[CANCER RESEARCH 52, 5110–5114, September 15, 1992]

Advances in Brief

Microvascular Pressure Is the Principal Driving Force for Interstitial Hypertension in Solid Tumors: Implications for Vascular Collapse[1]

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Abstract

The interstitial fluid pressure (IFP) has been found to be as high as 20 to 50 mm Hg in both experimental and human solid tumors. While the IFP is an important determinant of the delivery of therapeutic agents to neoplastic cells *in vivo*, the mechanisms responsible for interstitial hypertension are not completely understood. The high vascular permeability of tumor blood vessels and the absence of a functional lymphatic circulation suggest that the hydrostatic microvascular pressure (MVP) is the main force governing IFP in tumors. To test this hypothesis, we simultaneously measured IFP and MVP in 13 tissue-isolated R3230AC mammary adenocarcinomas transplanted in rats. The MVP in superficial postcapillary venules of diameters between 25 and 250 μm was measured with the micropuncture technique. MVP was compared to the IFP in the periphery (measured with micropuncture technique) and in the center (measured with wick-in-needle technique). Similar to our previous study, IFP rose rapidly and reached maximum values at a depth of 0.2 to 1.0 mm from the tumor surface. These maximum IFP values [16.5 ± 7.1 mm Hg (SD)] were equal to IFP in the tumor center [18.4 ± 9.3 mm Hg] [$R^2 = 0.86$, $P > 0.8$]. Superficial MVP (17.3 ± 6.1 mm Hg) was equal to both central ($P > 0.9$) and superficial IFP ($P > 0.7$). These results demonstrate that the main driving force for IFP in tumors is the MVP. Furthermore, the concept that blood vessel collapse is induced by higher hydrostatic pressures in the tumor interstitium compared to that in the vascular lumen is not supported by the present finding that elevated IFP is accompanied by equally elevated MVP.

Introduction

Since the pioneering studies of Young *et al.*(1), several investigators have shown that IFP[2] is elevated in experimental and human tumors (2–6).[3] To elucidate the mechanisms leading to interstitial hypertension in solid tumors, we have recently developed a mathematical model of fluid transport in tumors (7, 8). The model is based on the experimental findings that the tumors lack a functional lymphatic system (9, 10) and have both a relatively high vascular permeability (11) and vascular hydraulic conductivity (12). The model relates the radially outward fluid flow to the pressure difference between the tumor and the surrounding normal tissue and agrees with the data on the rate of fluid oozing out of the tumor (13). In addition the model suggests that IFP is uniformly elevated throughout a tumor growing as a single nodule but drops rapidly in the periphery of tissue-isolated tumors and at the tumor-normal tissue interface in tumors surrounded by normal tissue. The pressure profiles predicted by the model have been confirmed experimentally for both types of tumor preparations (3). Given a reduced protein osmotic gradient between the vascular and interstitial compartment, the model predicts that the fluid extravasation is negligible throughout most of the tumor and occurs predominantly from vessels in the periphery. As a result, MVP is the major force regulating IFP. If this prediction is true, then MVP in tumors should be elevated to values similar to those of IFP everywhere in the tumor except in the periphery. Furthermore, MVP should be greater than the IFP in the periphery to permit fluid extravasation from the peripheral vessels. However, there are no data on the simultaneous measurement of MVP and IFP in tumors. The available hydrostatic pressure measurements in tumor exchange vessels range from 6 to 13 mm Hg (14–17), which are considerably lower than the IFP values of 20 to 50 mm Hg measured in experimental (3, 18, 19) and human tumors *in situ* (4–6).[3] Therefore, the goal of the present study was to measure MVP and IFP simultaneously and to compare both parameters in tumors which exhibit IFPs greater than the tumor MVPs reported to date.

