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THE EFFECT OF CHANGES IN THE INTRAVASCULAR PRESSURE AND BLOOD FLOW RHEOLOGY ON MALIGNANT GROWTH

F. V. Rudenko*, A. V. Rutskii, and
Yu. D. Kovalenko

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Experiments with transplanted neoplasms have revealed that a decrease in intravascular pressure or introduction of polymers decreasing hydrodynamic resistance has an pronounced antitumor effect.

In recent years oncological research has been experiencing some kind of stagnation. In the overwhelming majority of works particular details of the research are only multiplied, which does not enable new generalizations. The importance of new approaches and theories of carcinogenesis increases. Investigation of the role of biomechanics and rheology of the blood flow in development, growth, and treatment-induced regression of malignant tumors seems to be one of the most promising trends. This opinion is based primarily on achievements in general pathology, which established an important and often decisive role for disturbances in the blood flow and transcapillary transfer in development of standard pathological processes such as tumor growth and on information gained by fundamental science in rheology and biomechanics [1, 2].

We have studied the effect of changes in the value of intravascular pressure and rheology on the probability of emergence of malignant tumors, their growth rates, and antitumor resistance of the organism. Experiments were carried out on 520 stock-bred laboratory albino Wistar rats with a body weight of 150–200 g. Biomechanical characteristics of the blood flow were varied by increasing or decreasing pressure in arteries and veins. The intravascular pressure was measured and controlled with the procedure described earlier [3, 4]. The blood rheology was varied using the Toms effect, and for this purpose polymers decreasing hydrodynamic resistance of the turbulent flow were injected into animals [5, 6].

In the first experimental series we studied the probability of emergence of malignant tumors in the case of decreased intravascular pressure. In the control group the average arterial pressure in the animals was 98.0 ± 3.4 mm Hg and in the experimental animals it was 59.0 ± 3.6 mm Hg, i.e., the average decrease in the pressure was 40% ($P < 0.001$). Six months later bone tumors induced by 3,4-benzpyrene appeared in 54% of the animals in the control group and in 5% of the experimental rats. Successful transplantations of 5% Sarcoma 45 (Sa-45) cell suspension were observed in 95% of the control animals and in 10% of the experimental animals ($P < 0.05$). Thus, results of this experimental series indicate that the tumor risk decreases with a decrease in the intravascular pressure.

In order to determine the effect of changes in the intravascular pressure on the growth rate of malignant tumors, six days after intramuscular transplantation of Sa-45 blastomas, arterial hypotension or venous stagnation were simulated. The animals were removed from the experiment on days 7, 14, and 21. The tumors were resected, weighed and then subjected to histological examination (Table 1).

As can be seen from the data presented, in the case of arterial hypotension the growth of Sarcoma 45 was retarded by more than 50% in comparison with the control ($P < 0.05$). One-week observation did not reveal any

* Deceased.

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TABLE 1. Effect of Arterial Hypotension and Venous Stagnation on Sa-45 Growth

Observation group	Number of animals, n	Tumor weight (g) in		
		7 days	14 days	21 days
Arterial hypotension				
Control	45	3.0 ± 0.4	7.5 ± 1.6	12.8 ± 2.8
Experimental	90	1.2 ± 0.2*	3.0 ± 1.0*	5.5 ± 0.8*
Venous stagnation				
Control	43	3.0 ± 0.4	5.8 ± 2.6	12.1 ± 2.4
Experimental	49	2.9 ± 0.5	9.9 ± 0.9*	15.6 ± 1.4*

* The differences are significant (for all the tables), $P < 0.01-0.05$.

TABLE 2. Effect of Arterial Hypotension on Survival of Animals with Tumor

Observation group	Number of animals, n	Survival (days) from start of	
		transplantation	hypotension
Control	18	13.5 ± 0.5	7.5 ± 0.5
Experimental	20	22.5 ± 0.9*	16.5 ± 0.7*

pronounced effect of increased venous pressure on the tumor growth. However, after a two-week period the tumors in the experimental animals were almost twice as large as those in the control animals ($P < 0.05$). Enhanced growth was also observed after three-week observation. Histological results have shown that the antitumor effect was realized on the level of the microcirculatory channel and caused by its anatomical and physiological peculiarities in malignant tumors [5].

