Viscous Resistance to Blood Flow in Solid Tumors: Effect of Hematocrit on Intratumor Blood Viscosity

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ABSTRACT

Blood flow rate in a vascular network is proportional to the arteriovenous pressure difference and inversely proportional to the geometric and viscous resistances. We have recently shown that the geometric resistance to blood flow increases with increasing tumor size and/or decreasing arterial pressure. In this study, the viscous resistance to blood flow within tumor microvasculature was determined by alternately perfusing mammary adenocarcinoma ([3230AC; N = 12; tumor weight, 2.2 ± 1.6 (SD) g] ex vivo with Krebs-Henseleit solution and with RBC suspensions at hematocrits between 1 and 60%. Our results demonstrate that: (a) intratumor blood viscosity increases with increasing hematocrit; and (b) for fixed hematocrits between 10 and 60%, the intratumor blood viscosity is significantly reduced (P < 0.0001) compared to bulk viscosity measured at shear rates of 460 s⁻¹ using a cone/plate viscometer. However, this reduction of intratumor blood viscosity is not as pronounced as in a previous study of skeletal muscle. Further comparison shows that as arterial pressure is lowered, intratumor blood viscosity increases at a greater rate and at lower hematocrits than in normal tissues. We attribute the increased viscous resistance in tumor microvasculature to (a) a less pronounced Fahraeus effect (i.e., reduction in hematocrit in small vessels) and a less pronounced Fahraeus-Lindqvist effect (i.e., reduction in blood viscosity in small vessels) in dilated tumor microvessels compared to normal microvessels; (b) low shear rates (i.e., velocity gradients) associated with tumor vessels which may facilitate rouleaux formation at moderate pressures and even at low hematocrits; and (c) vascular fluid losses of 5–14% which may also increase microvessel hematocrit. We also propose that intratumor blood viscosity may be even higher in vivo than ex vivo due to the presence of WBC and cancer cells in vivo; considerably more rigid than RBC, these cells may cause increased viscous resistance and transient vascular stasis in tumors. The implications of these results in tumor blood flow modulation using chemical and physical agents are discussed.

INTRODUCTION

Blood perfusion rate, q (cm³/h/g), in a tissue is given by the following relationship:

\[ q = \frac{\Delta p}{\eta \zeta} \]  

where \( \Delta p \) (mm Hg) is the arteriovenous pressure difference, \( \eta \) (g/m/s) (1 g/m/s = 2.08 × 10⁻⁴ mm Hg·h·g⁻¹·cm³) is the apparent blood viscosity, and \( \zeta \) (g/cm³) is the extrinsic geometric resistance. The product of \( \eta \) and \( \zeta \) is referred to as the FR (mm Hg·h·g/cm³). Despite the importance of blood flow: \( \Delta p \), \( \eta \), and \( \zeta \) (2). Recently, using an isolated tumor preparation, we have measured the geometric resistance as a function of tumor size and perfusion pressure. Below 40 mm Hg, we have shown that the intratumor geometric resistance, \( \zeta \), increases with decreasing perfusion pressure and, above 40 mm Hg, it reaches a constant value, \( \zeta_0 \), which is dependent upon tumor size (3). Here we report the first measurements of apparent blood viscosity, \( \eta \), in a solid tumor.

The apparent viscosity of blood is governed primarily by hematocrit and shear rate. As hematocrit increases, blood viscosity also increases. At low shear rates, RBC aggregate to form rouleaux, causing an increase in blood viscosity; as shear rates increase, rouleaux are disrupted and blood viscosity approaches a constant value. Furthermore in blood vessels RBC migrate due to their deformability toward the center of microvessels, leaving a cell-free marginal layer at the vessel wall. Since the RBC in the center of the vessel travel faster than the cell-free layer near the wall, the hematocrit in small vessels (<500 μm) is lowered (Fahraeus effect) and blood viscosity is consequently reduced (Fahraeus-Lindqvist effect). As vessel diameter decreases below 500 μm, the cell-free marginal layer constitutes a greater portion of the microvessel flow and the reductions in hematocrit and apparent blood viscosity become more pronounced. However, as the vessel diameter becomes comparable to RBC diameter, both vessel hematocrit and apparent viscosity begin to increase.