We chose the tissue-isolated R3230AC mammary adenocarcinoma to test our hypothesis for the following reasons: (*a*) we have measured IFPs as high as 35 mm Hg in this tumor (3); (*b*) this tumor oozes fluid from its periphery at approximately 10% of plasma flow rate (20); (*c*) the viscous (21) and geometric (22) resistance to blood flow and the vascular hydraulic conductivity (12) of this tumor are very high compared to that of several normal tissues; (*d*) the vascular architecture of this tumor shows that the arteries and arterioles are located in the center whereas the exchange vessels are distributed throughout the tumor (23); (*e*) with a tissue-isolated tumor, there are no concerns of possible artifacts associated with either inserting the micropipet through the overlying skin or removing the skin to perform the measurements. The central and superficial IFPs were measured with the WIN and MP technique, respectively. The hydrostatic pressure in superficial PCVs (25–250 μm diameter) was measured with the MP technique. Since the exchange vessels in a tumor are mostly PCVs, we will refer to pressures measured in these vessels as MVP.

Materials and Methods

Animal and Tumors. The R3230AC mammary adenocarcinoma was grown as an ovarian, isolated tumor in Fischer 344 rats (110–160 g). The tissue-isolated tumor developed originally by Gullino and Grantham (24) was prepared as adapted by Sevick and Jain (20). In brief, the right ovary was removed, and tumor slurry was injected in the fat pad which is connected to the host's circulation by the ovarian artery and vein. The tumor was placed in a Parafilm bag. After 10–15 days of growth, the tumor was exteriorized for pressure measurements. A total

Received 6/25/92; accepted 7/31/92.

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[1] This work was supported by grants from the National Cancer Institute (CA-36902, CA-37239, and CA-49792). Preliminary reports of this work were presented at the 40th Annual Meeting of the Radiation Research Society, Salt Lake City, UT, March 14–18, 1992, and at the 39th Annual Meeting of the Microcirculatory Society, Anaheim, CA, April 3–5, 1992.

[2] The abbreviations used are: BP, blood pressure; IFP, interstitial fluid pressure; MP, micropuncture; MVP, microvascular pressure; PCV, postcapillary venule; WIN, wick-in-needle.

[3] J. R. Less, M. C. Posner, Y. Boucher, D. Borochovitz, N. Wolmark, and R. K. Jain. Interstitial hypertension in human breast and colorectal tumors, submitted for publication.

of 13 animals were used to collect these data. Tumor size varied between 0.7 and 2.5 g and did not correlate with the number of days postimplant.

MP Technique. The characteristics of the servo-null device, pressure transducer, preamplifier, and chart recorder for measuring IFP and MVP; the capillary tubing used to prepare micropipets; and the equipment (graded micromanipulator, stereomicroscope, fiberoptic light source) used to introduce the micropipets into tumors were similar to those used in our previous study (3). Micropipets with a tip diameter of 2–4 μm were filled by capillary action with 1 M NaCl with or without Evans blue dye (0.05% by weight).

WIN Technique. IFP was measured in two different locations in the center of tissue-isolated tumors, with the WIN technique developed by Fadnes *et al.*(25). A 23-gauge needle with a 2–3-mm side hole 4–5 mm from the tip was filled with five surgical sutures (6-0 Ethilon). The needle was connected to a pressure transducer (model P23XL; Spectramed, Inc., Oxnard, CA) by polyethylene tubing filled with heparinized (70 units/ml) saline. The pressure transducer was linked to a preamplifier (model 11-4113-01; Gould, Inc., Cleveland, OH) and the amplified signal was sent to a dual-channel chart recorder (model 30-V7202-11; Gould) or an analogue-to-digital converter (MacLab 8; World Precision Instruments, Sarasota, FL) linked to a computer (Macintosh Classic II; Apple Computer, Inc., Cupertino, CA).