For determination of the effect of the value of intravascular pressure on the tumor resistance of the organism and tissues, we measured intensities of immune responses of cellular type and survival of the animals with blastoma. The expression of immune responses was estimated from the size of edema in the region of injection of a resolving antigen dose in presensitized animals. The animals were sensitized by intraperitoneal injection of 5 mg of living BCG vaccine. A month later the conditions of arterial hypotension were simulated in the experimental animals. After two weeks more a resolving antigen dose (1 mg of Koch's tuberculin) was injected in the cushion of the animals' right hind foot, and a control (physiological) solution in their left foot. Expression of the slow hypersensitivity reaction (SHR) was estimated by the size of the foot edema 24 and 48 h after the injection. The edema was measured by a micrometer within 0.01 m. The SHR, which is an integrative indicator of the condition of cell immunity, appeared significantly more expressed ($P < 0.05$) in the experimental animals at all observation terms.

The effect of arterial hypotension on the survival was studied in animals with Walker 265 sarcoma transplanted in the form of a 20% cell suspension in the femoral muscles of both feet of the rats. Six days after the transplantation arterial hypotension was simulated in the experimental animals. The survival was measured in days survived after the transplantation of the tumor and/or simulation of arterial hypotension (Table 2).

As can be seen, the survival in the group of animals with lower intravascular pressure is longer. The antitumor effect of arterial hypotension is more pronounced if we compare the survivals after the initial action of the hypotensive factor. In this case the survival of the experimental animals is more than twice as long as the survival of the control animals.

The summarized data indicate that a decrease in the intravascular pressure is accompanied by a higher tumor resistance of tissues and the entire organism.

TABLE 3. Changes in Intravascular Pressure and Heart Rate after Injection of Polyethylene Glycol

Observation group	Number of observation, n	Pressure, mm Hg			Heart rate
		maximal	mean	minimal	
Control	12	103 ± 2	94 ± 2	89 ± 2	464 ± 26
After injection of PEG-400	27	77 ± 3*	66 ± 2*	60 ± 3*	468 ± 14*

The hydrodynamic resistance of the blood flow was reduced with the use of polyethylene glycol with a molecular mass 400 M.G. (PEG-400) with the formula $H(OCH_2CH_2)_n \cdot OH$ that was injected intraperitoneally diluted 1:10 at a dose of 0.5 cm^3 per 10 g of animal mass. The growth rates of tumors were determined by measuring their masses in the control and experimental animals two weeks after the transplantation of Sa-45 (Table 3).

It can be seen that the intraperitoneal injection of PEG-400 reduces the systematic hydrodynamic resistance, on average by 30% of the initial resistance, and inhibition of the tumor growth was 55% in this case.

Similar data were obtained in the case of intravenous injection of polyacrylamide with its final blood concentration of 10 g/ml.

Thus, these results indicate that changes in the intravascular pressure and rheology of the blood flow have a great effect on the probability of emergence and progression of malignant tumors. These findings confirm the new hypothesis of carcinogenesis suggested earlier, which states that in conditions of integral organism local and regional changes in the blood flow constitute the same necessary condition of emergence of tumors as cancer regeneration of cells does [7].

As regards practical importance, the present data expand the stock of antitumor actions due to directed changes in pressure and rheology toward a decrease in the total vascular resistance. Effective development of this trend is viewed as integration of information accumulated by basic science in fluid biomechanics and rheology and by experimental and clinical oncology.

REFERENCES

1. A. M. Chernukh, P. N. Aleksandrov, and O. V. Alekseev, Microcirculation [in Russian], Moscow (1975).
2. S. A. Regirer and A. A. Shtein, in: Achievements in Science and Technology. Complex and Special Sections of Mechanics [in Russian], Moscow (1985), Vol. 1, pp. 3-142.
3. F. V. Rudenko, Éksper. Onkol., 2, No. 5, 59-63 (1980).
4. F. V. Rudenko, Éksper. Onkol., 4, No. 1, 68-70 (1982).
5. S. S. Grigoryan, I. V. Gannushkina, M. V. Kameneva, et al., in: Mechanics of Biological Media [in Russian], Moscow (1986), pp. 76-88.
6. B. A. Toms, Proc. Int. Congr. Rheol., Amsterdam (1949), Vol. 2, p. 135.
7. F. V. Rudenko and A. V. Furmanchuk, in: Injuries and Regulatory Processes in the Organism [in Russian], Book of Abstr., III All-Union Congr. Pathophysiologists, Tbilisi (1982), p. 323.