As a result of these phenomena, the viscosity of blood measured in vitro using a cone/plate viscometer is higher than in several normal tissues (4–11). However, in solid tumors, experimental evidence of (a) increased caliber of microvessel diameter, (b) sluggish blood flow or flow reversal, and (c) significant vascular fluid losses suggests that the Fahraeus-Lindqvist effect may be less pronounced in tumors, rouleaux formation may be prevalent in tumor vessels, and local hemoconcentration may increase viscous resistance in solid tumors (for a review, see Ref. 2). On the basis of these experimental data, Jain (2) hypothesized that the intratumor blood viscosity, \( \eta \), may be higher than the blood viscosity in normal tissues. However, whether this hypothesis is true and to what extent viscosity in normal tissues is lower than that in solid tumors are not known.

The objective of this study was, therefore, to directly measure the intratumor blood viscosity as a function of arterial hematocrit using the methodology of alternate perfusion developed by Whittaker and Winton (4). In this method (Fig. 1) an isolated tissue is first perfused ex vivo with an acellular medium of known Newtonian viscosity to calculate the constant geometric resistance, \( \zeta_0 \), from the reciprocal slope of the linear pressure-flow curves. Assuming that the geometric resistance remains unchanged with change of perfusate, a second, alternate perfusion with an RBC suspension of known hematocrit permits calculation of the blood viscosity within the tissue, \( \eta \). This approach to determine blood viscosity in vascular preparations under ex vivo conditions allows one to extrapolate to the in vivo situation. A prerequisite to measure intratumor viscosity using this methodology is the availability of an isolated tumor connected to the host by a single artery and a single vein. As
outflow was collected at atmospheric pressure.

varied between 5 and 120 mm Hg as perfusion rates were increased (and decreased) in a stepwise fashion from 4 to 60 ml/h. Venous isolated tumor housed in a humid perfusion chamber maintained at 37°C. Arterial pressure, measured proximal to the perfusion chamber, through a Silastic tube for oxygenation and into the artery of the tumor, was obtained. The preparation consisted exclusively of the tumor network.

Briefly the perfusion circuit consisted of a stirred reservoir and a multichannel peristaltic perfusion pump which delivered perfusate through a Silastic tube for oxygenation and into the artery of the tumor preparation of Cullino and Grantham (12, 13) to measure the geometric resistance of tumors. In the present investigation, by perfusing mammary adenocarcinoma ex vivo with an acellular KH medium of known Newtonian viscosity, \( \eta_{\text{known}} \), to obtain the geometric resistance, \( z_0 \). In the second step, an alternate perfusion with a RBC suspension allows calculation of the blood viscosity, \( \eta_{\text{intra}} \), if it is assumed that \( z_0 \) remains constant with change of perfusate.

discussed by Sevick and Jain (3), we have adapted the isolated tumor preparation of Gullino and Grantham (12, 13) to measure the geometric resistance of tumors. In the present investigation, by perfusing mammary adenocarcinoma ex vivo with an acellular KH medium of known Newtonian viscosity and alternately with RBC suspensions of varying hematocrit, the geometric resistance, \( z_0 \), and the intratumor blood viscosity, \( \eta \), are directly obtained. Results of intratumor blood viscosity are compared with those available for normal tissues in the literature, and clinical implications are discussed.

MATERIALS AND METHODS

Animals and Tumor. Mammary adenocarcinoma R3230AC (obtained from Biomeasure Laboratories, Hopkinton, MA) was carried s.c. in female Fischer 344 weanlings (Harlan Sprague-Dawley, Inc., Madison, WI) up to the 20th generation. The rats were fed ad libitum a standard laboratory diet (Purina, Ralston, NC) and subjected to alternating light and darkness for 12 h. Preparation of “Tissue-isolated” Tumors. Ovarian tissue-isolated tumors were prepared following the method of Cullino and Grantham (12, 13) to measure the geometric resistance of tumors. In the present investigation, by perfusing mammary adenocarcinoma ex vivo with an acellular KH medium of known Newtonian viscosity and alternately with RBC suspensions of varying hematocrit, the geometric resistance, \( z_0 \), and the intratumor blood viscosity, \( \eta \), are directly obtained. Results of intratumor blood viscosity are compared with those available for normal tissues in the literature, and clinical implications are discussed.