Experimental Procedure. The rats were anesthetized with ketamine/xylazine (90/10 mg/kg i.m.). The left carotid artery was cannulated to measure arterial pressure. The rats were placed on a temperature-regulated heating pad and the body temperature was maintained between 37.0 and 38.0°C. Following a small skin incision, the Parafilm bag enclosing the isolated tumor was removed, and warm isotonic saline (~37°C) was dripped continuously on the tumor surface. To minimize tumor movements due to respiration, two 23-gauge needles were passed through the muscle wall on each side of the tumor pedicle and fixed to a cork taped onto a Plexiglas surface. The measurement of IFP with the WIN technique before and during tumor immobilization demonstrated that IFP could be artificially increased by the immobilization procedure. In order to detect possible increases in IFP induced by tumor immobilization, IFP was measured continuously with the WIN technique before, during, and after tumor stabilization. When tumor IFP was increased by more than 10%, tumor stabilization was modified by pulling slightly on the needles or by repositioning the needles. In general, slight modifications of the immobilization procedure returned IFP to prestabilization levels.

Our previous study of IFP profiles in the tissue-isolated R3230AC mammary adenocarcinoma has demonstrated that IFP rises rapidly in the tumor and reaches a plateau at a distance of 0.2–1.1 mm from the surface (3). In the present study, the micropipets were introduced perpendicular to the tumor surface, to depths of 1.0 to 1.5 mm with a graded micromanipulator. When the tumor surface was flat, IFP measurements were attempted at intervals of 0.2–0.3 mm while the micropipets were retracted. Each pressure measurement was recorded for at least 10 s. The IFP values were accepted as valid when (*a*) the fluid communication between the micropipet and the tissue could be confirmed electrically and (*b*) the zero pressure in the saline at the surface was not modified during the insertion and withdrawal of the micropipet. Generally, IFP measurements were restricted to one or two regions (10 x 10 mm) per tumor. At least two good tracks were required per tumor to validate the results.

MVP was measured in PCVs of diameters between 25 and 250 μm located at 0.07–0.4 mm from the surface of tumors. Vascular casts (23), histology, and electron microscopy demonstrated that the superficial vessels were exclusively PCVs. The wall of the PCVs was formed by a layer of endothelial cells lying on a discontinuous basal lamina. Even the larger PCVs (100–250 μm in diameter) were not surrounded by a smooth muscle layer.[4] The micropipets were introduced perpendicularly to the vascular wall. Following the completion of a successful measurement, a small volume of Evans blue was injected manually to verify the proper location of the micropipet in the lumen of the vessel (16). The distance between the tumor surface and the vessel was recorded. The diameter of a vessel was measured with a calibrated ocular. MVP was measured in two to four vessels per tumor. The pressure measurements were accepted when criteria *a* and *b* stated above for IFP were satisfied, and also (*c*) erythrocyte velocity was not modified by micropipet insertion and (*d*) Evans blue dye localized in the vessels, as demonstrated by the dye moving with blood flow. Following the completion of the IFP and MVP measurements, the animals were sacrificed by ether or halothane inhalation.

Data Analysis. An analysis of covariance model was used to assess main effect group differences, controlling for arterial pressure, days after tumor implantation, and their interaction. Based upon multivariate log-normal plots, the data were log transformed prior to analysis. *P* values were calculated using the least-square means procedure. Treatment means were determined to be statistically significant for $P < 0.05$. All values are presented as the mean ± SD. Since in 3 of 13 tumors size measurements were not available, the relationship between size and pressures was examined using a simple linear regression model without covariate terms. The null hypothesis was rejected if the β_1 coefficient differed from zero at $P = 0.05$.

Results

In order to minimize tumor movements during the MP measurements of IFP and MVP, the tumors had to be immobilized. In 4 of 13 tumors immobilization was found to artificially increase IFP. IFP returned to prestabilization levels following modification of the immobilization. In one tumor, IFP measured with the WIN was 30 mm Hg before immobilization. Following fixation the mean MVP and IFP were respectively 48 ± 5.2 mm Hg ($n = 3$) and 44 ± 1.4 mm Hg ($n = 2$). By slightly modifying the immobilization procedure, mean MVP and IFP dropped respectively, to 31 ± 2.4 mm Hg ($n = 4$) and 30 ± 2.5 mm Hg ($n = 2$).

