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Research Paper

Solid–extracellular fluid interaction and damage in the mechanical response of rat brain tissue under confined compression

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ABSTRACT

The mechanical processes that underlie mild traumatic brain injury from physical insults are not well understood. One aspect in particular that has not been examined is the tissue fluid, which is known to be critical in the mechanical function of other organs. To investigate the contributions of solid–fluid interactions to brain tissue mechanics, we performed confined compression tests, that force the extracellular fluid (ECF) to flow in the direction of the deformation, on 6.35 mm diameter, 3 mm long cylindrical samples excised from various regions of rat brains. Two types of tests in deformation control, (1) quasi-static, slow and moderate constant strain rate tests at 0.64×10^{-5}/s, 0.001/s and 1/s to large strains and (2) several applications of slow linear deformation to 5% strain each followed by stress relaxation are employed to explore the solid–fluid interaction. At slow and moderate compressive strain rates, we observed stress peaks in the applied strain range at about 11%, whose magnitudes exhibited statistically significant dependence on strain rate. These data suggest that the ECF carries load until the tissue is sufficiently damaged to permit pathological fluid flow. Under the slow ramp rate in the ramp-relaxation cycles protocol, commonly used to estimate permeability, the stress relaxes to zero after the first cycle, rather than to a non-zero equilibrium stress corresponding to the applied strain, which further implicates mechanical damage. Magnetic resonance imaging (MRI) of changes in tissue microstructure during confined compression, before and after compression, provides further evidence of tissue damage. The solid–fluid interactions, reflected in the morphology of the stress–stretch curves and supported by the MRI data, suggest that increases in hydrostatic pressure in the ECF may contribute to mechanical damage of brain tissue.

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1. Introduction

Subtle small-scale mechanical damage mechanisms in brain tissue that can modify brain function may be involved in the initial cause of mild traumatic brain injury (mTBI). Exposure to an external blast or to an impact may induce in the brain tissue a deformation wave whose longitudinal component compresses the tissue, and compression is known to induce cell damage in brain cell cultures (Cullen et al., 2011). Here we focus on the mechanical effect of compression on the integrity of the brain tissue rather than on shearing as might result from the shear component of the wave. Often overlooked in mechanical testing is the fact that brain tissue is biphasic, composed of water and solid phases, and its mechanical response is strongly influenced by the high fluid content of the brain tissue itself, whether extracellular or intracellular. Brain tissue may have a different mechanical response than load-bearing soft tissue with high fluid content because of structural differences. Brain tissue carries little load in vivo, in contrast to other soft tissues, such as cartilage or arteries, which are structured to return to the original configuration without damage after normal physiological deformation.

The configuration of brain tissue is maintained by interaction between the cellular solid matter and the brain extracellular fluid (ECF). The pattern of links between neurons, astrocytes and each other forms a mechanically weak network structure that maintains, along with the capillaries, the structural integrity of the brain by a combination of tension in axons, dendrites, and glial processes that is balanced by hydrostatic pressure in the ECF (Van Essen, 1997). Under mechanical deformation, disruption of the equilibrium balance of tension in the axons, dendrites and glial processes with the ECF hydrostatic pressure may lead to mechanical damage. One possible related mechanism is excessive axonal strain because stretch tests on isolated neurons show that the critical axonal tensile strain for axonal damage is about 20% (Bain and Meaney, 2000).

Brain injuries have been associated with the internal stress and strain that the brain undergoes during an external insult. However, no technique is available to determine the stress–strain relation inside the brain in vivo during the insult. In order to improve our understanding of these internal phenomena, the confined compression test can be used to investigate uniaxial solid–fluid interaction in the biphasic tissue. Confined compression testing offers advantages over experimental techniques that others have used to investigate the mechanical properties of brain tissue because a confined compression test, which may be idealized as uniaxial, applies a uniaxial deformation and ensures nearly parallel uniaxial flow of the ECF under the load. Interpretations of fluid flow cannot be made analytically from unconfined compression tests, which have traditionally been used to obtain uniaxial data for brain tissue (e.g. Prevost et al., 2011; Miller and Chinzei, 2002; Prange and Margulies, 2002), because in such tests fluid can move in bulk flow transversely to the direction of compression. Also, the unconfined compression test and the confined compression test have different boundary conditions. The internal fluid flow in confined compression is commonly assumed to be uniaxial to estimate the permeability of load-bearing soft tissue like cartilage (e.g. Ateshian et al., 1997), but the test rarely has been applied to brain tissue.

In this study, we investigate the mechanical response to compression of brain tissues from rats, which are routinely used in brain tissue research. Here the confined compression test is employed to explore the influence of fluid content on the uniaxial compressive deformation of rat brain tissue and to attempt a computation of the permeability coefficient. Our hypothesis is that some aspects of the non-equilibrium mechanical response of brain tissue to compression are due to solid–fluid interactions that depend on changes in the ECF hydrostatic pressure and that may induce tissue damage, in contrast to load-bearing soft tissue such as cartilage.

Standard techniques of measuring damage do not apply to our tests that seek the transient initial response to compression. Subsequent cyclic loading is not useful because brain tissue differs from load-bearing soft tissue, such as cartilage or arteries, in that a single load application of moderate strain can change its mechanical properties, as we show. Similarly, preconditioning specimens to reach a steady state (e.g. Cheng and Bilston, 2007) eliminates the transient response. Another common practice is to verify soft tissue damage using histology, but reported applications to brain tissue suggest that histology might not detect the subtle rearrangement of substructures that may be involved in our tests (e.g. Shulyakov et al., 2009; Prange and Margulies, 2002), as opposed to severe loads for which silver staining captures axoplasm flow from the severed ends of axons (e.g. Strich, 1961). Our main alternative technique examines the morphology of stress–stretch curves for the compressive response that may include indicators of damage, such as spikes on the curve due to reaction force drops, peaks in the stress, relaxation of the tissue to zero stress, and softening. The assumption is that many types of biodamage alter the stress carrying capability of the brain tissue. Changes in permeability may also indicate damage. Since dynamic imaging of the substructures of the brain during injury is not currently possible, we statically apply diffusion MRI after deformation to seek further indicators of damage. These results suggest that the confined compression test might serve as a useful in vitro model for studying fluid–solid related damage. The tests presented establish a baseline that may be later compared to the mechanical response under high strain rate deformation of brain tissue.

2. Methods and materials

2.1. *Specimen preparation*

Whole rat brains were harvested from freshly euthanized Sprague Dawley rats (6–9 months), whose brains are approximately 2 cm long and 1.2 cm wide. To produce 6 specimens from each rat brain for the confined compression tests, the specimens are carefully dissected using a scalpel, guided by a specially built fixture, to slice four 3 mm thick sagittal planar slabs from the cerebrum, two from each hemisphere, and two 3 mm thick frontal planar slabs from the cerebellum. Tissue slices were placed in Phosphate Buffered Saline (PBS) to

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