-day-old piglets						
	CBV	72±1.8	52±1.7	46±2.4		
	CPV	45±1.3	34±1.4	31±1.7		
		n=16	*n*=16	*n*=8		
Adult cats						
	CBV	63±2.4	43±3.1	41±3.2	40±2.8	44±11.4
	CPV	35±1.8	24±1.9	25±3.1	23±3.9	26±9.1
		n=15	*n*=15	*n*=9	*n*=7	*n*=3

Note. *Significantly different from the value recorded 0.1 h after blood loss.

acidosis, increase in hydrophilicity of interstitial gel and collagen [10], and accumulation of osmotically active substances in the intercellular space. At this stage CBV can be maintained at a level close to normal by infusions of crystalloid solutions in volumes much higher than the volume of lost blood. This effect may be associated with saturation of the interstitial gel with fluid, appearance of free fluid in the intercellular spaces, and increased hydrostatic pressure in the interstitium, which provides a kind of "support" for CBV outside the capillaries.

In fact, even a slight increase in the volume of interstitial fluid caused by transient venous stasis leads to an increase in the tissue hydrostatic pressure by 4 mm Hg [9]. However, conflicting results were obtained in chronic experiments. Elevation of venous blood pressure to 12 mm Hg over 24-48 h was attended by fluid extravasation, while hydrostatic pressure in subcutaneous tissue remained virtually unchanged [11]. Only after a further rise of venous did pressure and fluid extravasation tissue pressure increase by 1-3 mm Hg, which led to the development of edema seen with the unaided eye. Similar results were obtained for the skeletal muscle. Tissue hydrostatic pressure grow by 1-3 mm Hg only after the volume of interstitial fluid had increased by 100% or more as a result of hypoproteinemia or elevation of venous blood pressure to 12 mm Hg [15].

Terminal phases of shock are characterized by inhibition of GAG synthesis [7], disintegration of cell structures, and the appearance of collagen- and GAG-degrading enzymes in the intercellular spaces. This provokes a sharp increase of the interstitial gel compliance, which, together with unbalanced Starling equilibrium, predetermines the impossibility of CBV restoration because of fluid extravasation.

Taken together with published data, our findings indicate that the absence of spontaneous restoration of CBV and low efficacy of anti-shock infusion therapy in adult mammals are determined by the properties of the interstitial gel whose main constituents are GAG. This suggests that the effectiveness of CBV restoration in shock can be increased by modifying the properties of the interstitial gel.

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