In the 13 animals the mean arterial pressure ranged from 74 to 100 mm Hg with a grand mean of 86 ± 9 mm Hg. During the measurements of IFP and MVP the arterial pressure fluctuated between 10 and 20%. Superficial measurements with the MP technique demonstrated that IFP rises rapidly in the tumor periphery and reaches a plateau (maximum values) within a distance of 0.2 to 1.0 mm from the surface. The distance between the surface and the plateau region varied within a tumor and from one tumor to another. Fig. 1 and Table 1 demonstrate that the maximum IFP in the superficial region (measured with MP) was identical to central IFP (measured with WIN). From

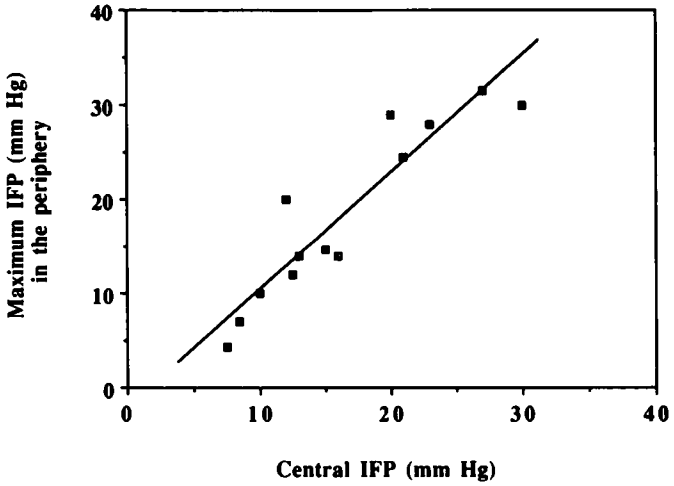

Fig. 1. The linear regression analysis ($y = -1.7297 + 1.2134x$; $R^2 = 0.856$) demonstrates that the IFPs in the center and periphery of the tumors are closely related. Central and peripheral IFPs were respectively measured by the WIN and MP techniques.

[4] Y. Boucher, R. Jones, K. Rock, and R. K. Jain, unpublished results.

Table 1 *IFP and MVP (mm Hg)*

Location	No. of tumors	Range	Mean ± SD
MVP	13	7.0–31	17.3 ± 6.1
Superficial IFP (0.07–0.4 mm from surface)	13	0.0–18	6.5 ± 3.3[a]
Maximum superficial IFP (0.2–1.0 mm from surface)	13	7.5–30	16.5 ± 7.1
Central IFP (WIN)	13	4.4–31.5	18.4 ± 9.3

[a] Different from the 3 other groups ($P < 0.0001$).

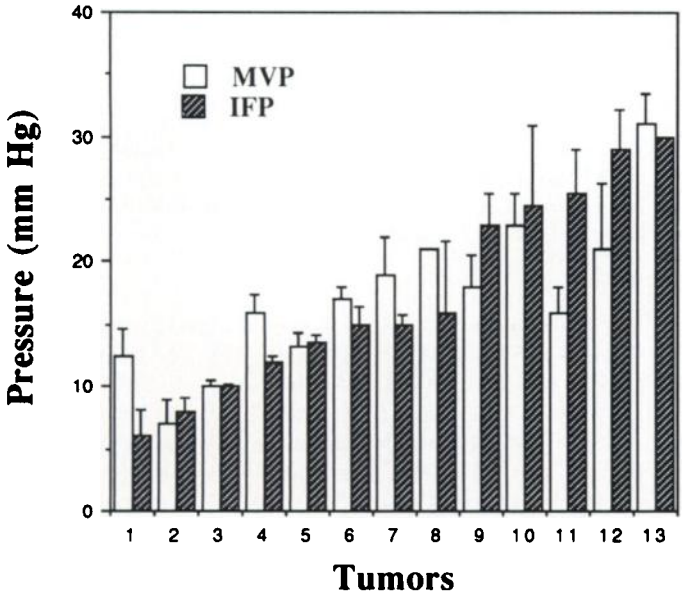

Fig. 2. Histograms representing the IFP and MVP in 13 tissue-isolated tumors. The IFPs are the mean of the peripheral and central IFP of each tumor. In most tumors MVP and IFP are equal. The variations in MVP and IFP for a given tumor are small as indicated by the *error bars* (SD).