Materials and Methods

Step 1 Acellular perfusate

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\[ \text{Step 2 Cellular perfusate} \]

\[ (\eta_{\text{known}}, z_0_{\text{unknown}}) \]

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Fig. 1. Methodology for study of the determinants of blood flow in any tissue developed by Whitaker and Winton (4) and illustrated in this plot of perfusion rate versus pressure drop across the vascular bed. The first step of the procedure involves perfusing with an acellular medium of known Newtonian viscosity, \( \eta_{\text{known}} \), to obtain the geometric resistance, \( z_0 \). In the second step, an alternate perfusion with a RBC suspension allows calculation of the blood viscosity, \( \eta_{\text{intra}} \), if it is assumed that \( z_0 \) remains constant with change of perfusate.

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MATERIALS AND METHODS

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Preparation of “Tissue-isolated” Tumors. Ovarian tissue-isolated tumors were prepared following the method of Gullino and Grantham (12, 13) as adapted in our laboratory (14). The preparation consisted of the fat pad of the left ovary in which 0.1-0.2 cm³ of tumor slurry was implanted; all contralateral vessels as well as the ovary itself were ligated away prior to implantation and the former ovarian artery and vein remained as the only vessels feeding and draining the implanted tumors, such as edema formation and vascular integrity, and criteria for successful tumor perfusion were discussed by Sevick and Jain (3). These criteria were satisfied in the current experiments.

In another set of experiments, ex vivo alternate perfusion was performed with acellular KH of increasing Newtonian viscosities to verify that our technique could accurately detect changes in viscosity. As above, pressure measurements were made at varying perfusion rates first with KH and then with the more viscous KH in which high molecular weight dextran was added. In all of the alternate perfusions, the multichannel pump allowed simultaneous delivery of the alternate perfusates; the flow to the tumor was never stopped.

At the end of all tumor perfusions, vascular casts were made of the microvasculature through the infusion of either Microfil or methylmethacrylate polymer mixture (3). Only those experiments in which there were no vascular “leaks” of casting media are included in the results below.

Viscosity Measurements. The viscosities of all perfusates as well as that of tumor-effluent samples were measured at 37°C at a shear rate of 460 s⁻¹ using a cone/pllate digital viscometer (Model LVTDCP, Brookfield Engineering Laboratories, Stoughton, NJ). The viscosity of KH Perfusate 1 was found to be 0.9 g/m/s. Intratumor viscosity determinations were made from ratios of the linear pressure-flow slopes and the measurement of KH Newtonian viscosity as depicted in Fig. 1.

RBC Volume Determination. Hematocrit measurements of tumor-effluent and perfusable RBC suspensions were made using the microhematocrit capillary technique (Fisher Scientific, Pittsburgh, PA). Hemoglobin measurements were also obtained spectrophotometrically (ABL 3; Radiometer, Copenhagen, Denmark).

Tumor Volume Determination. After perfusion, tumor volume was determined from three tumor dimensions using the formula

\[ V = \pi L_1 L_2 L_3 / 6 \]  

where \( L_1 \), \( L_2 \), and \( L_3 \) are the three characteristic lengths of an ellipsoid. Tumor weight was calculated assuming the wet weight density of 1 g/cm³. Injection of polymer materials used for vascular casting and detection of vascular leaks prevented direct and accurate measurement of tumor weight.

