BIOPHYSICAL MODEL OF INTERSTITIAL FLUID PRESSURE IN CERVICAL TUMORS

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INTRODUCTION

Interstitial fluid pressure (IFP) was measured prior to treatment in patients with cervix cancer at Toronto's Princess Margaret Hospital as part of a prospective clinical study (Milosevic *et al*, 2001). The results showed that there was a strong correlation between elevated IFP and patient survival, regardless of other prognostic factors such as patient age, stage or lymphatic involvement. With a view to understanding this important correlation, we developed a biophysical model of interstitial fluid flow in cancer tissue based on Darcy's law (a mathematical law developed originally to describe water flow through porous media). Flow through the pressure-recording device was also modeled. The result is a mathematical expression showing how measured IFP changes as a function of time, after insertion of the measurement needle into the tumor.

CLINICAL MEASUREMENTS

The technique for measuring IFP in patients with cervix cancer has been described fully (Milosevic *et al*, 2001). We review it very briefly here. An anesthetized patient was examined in the lithotomy position. A 22-gauge spinal needle whose length was 6.5 cm and internal diameter 0.02 cm was constructed with a side-port 2 – 4 cm in length. The needle tip was inserted horizontally into the tumor to a depth of 2 cm; the other end of the needle was connected to a polyethylene tube, which led to a manometer for measurement of pressure. After insertion, measured pressure rose for half to one minute, approaching its steady state value asymptotically, as shown in Fig. 1.

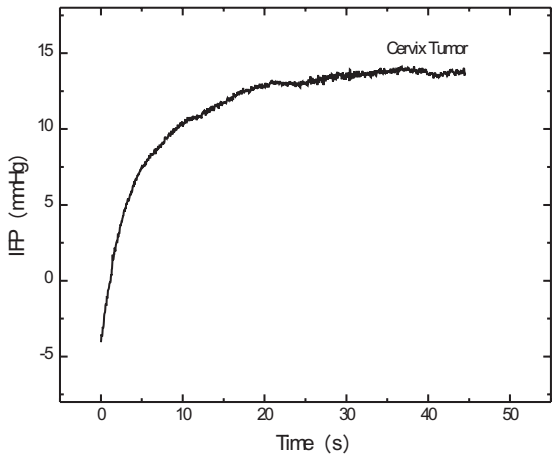

Figure 1. Rise of interstitial fluid pressure in cervix tumor after insertion of needle.

The time constant of the measurement system itself was measured (needle + tubing + manometer + fluid) using the "pop test" described by Milnor (1989). Briefly, a balloon was inflated over the end of the measurement needle, which had been filled with fluid. The balloon was then burst, and the time constant of the system was recorded.

MATHEMATICAL MODEL

Referring now to Fig. 2, we see that the flow system consists of two components: the pressure measuring system at the left-hand side joined to a horizontal cylinder of tissue, which is modeled as a filter bed, on the right-hand side.

Measurement System

Flow through the needle was taken to be laminar in nature and governed by Poiseuille's law, which can be represented here simply in the form

$$Q = \Delta P / R \qquad (1)$$

where Q is the flow rate, R the resistance, and ΔP the pressure drop across the length, L, of the needle. In Fig. 2 we see that ΔP is given by

$$\Delta P = p_1 - \rho g h \qquad (2)$$

where p_1 is the IFP at the exit from the filter bed, ρ is the density of water, g the acceleration due to gravity and h the height of a column of water representing the manometer. Expressing flow in terms of the height of the water column, h, and the internal cross-sectional area of the needle, A, we have