the superficial (maximum pressures) and central IFP measurements a mean IFP for each tumor was calculated and compared to the mean MVP (Fig. 2). In 13 tumors, mean MVP varied between 7 and 31 mm Hg and mean IFP between 8 and 30 mm Hg. In 11 of 13 tumors mean IFP and MVP differed by less than 38%. In one tumor MVP was 108% greater than IFP, whereas in another tumor IFP was 60% higher than MVP. The overall mean for the 13 tumors demonstrated that IFP (17.5 ± 8.0 mm Hg) and MVP (17.3 ± 6.1 mm Hg) were similar. MVP was measured in exchange vessels located at 0.07 to 0.4 mm from the tumor surface since it was not possible to visualize deeper vessels. At 0.07–0.4 mm from the tumor surface, mean IFP (6.5 ± 3.3 mm Hg) was significantly lower ($P < 0.0001$) compared to the mean MVP (17.3 ± 6.1 mm Hg) (Table 1). The MVP or IFP was not related to the tumor mass. IFP and MVP were found to increase significantly ($P < 0.001$) with days after tumor implantation (Fig. 3).

The variation in MVP between vessels of a given tumor was in general very small as shown by the small standard deviations in Fig. 2. The largest difference was 7 mm Hg between two large vessels with MVPs of 18 and 25 mm Hg. The intertumor variation was found to be more significant (Fig. 2).

Discussion

The primary goal of this study was to determine the relationship between the hydrostatic pressures in the interstitial space and exchange vessels of a solid tumor. The results demonstrate that: (*a*) except for distances less than 1.0 mm from the tumor surface, IFP is equal to the MVP of tumor exchange vessels located in the tumor periphery; (*b*) a significant pressure difference exists between the tumor exchange vessels and the interstitial space at a depth of 70–400 μm from the tumor surface; (*c*) significant variations in both IFP and MVP were found between tumors; and (*d*) MVPs measured in this study were higher than in previous studies (14–17).

The main limitation of the present study is that since it is impossible to visualize the central blood vessels of tumors, it is also difficult to measure their pressures. Arteries and arterioles are located in the center of the tissue-isolated R3230AC mammary adenocarcinoma, whereas exchange vessels are observed throughout the tumor (23). Superficial MVP and central IFP were similar, suggesting that superficial and central exchange vessels have similar pressures due to the elevated hydraulic conductivity of tumor exchange vessels (12).

Direct measurements of the mean hydrostatic pressure of exchange vessels larger than 50 μm of a mammary adenocarcinoma implanted in a rat dorsal skin chamber (14) and of a 7,12-dimethylbenz(*a*)anthracene-induced mammary carcinoma (16) were found to be approximately 6.0 and 9.5 mm Hg, respectively. In the tissue-isolated R3230AC mammary adenocarcinoma, MVP was found to be of greater magnitude, with a mean of 17.3 mm Hg for vessels >50 μm. While it is quite possible that the different tumor histologies could have different MVPs, the three different types of tumor preparation [dorsal skin chamber preparation (14), chemically induced adenocarcinoma (16), and tissue-isolated tumor (present study)] could also be an important factor in explaining the differences in pressure.