RESULTS

Verification of Alternate Perfusion Technique for Viscometry. Table 1 lists the tumor weights and perfusable viscosities for 5 tumors (range, 0.6-9.8 g) alternately perfused with viscous KH...
(1.2–2.1 cP). In vitro (bulk) and intratumor perfusate viscosities were measured with a cone/plate viscometer and calculated from the ratio of the linear pressure-flow slopes, respectively. These two viscosities are not significantly different (P = 0.163, Student’s t-test). Fig. 2A is an example of a typical flow-pressure (Q-Ap) behavior of alternate tumor perfusion with 0.9 and 2.1 cP Krebs-Henseleit solutions. Fig. 2B illustrates the flow resistance, FR (mm Hg • h • g/cm³), calculated by dividing the arteriovenous pressure difference, Δp, by the perfusion rate, q, plotted against Δp. The FRs, calculated by dividing FR by z₀ obtained from the linear slope of the flow-pressure curve, are shown for the two alternate perfusions in Fig. 2C.

Blood Flow Resistances at Varying Hematocrit. Twelve tumors [2.2 ± 1.6 (SD) g; range, 0.5–6.6 g] were perfused with RBC suspensions of hematocrits between 1 and 60%. Fig. 3 is a plot of the tumor FR, Δp/q (mm Hg • h • g/cm³), versus venous hematocrit (%). For comparison, values obtained from in vivo perfusion of DS carcinosarcoma implanted in rat kidneys (15, 16) are also shown.

Intratumor Blood Viscosity at Varying Hematocrit. Fig. 4A shows the typical flow-pressure (Q-Δp) behavior at 0, 11, 35, and 57% HCT for a 2.1-g tumor and Table 2 lists the ratio of in vitro and intratumor blood viscosities measured with a cone/plate viscometer and calculated from the linear pressure-flow slopes, respectively. The composite of the apparent normal tissue and intratumor blood viscosities as a function of hematocrit for all 12 alternate perfusions is shown in Fig. 5. Paired Student t test analysis indicates that the intratumor blood viscosity is significantly lower (P < 0.0001) than that measured in vitro. To compare this reduction of intratumor blood viscosity with those for normal tissues, blood viscosities from previous studies of isolated dog hindlimb (4, 5, 9, 10, 17), isolated rabbit ear (7), rabbit hindlimb (6), rabbit heart (11), and dilated cat calf muscle (8) are included in Fig. 6A. Fig. 6B shows the 95% confidence level fits to the Casson model (18) for the current measurements of intratumor blood viscosity as well as for the original data taken from a previous study of the skeletal muscle of the dog hindlimb (4):

\[
\eta = \frac{1}{(1 - \text{HCT})^2}
\]

where HCT is expressed as a fraction. For intratumor measurements \(\alpha = 1.4 \pm 0.2\), and for intramuscle measurements \(\alpha = 0.7 \pm 0.3\) (±95% confidence interval). Above hematocrits of 20%, intratumor blood viscosity is elevated in comparison to that in skeletal muscle.

Intratumor Blood Viscosity as a Function of Perfusion Pressure. Fig. 4B illustrates the flow resistance, FR (mm Hg • h • g/cm³), plotted against arteriovenous pressure difference, Δp (mm Hg), for the typical alternate blood perfusion shown in Fig. 4A. The FRs, calculated by dividing the flow resistances with the linear slope of the flow-pressure-flow curve (i.e., with the product of z₀ and \(\eta\) as depicted in Fig. 1), do not collapse upon one another for alternate blood perfusion as shown in Fig. 4C as they do for alternate KH perfusion (Fig. 2C). For the same typical alternate tumor perfusion, the ratio of the FR interpolated from blood to FR interpolated from KH alternate perfusions is plotted against arteriovenous pressure difference, Δp (mm Hg), in Fig. 7. Assuming that geometric resistance remains unchanged with perfusate, Fig. 7 represents the relative intratumor blood viscosity, \(\eta\), versus arteriovenous pressure difference, Δp.