$$Q = A\frac{dh}{dt} \qquad (3)$$

Assembling the latter three equations,

$$\frac{dh}{dt} + \frac{\rho g}{AR} h = \frac{p_1}{AR} \qquad (4)$$

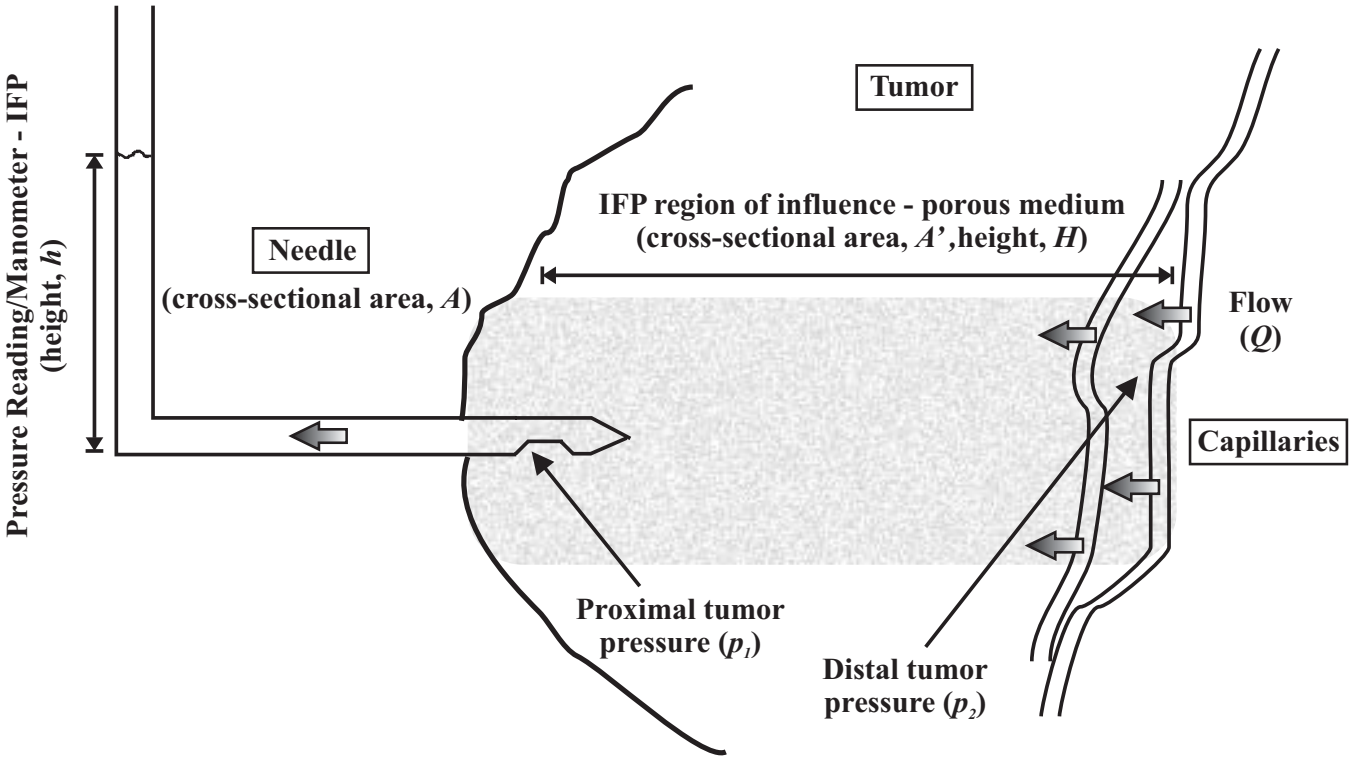

Figure 2. Schematic diagram of needle and manometer system (on left) and cylinder of tumor tissue (on right). Flow in the needle is assumed to laminar in nature and expressed by Poiseuille's law; flow in the tissue is assumed to be governed by Darcy's law.

Solving this differential equation we find that the time constant, τ_n governing the rise of fluid in the manometer is equal to $AR/\rho g \approx 1.3$ s, using the dimensions of the measuring system and evaluating R from Poiseuille's law.

Cylinder of tumor tissue

For the geometrical details governing the use of Darcy's law in the present context please refer to the recent paper by Khosravani *et al* (Khosravani *et al*, 2004, in press). In the final analysis, Darcy's law assumes a form not unlike that of Poiseuille's law:

$$Q = \frac{K'A'}{H}(p_2 - p_1) \qquad (5)$$

where K' is a constant that incorporates properties of the fluid and the porous (cellular) medium (cf *hydraulic conductivity*), A' and H are the sectional area and height respectively of the cylinder of tissue. p_2 is the IFP at entrance to the cylinder of tissue (Fig. 2).

Again replacing flow rate, Q, by its value in Eq. (3), and eliminating the variable p_1 using Eq. (4), we have the final form of our differential equation:

$$\frac{dh}{dt}\left[1+\frac{R'}{R}\right]+\frac{\rho g}{AR}h=\frac{p_2}{AR} \qquad (6)$$

where $R' = H/(K'A')$. The linear differential equation is solved by standard methods to give $P_{IPF}(t) = \rho gh(t)$, the manometer pressure at anytime, t, in terms of the initial pressure, $p_0 = \rho gh(0)$:

$$P_{IFP}(t) = p_2 + (p_0 - p_2)\exp\left[\frac{-\rho g t}{AR[1+R'/R]}\right] \qquad (7)$$

We expect, then, a monoexponential rise in manometer pressure, with time constant for the whole system given by

$$\tau_{n+t} = \frac{A}{\rho g}[R + R'] \qquad (8)$$

When t becomes large, P_{IFP} approaches a steady state.