In normal and tumor tissues, IFP is given by the following alternate form of Starling's law (2):

$$\text{IFP} = \text{MVP} - \sigma(\pi_p - \pi_i) - \frac{J_v}{L_p}$$

where σ is the osmotic reflection coefficient for plasma proteins; $(\pi_p - \pi_i)$ is the difference in protein osmotic pressure between the vascular and interstitial fluids; and J_v/L_p is the ratio of fluid flux across the blood vessels to the hydraulic conductivity of the

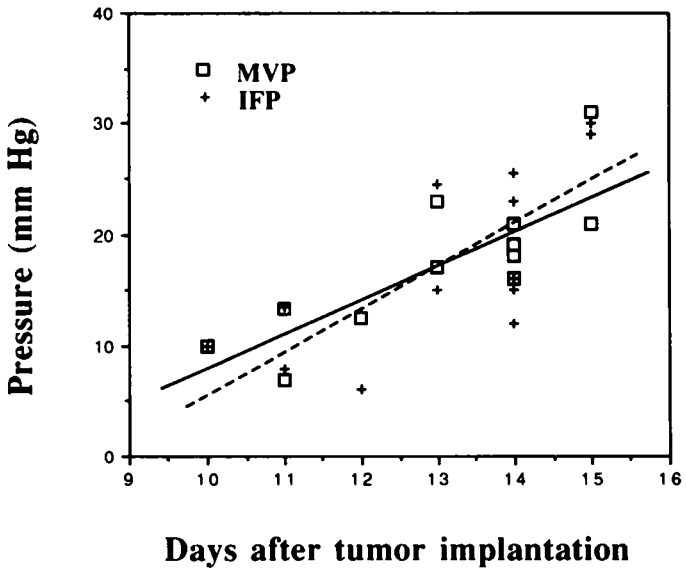

Fig. 3. MVP ($y = -22.341 + 3.0305x$; $R^2 = 0.627$, ——) and IFP ($y = -30.286 + 3.6542x$; $R^2 = 0.535$, - - - -) were found to increase with time after tumor implantation. No relationship of IFP or MVP with tumor size was found.

vascular wall. For fixed $(\pi_p - \pi_i)$ and J_v, the only force that will increase IFP is the MVP. The similar IFP and MVP values measured in tissue-isolated R3230AC mammary adenocarcinomas suggest that the protein osmotic pressure difference is close to zero in this tumor. This conclusion is supported by the results of Sylvén and Bois (26) who found that tumor interstitial fluid sampled with micropipets contained protein concentrations between 67 and 97% of the plasma concentration. However, in semipermeable chambers surrounded by tumor, Gullino *et al.* (27) measured protein concentrations of only 60% of the plasma concentration. In the present study, in one tumor (Fig. 2) MVP was found to be 100% higher than IFP suggesting that the protein osmotic pressure was higher in exchange vessels than in the interstitium. In another tumor IFP was 60% greater than the MVP which could be explained by higher MVPs in other locations in the periphery or in the center of the tumor.

IFP has been shown to increase with tumor size in several experimental (3, 18, 28, 29) and human tumors (4, 6).[3] Similar to our previous study with the tissue-isolated R3230AC mammary adenocarcinoma (3), no relationship was found between IFP and tumor mass. However, both IFP and MVP were related to the number of days following tumor implantation (Fig. 3). What mechanisms would elevate MVP from 7 to 31 mm Hg and IFP from 8 to 30 mm Hg (Fig. 2)? We suggest two possible mechanisms to explain this phenomenon. In normal tissues a significant fraction of the systemic arterial pressure drop occurs in the precapillary arterioles. The resistance offered by the arterioles will influence the pressure magnitude in exchange vessels. In the normal microcirculation of different tissues, the hydrostatic pressure can vary from 10 to 25 mm Hg for exchange vessels of $\approx$50 μm in diameter (30). We propose that the arterioles become less effective in controlling MVP with the number of days post-tumor implant. Our second hypothesis is that the MVP increase is due to an increase in viscous and/or geometric resistance in the venous side of the circulation. For example, the increased vascular resistance could result from the mechanical obstruction of exchange vessels. The obstruction of an exchange vessel will increase the MVP on the proximal side of the blockage thus increasing IFP. The increased MVP in proximal vessels will depend upon the type, size, and number of vessels occluded, but eventually the MVP could reach the pressure in the arterioles. Wiig and Gadeholt (19) have demonstrated that IFP increased from 25 to 50 mm Hg following the experimental occlusion of the venous drainage of a sarcoma implanted in the rat tail. The blockage of the tumor vasculature by different pathophysiological conditions has been documented in rodent and human solid tumors. Falk (31) has shown that when spontaneous C3H mouse mammary carcinoma reached a diameter of 15–20 mm, the major veins were collapsed between different lobes of the tumor. Formation of thrombi and the invasion or compression of the vascular lumen by neoplastic cells are other plausible mechanisms of vascular occlusion which could lead to higher MVPs.