**DISCUSSION**

Several investigators have suggested changes in intratumor blood viscosity as a possible mechanism for tumor blood flow modifications due to physical (e.g., heat, hemodilution) and...
Accuracy of Methodology. Unlike blood, the viscosity of a Newtonian fluid (e.g., KH, KH with high molecular weight dextran) is independent of shear rate or vessel diameter. Therefore, the viscosity of KH with high molecular weight dextran solutions measured using an alternate perfusion method should be equal to that obtained using a cone/plate viscometer, as shown in Table 1. Furthermore, when the FR ($\Delta p/q$) is divided by the Newtonian perfusate viscosity ($\eta$) and constant geometric resistance, $z_0$, the resulting quantity, referred to as the RFR should be the same for perfusates of differing Newtonian viscosities and should reflect changes in geometric resistance with perfusion pressure ($\Delta p$). Only if this condition is satisfied can the alternate perfusion method be used to measure intratumor viscosity, $\eta$. As shown in Fig. 2C, the RFR curves for the viscous perfusates collapse upon one another; this observation confirms that the tissue preparation remains intact during the course of the experiment, and that geometric resistance and the dependence upon perfusion pressure ($\Delta p$) remain unchanged with the change of perfusate.

Blood Flow Resistances in Neoplastic Tissues. Since tumors exhibit poor perfusion characteristics, intratumor flow resistance ($FR = A/\Delta p$) is expected to be elevated in comparison to normal tissues. Fig. 3 shows the FR obtained from the linear portion of the flow-pressure ($Q-\Delta p$) curves at moderate to high perfusion pressures. Using in vivo perfusion of kidneys implanted with DS carcinosarcoma, Vaupel and Mueller-Klieser (16) also demonstrated increased intratumor FR. However, the values of FR in DS carcinosarcoma are significantly higher than those in R3230AC mammary adenocarcinoma; whether these differences are due to intertumor variations or due to differences in methodology is not known. In ex vivo perfusion, WBC and cancer cells are absent, whereas in in vivo perfusion, these cells are present. WBC and cancer cells are more rigid than RBC; as a result, their presence in perfusate would increase both intratumor blood viscosity, $\eta$, and flow resistance, FR ($2$).

Blood Viscosity in Normal and Neoplastic Tissues. The bulk viscosity of blood decreases with increasing shear rates and asymptotically reaches a constant value above shear rates of 100 $s^{-1}$. Furthermore, shear rate in a blood vessel is proportional to the blood velocity, $v$, and inversely proportional to the vessel diameter, $D$; since both $v$ and $D$ vary throughout the vasculature, it is not possible to ascribe a shear rate for a whole vascular bed. How, then, does one estimate the asymptotic viscosity for isolated tumor perfusion? In the work of Sevick and Jain (3) and in Fig. 2C, we have shown that the intratumor geometric resistance becomes a constant, $z_0$, above perfusion pressures of 20–40 mm Hg; since the flow-pressure ($Q-\Delta p$)
Therefore, by dividing the FR from RBC perfusion by the FR perfusate and that any increase in FR with alternate perfusion be attributed to both increases in $z$ and $\eta$. Fig. 2 demonstrates as the arterial pressure is lowered. Thus, increases in FR may viscosity, coupled with increased geometric resistance, is responsible for the poor perfusion characteristics of solid tumors. Therefore, one would expect intratumor $\eta$ to increase as the arterial pressure and, hence, intravascular shear rates are lowered due to rouleaux formation. This increased intratumor blood viscosity, coupled with increased geometric resistance, is responsible for the poor perfusion characteristics of solid tumors.