RESULTS

From Eq. (7) we are led to believe that measured pressure curves will be governed by an equation of the simple form

$$y = A_1 - A_2 e^{-kt}$$

where A_1 and A_2 are constants. This was confirmed by semi-log plots made on 152 clinically measured curves from 42 patients. Typical results are shown in Fig. 3:

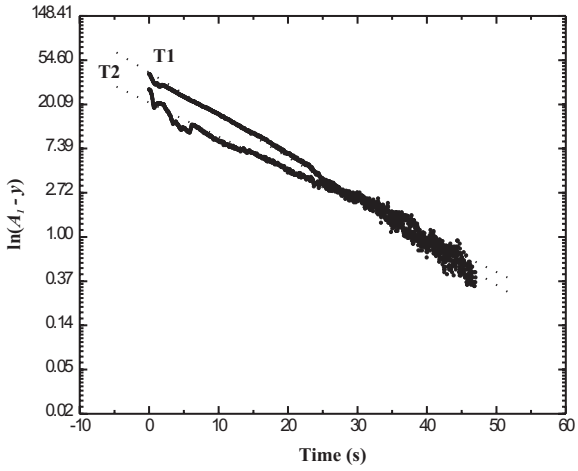

Figure 3. ln (A_1 –y) plotted against t for two measured pressure-time curves. The results show that the data fall nearly on a straight line, as expected.

One is led, by the mathematical model, to expect no correlation between the maximum or steady state IFP and the time constant governing passage to the steady state. Indeed, statistical studies bore out this prediction: the two variables showed a correlation coefficient of about 0.09.

Measured values of τ_n, the time constant of the measurement system, were 0.30 ± 0.05 s, which compares with the theoretical value of 1.3 s, based on the laminar flow assumption.

The overall time constant of the system was measured to be 10 – 20 s. That is, the time constant of the cylinder of tissue is considerably greater than that of the measurement system alone. Hence, in Eq.(8), we may, for purposes of approximation, neglect the first term on the right-hand side, and set

$$\tau_{n+t} \approx \frac{AR'}{\rho g} = \frac{A}{\rho g}\frac{H}{A'K'} \qquad (9)$$

or

$$K' = \frac{A}{\rho g \tau_{n+t}}\frac{H}{A'} \qquad (10)$$

Using values obtained from tissue histology, we can estimate the value of K' to be about 3.24×10^{-9} cm^4 / (dyn s).

Table 1: Summary of observations from 42 patients, providing 152 IPF recordings; randomly selected from a large group of patients studied by Milosevic *et al*.

	Mean of means	Std Deviation
Steady state IFP (mm Hg.)	22 ± 2	9
IFP time constant (s)	14 ± 1	9

The two variables, steady state IFP and time constant, are not significantly correlated.

DISCUSSION

We used a randomly selected subset of measurements of interstitial fluid pressure (IFP), taken in clinic from tumors in patients with cervix cancer. Milosevic *et al* (2001) had observed a strong correlation between elevated IFP and patient mortality, independent of other factors. We constructed a biophysical model of fluid flow in the tumor and fluid flow in the measurement apparatus. In this way we derived a mathematical function, Eq. (7), relating the time course of IFP immediately after penetration of the tumor by a needle connected to the manometer. The model revealed no correlation between steady state IFP and the time constant governing rise in IFP; and none was measured clinically. The model permitted estimation of an index of hydraulic conductivity, *K′*, from *in vivo* measurements. The value agreed well with previous measurements made by other investigators in animal studies.

As may be seen from Eq. (7), $P_{IFP}(t) \to p_2$ as $t \to \infty$. Referring to Fig. 2, we see that p_2 is the steady pressure at the capillary end of the cylinder of tumor tissue. Hence we are led to suspect that it is capillary blood pressure rather than tissue factors that contribute most strongly to the steady, elevated tumor interstitial fluid pressure.

ACKNOWLEDGEMENTS

This research has been supported by the National Cancer Institute of Canada, and by the Natural Sciences and Engineering Research Council of Canada.

REFERENCES

Khosravani, H., Chugh, B., Milosevic, M.F., and Norwich, K.H. 2004. Time response of interstitial fluid pressure measurements in cervix cancer. *Microvascular Research*, in press.

Milnor, W.R. 1989. *Hemodynamics*, 2nd edition, Williams & Wilkins, Baltimore, page 312.

Milosevic, M., Fyles, A., Hedley, D, Pintilie, M., Levin, W., Manchul, L., and Hill, R. 2001. Interstitial fluid pressure predicts survival in patients with cervix cancer independent of clinical prognostic factors and tumor oxygen measurements. *Cancer Research*, 61 (17), 6400 – 6405.