In several tumors with growth, there is a decrease in perfusion rate and an increase in IFP. Some authors have hypothesized that the decreased perfusion of tumors is due to the collapse of tumor vessels by higher hydrostatic pressures in the interstitium compared to that in the vascular lumen (16, 29). This hypothesis is not supported by the measurement of similar hydrostatic pressures in the interstitium and in exchange vessels in this study. Furthermore, if IFP is transiently higher than MVP, both pressures should reach equilibrium because of the high hydraulic conductivity of tumor vessels (12). Vascular collapse of a thin walled vessel is a function of the average circumferential wall stress which is governed by the difference in external and internal hydrostatic pressures, the thickness and the mechanical properties of the vessel wall, as well as the radius of the vessel (32). Therefore, for an elevated external pressure (such as IFP) to collapse a blood vessel, it must exceed the MVP and the resistance offered by the vessel wall itself. Therefore, as mentioned previously, the collapse of tumor blood vessels is probably induced by cancer cells growing in a relatively confined, noncompliant space.

Recently, a mathematical model was developed by our group to explain the transvascular passage of fluid and macromolecules (*e.g.*, monoclonal antibodies) in solid tumors (7, 8). Because of the high hydraulic conductivity of tumor exchange vessels and the absence of a functional lymphatic system in tumors, the model predicted that the hydrostatic pressures in the interstitial and vascular space would be essentially equal, thus leading to nearly zero filtration and transvascular convective flux of macromolecules in the central regions of tumors. The conclusions of the model are supported by the measurements of similar hydrostatic pressures in the interstitium and in exchange vessels in the present study. The only mode of extravasation from vessels with zero filtration would be by diffusion which is relatively slow for macromolecules. In the tumor periphery (within 1 mm from the surface), the drop in IFP results in hydrostatic pressure differences between the vascular and interstitial space (Table 1) that would favor both fluid filtration and the extravasation of macromolecules by convection. In tumors surrounded by normal tissue, we demonstrated that the IFP drop occurs at the normal tissue-tumor interface or in the normal tissue (3, 8), thus restricting the filtration of fluid and the extravasation of macromolecules by convection even in the tumor periphery.

In conclusion, the results of this study show that IFP and MVP in tissue-isolated R3230AC mammary adenocarcinoma are nearly equal except in the tumor periphery where MVP > IFP. The similarity in hydrostatic pressure between tumor exchange vessels and the interstitial space demonstrates that the main driving force for interstitial hypertension is the MVP and also suggests that the elevated IFP cannot be the exclusive cause of vascular collapse in solid tumors. Future studies are needed to determine the exact mechanisms responsible for the elevated MVP in solid tumors.

Acknowledgments

The authors express their thanks to Sylvie Roberge for her technical assistance, to Dr. J. Efird for the statistical analysis and to Drs. L. T. Baxter, J. Bhattacharya, C. Eskey, P. M. Gullino, I. Lee, M. Leunig, J. Less, E. M. Renkin, E. M. Sevick, H. D. Suit, A. E. Taylor, H. Wiig, F. Yuan, and R. Zlotecki for their careful review of the manuscript.

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