Dependence of Intratumor Blood Viscosity upon Perfusion Pressure. As stated in the “Introduction,” the viscosity of blood increases as shear rate is lowered due to rouleaux formation. Therefore, one would expect intratumor $\eta$ to increase as the arterial pressure and, hence, intravascular shear rates are lowered. However, as shown by Sewick and Jain (3), $z$ also increases as the arterial pressure is lowered. Thus, increases in FR may be attributed to both increases in $z$ and $\eta$. Fig. 2 demonstrates that, at a fixed pressure, $z$ remains unchanged with change of perfusate and that any increase in FR with alternate perfusion at a fixed pressure can be attributed to increased intratumor $\eta$. Therefore, by dividing the FR from RBC perfusion by the FR from KH perfusion at fixed pressures, we can obtain the relative intratumor $\eta$ as a function of perfusion pressure and independent of $z$ (Fig. 7). As expected, $\eta$ increases with decreasing $p_A$, and this increase in $\eta$ is more pronounced at higher hematocrits. Therefore, the higher the hematocrit and lower the perfusion pressure, the greater is the intratumor $\eta$. Using a similar method, Gustafsson et al. (9, 10) calculated the relative blood viscosity at varying perfusion pressures in the vasodilated dog hindlimb; their results are reproduced in Fig. 7, inset. This limited comparison indicates that the intratumor blood viscosity may substantially increase at higher perfusion pressures and lower hematocrits as compared to the blood viscosity in normal tissues. In fact, as shown for a typical tumor perfusion in Fig. 7, rouleaux formation may even prevent intratumor blood viscosity from reaching the asymptotic value at arterial pressures as high as 60 mm Hg at a hematocrit of 57%.

Mechanisms of Increased Viscous Resistance in Solid Tumors. As discussed in detail by Jain (2), there are at least three mechanisms responsible for the increased viscosity in tumors: (a) since tumor microvessels have relatively large diameters (25–27), the Fahraeus-Lindqvist effect (i.e., a reduction in blood viscosity in small vessels) may be less pronounced in tumors than in normal tissues; (b) due to larger vessel diameter and sluggish flow, the low shear rate in tumor vessels should be reflected in an increased intratumor blood viscosity; and (c) as blood passes through the tumor microvasculature, plasma losses between 5 and 14% cause an increase in intravascular hematocrit (14, 28, 29). This increase in microvessel HCT may also contribute towards increased $\eta$ in tumors. There are two factors which may contribute to a reduction $\eta$ in tumors: (a) reduction in systemic hematocrit with tumor growth; and (b) presence of RBC-free plasma channels (2). Our hypothesis that the factors contributing to an increase in viscosity dominate those causing a decrease in viscosity is substantiated by the current results. Some investigators have proposed that systemic hematocrit in cancer patients be increased through transfusion of erythrocytes to improve tumor oxygenation and radiosensitivity (30). While an increase in hematocrit would indeed enhance the oxygen-carrying capacity of blood in the tumor microcirculation, it also increases the intratumor blood viscosity (see Fig. 5) and proportionately decreases the tumor perfusion rate (see Equation A). Not surprisingly, Jung et al. (31) have demonstrated that within a certain range of hematocrits, the oxygen availability in tumors actually increases with decreasing hematocrit, suggesting hemodilution may improve radiosensitivity. This interplay between increased oxygen carrying capacity and viscosity may be responsible for the lack of radiosensitization with hemocoencentration seen in some studies (32).

We also propose here a fourth mechanism for increased intratumor $\eta$ involving the vascular morphology of tumors. It is evident from the microvascular casts resulting from polymer infusion that tumor microvessels are strikingly tortuous and winding as compared to the skeletal muscle microvessels (33). The secondary flow patterns in the tortuous tumor microvessels may tend to “mix” the two-phase flow described above thereby reducing the cell-free marginal layer and increasing microvessel hematocrit. Furthermore, several investigators have shown that the vessel length decreases with tumor growth (25–27). The decrease in vessel lengths effectively diminishes the development of two-phase flow in solid tumors. In normal tissues, as blood passes through the microvascular tree, a consistent resistance (30) of erythrocytes to improve tumor oxygenation and radiosensitivity (30). While an increase in hematocrit would indeed enhance the oxygen-carrying capacity of blood in the tumor microcirculation, it also increases the intratumor blood viscosity (see Fig. 5) and proportionately decreases the tumor perfusion rate (see Equation A). Not surprisingly, Jung et al. (31) have demonstrated that within a certain range of hematocrits, the oxygen availability in tumors actually increases with decreasing hematocrit, suggesting hemodilution may improve radiosensitivity. This interplay between increased oxygen carrying capacity and viscosity may be responsible for the lack of radiosensitization with hemocoencentration seen in some studies (32).

