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A CONFINED COMPRESSION TECHNIQUE FOR HYDRAULIC CONDUCTIVITY MEASUREMENT IN SOFT TISSUES

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INTRODUCTION

Multiphasic tissue models have been used extensively to predict the behavior of cartilaginous tissues [1]. Their application to other soft tissues, however, has often been overlooked. Unlike the more commonly used continuum model of the viscoelastic solid [2], multiphasic models allow us to infer the behaviors and properties of tissue subcomponents by observing the behavior of the tissue whole. As a great deal of tissue function and structure is related to the control and transport of fluids and fluid-borne agents, there is clearly a need for this insight in all tissues. For example, there has been a great deal of interest recently in the possibility of modifying the flow properties of solid tumors and other tissues to allow the targeted delivery of large molecular weight drugs, such as chemotherapeutic or genetic agents [3-4]. It is well known that the high interstitial fluid pressures, confused vasculature, and lack of a lymphatic system prevent the effective distribution of directly injected or systemically administered drugs into tumors [3]. Increasing the effective permeability of these tumors can ameliorate these issues and allow for more effective treatment. A handful of studies have found that the biphasic model, along with some basic experimental tools, can reasonably represent the flow properties of tumors [4-5]. In this paper, we describe a technique using a simple confined compression experiment with the biphasic model to measure the hydraulic conductivity of samples of cardiac tissue.

THEORETICAL MODEL

The biphasic model treats tissue as a mixture of an incompressible fluid and porous elastic solid. In mixture theory, each point in physical space is considered to be simultaneously occupied by some volume fraction of each phase, such that a vacuum is disallowed. That is, if ϕ^f and ϕ^s are respectively the volume fractions of the fluid and the solid, then $\phi^f + \phi^s = 1$. The phases move independently with velocities $\mathbf{v}^f$ and $\mathbf{v}^s$, but interact such that each phase independently as well as the entire mixture obey the laws of physics. The interaction equations express the overall conservation of matter, momentum and energy.

The constitutive equations of each phase must ultimately be inferred from experiment or the fundamental principles of statistical mechanics. In our case, it makes sense to model the fluid as incompressible and the solid as elastic, so that:

$$\sigma_{ij}^f = -p\phi^f \delta_{ij} \tag{1}$$

$$\sigma_{ij}^s = -p\phi^s \delta_{ij} + H_{ijkl}\varepsilon_{kl}\,, \tag{2}$$

where p is the fluid pressure, ε_{ij} the strain, H_{ijkl} the elastic constants and σ_{ij}^f and σ_{ij}^s the stresses in the fluid and solid. The volumetric force felt by fluid flowing through the solid may be written

$$\boldsymbol{\pi}_i^f = D\left(\mathbf{v}_i^s - \mathbf{v}_i^f\right) - p\partial_i\phi^f\,, \tag{3}$$

where D is a constant and $\boldsymbol{\pi}_i^s = -\boldsymbol{\pi}_i^f$.

The confined compression experiment is set up to reduce the problem to 1D as follows. A plug of tissue is placed in a constricting chamber where it may be compressed by a piston. At one end of the tissue ($z=0$) is a filter which allows fluid to flow relatively freely from that end of the tissue. Thus the fluid pressure here must be zero. The

other end ($z=h$) is closed so that fluid cannot flow. Because the fluid is relatively incompressible, the tissue will only deform from the filter end as the fluid escapes. As the tissue is compressed, the net displacement and stress,

$$U(t) = u(0,t) - u(h,t) = u(0,t), \tag{4}$$

$$\Sigma(t) = \sigma^s(0,t) + \sigma^f(0,t) = H\partial_z u(0,t), \tag{5}$$

(with $p(0,t) = 0$) are measured. Because of eq. (5), an *a priori* estimate of the maximum local strain is available given an estimate of the tissue elastic constant. Combining equations (1), (3), and the balance of forces, we arrive at:

$$\phi^f H\partial_z^2 u = D\left(v^s - v^f\right). \tag{6}$$

The continuity condition:

$$\phi^f v^f + \phi^s v^s = 0, \tag{7}$$

may be finally used to replace v^f in terms of v^s:

$$\partial_z^2 u = \left[D / C\left(\phi^f\right)^2\right] v^s \approx K_{eff} C^{-1} \partial_t u, \tag{8}$$

where $K_{eff}^{-1} \equiv \left(\phi^f\right)^2 / D$ can be identified as the Darcy law hydraulic conductivity. ϕ^f is generally compression dependent, so that K_{eff} is often empirically written as $K_0 \exp\left(-M\partial_z u\right)$. For small strains, ϕ^f may be taken as a constant, and eq. (8) is just the equation of linear diffusion ("heat equation"). The linear version of the equation may be solved analytically as an infinite series of decaying cosines, however, no analytic solution exists for the nonlinear equation.

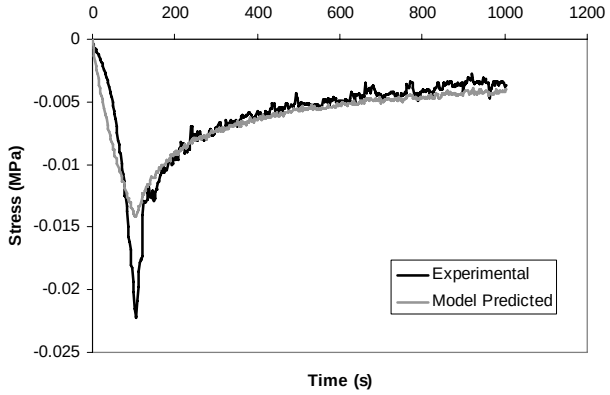

Figure 1. The model vs. experimental stress for the second load cycle of sample 5.

EXPERIMENTAL PROCEDURE

Ten right circular cylinders, about 12.5 mm in diameter and 5 mm in height, were cut from fresh bovine heart muscle and tested within 24 hours of sacrifice. Samples were placed in a 12.50 mm polycarbonate cylinder with a close fitting piston (-0.01 mm). A 40 μm sintered filter allowed fluid to escape from the bottom of the cylinder. The piston was placed in a bath of buffered saline maintained at 36 ^{o}C that was mounted in a commercial tensile machine. A 100 N load cell (0.1 % absolute error) measured load while a LVDT measured displacement (0.1 % absolute error). The sample was ramped in compression with displacement control at 0.003 mm/s until a peak force of 3 N was reached. The peak displacement was then held for 900 s. The sample was then unloaded and allowed to recover for a several minutes before loading again. The applied displacement and the resulting force data were collected.

Using the applied displacement as the boundary condition, the solution of eq. 8 was approximated with forward finite differences in time and central finite differences in space as a function of the material constants H and K_{eff}. The resulting stress at the boundary was then predicted. The rms error between the measured stress at the boundary and the model predicted stress was minimized by varying H and K_{eff} with a Levenberg-Marquardt algorithm. The optimal H and K_{eff} were determined for each of the first two cycles.

RESULTS

The linearized model could not capture the relatively fast changes in the stress as it reached the peak load, but was able to predict the stress relaxation portion of the test (Figure 1). For the 10 samples tested H = 0.007 ± 0.004 MPa and K_{eff} = 16 ± 12 MPa·s/mm^2 for the first cycle and H = 0.011 ± 0.008 MPa and K_{eff} = 48 ± 30 MPa·s/mm^2 for the second cycle. H (p = 0.01) and K_{eff} (p = 0.0007) were significantly different from cycle one to cycle two using a paired two-tailed t-test. For comparison, measured values for the series of tumor types tested in ref. 4 ranged from H = (0.007 to 0.040) MPa and K_{eff} = (0.54 to 14.5) MPa·s/mm^2.

As the fluid flows out of one end of the tissue, the fluid channels at this end collapse, resulting in an effective reduction in the local permeability. A higher load is then needed to push additional fluid out. This behavior is not modeled by the linearized equation and is responsible for the mismatch in the load peaks. Since the samples were not allowed to relax completely back to the zero state between cycles, the effect carries over into the second cycle, resulting in new effective values for H, and particularly for K_{eff}.

CONCLUSION

Using the equations of the biphasic tissue model, we found it possible to measure soft tissue flow properties in a simple compression test. If large local strains are expected, a nonlinear correction is needed.

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