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BLOOD VISCOSITY IN SOLID TUMORS

Fig. 6. (A) Composite of relative intratumor blood viscosity measured at high perfusion pressures in the current study and in previous studies of normal tissues (see legend for details) versus perfusate hematocrit (%). (B) 95% confidence regions for the least squares fit to the Casson model (Equation C) which describes relative blood viscosity as a function of hematocrit. For the current measurements of intratumor blood viscosity $\alpha = 1.4 \pm 0.2$, and for those from a previous study of skeletal muscle $\alpha = 0.7 \pm 0.3$.

Fig. 7. Relative intratumor blood viscosity of the tumor perfusion illustrated in Fig. 4 versus perfusion pressure (mm Hg) for 11, 35, and 57% hematocrits. Inset, relative blood viscosity versus perfusion pressure in a skeletal muscle perfusion (9, 10).

Cell-free marginal layer (for a review see Ref. 34). The unique vascular structure of tumor microvessels may not permit the two-phase flow regimes required for consistent reduction in branching microvessels. Preliminary morphological investigation of the corrosion casts made from perfused tumors has shown the unusual pattern of small daughter vessels branching off of much larger feeding vessels; for example, we have observed a 10-µm vessel branching from a 300-µm vessel (33). This morphology may effectively reduce microvessel hematocrit (and thereby microvessel viscosity) in daughter vessels only if the cell-free marginal layer predominates in the tortuous tumor microvessels and in normal microvasculature.

Since RBC are numerically dominant in blood flow, we have examined the effect of RBC concentration (i.e., hematocrit) on the viscous resistance in the present work. In a cancer patient, both WBC and cancer cells are present in blood. Since cancer cells and WBC are significantly more rigid than RBC (35-37), their presence in the tumor microvasculature should increase intratumor $\alpha$ beyond the values reported in the current investigation. As discussed by Jain (2), the presence of these cells may be partially responsible for transient stasis and intermittent flow observed in both two- and three-dimensional tumors (38). On the basis of these studies of the determinants of tumor blood flow, we propose that short term or transient changes in tumor blood flow are mediated primarily by rheological factors while the long term flow reductions are mediated primarily by geometric factors as discussed by Sevick and Jain (3). This hypothesis, if general for various tumor types, could be useful in developing novel strategies for modulating tumor blood flow for therapeutic benefit. For example, our recent work has shown that interleukin 2-activated lymphocytes (referred to as lymphokine-activated killer cells) are considerably more rigid than unactivated lymphocytes.5 Therefore, injection of lymphokine-activated killer cells with interleukin 2 may increase viscous resistance in all normal organs of the body, but even more so in tumors. Hence, a preferential reduction in tumor flow would occur. Similar rheological mechanisms may be responsible for tumor blood flow reduction caused by other lymphokines, e.g., tumor necrosis factor.

The extent to which each of these five mechanisms (the effect of glycolcalyx on the luminal side of the endothelium on the intratumor viscosity is not known) outlined above contributes to increased viscous resistance in solid tumors is not known. Presumably, these contributions vary spatially, temporally, and...
from one tumor to another, giving rise to the dynamic and heterogeneous blood flow characteristics which have made the study of tumor blood flow difficult.

Implications. The efficacy of various therapies depends crucially upon tumor blood flow. For example, in radiotherapy, chemotherapy, and immunotherapy, the delivery of blood-borne substances to the tumor (e.g., oxygen, cytotoxic agents, antibodies, killer cells) would be improved if tumor blood flow rate could be increased and/or made spatially and temporally more uniform. On the other hand, the ability to heat a tumor during hyperthermia could be facilitated by reducing the tumor blood flow and thereby reducing the convective transport of heat. We have presented here an approach which can be used to measure the three determinants of tumor blood flow: Δp, z, and ϑ. This methodology can be now used to screen various physical and chemical agents which modulate blood flow by changing one or more of these parameters. An improved understanding of the mechanisms of tumor blood flow modification is likely to lead to novel strategies for management of solid tumors.

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