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● *Original Contribution*

A CUMULATIVE SHEAR MECHANISM FOR TISSUE DAMAGE INITIATION IN SHOCK-WAVE LITHOTRIPSY

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Abstract—Evidence suggests that inertial cavitation plays an important role in the renal injury incurred during shock-wave lithotripsy. However, it is unclear how tissue damage is initiated, and significant injury typically occurs only after a sufficient dose of shock waves. Although it has been suggested that shock-induced shearing might initiate injury, estimates indicate that individual shocks do not produce sufficient shear to do so. In this paper, we hypothesize that the cumulative shear of the many shocks is damaging. This mechanism depends on whether there is sufficient time between shocks for tissue to relax to its unstrained state. We investigate the mechanism with a physics-based simulation model, wherein the basement membranes that define the tubules and vessels in the inner medulla are represented as elastic shells surrounded by viscous fluid. Material properties are estimated from *in-vitro* tests of renal basement membranes and documented mechanical properties of cells and extracellular gels. Estimates for the net shear deformation from a typical lithotripter shock (~0.1%) are found from a separate dynamic shock simulation. The results suggest that the larger interstitial volume (~40%) near the papilla tip gives the tissue there a relaxation time comparable to clinical shock delivery rates (~1 Hz), thus allowing shear to accumulate. Away from the papilla tip, where the interstitial volume is smaller (~20%), the model tissue relaxes completely before the next shock would be delivered. Implications of the model are that slower delivery rates and broader focal zones should both decrease injury, consistent with some recent observations. (E-mail: jbfreund@uiuc.edu)

Key Words: **Shock-wave lithotripsy, Renal injury, Tissue damage, Numerical simulation.**

INTRODUCTION

Shock wave lithotripsy (SWL) is a treatment widely used for urinary tract calculi, but it has been found that more renal trauma accompanies treatment than initially thought (Evan and McAteer 1996; Evan et al. 1998). Acute renal injury occurs to some degree in virtually all patients, and some cases have been reported in which damage is severe. This trauma is thought to lead to chronic complications such as an increased risk of hypertension (Lingeman et al. 2003; Krambeck et al. 2006) and there appears to be a link between SWL and the occurrence of new-onset diabetes (Krambeck et al. 2006). Studies of pig kidneys (*e.g.*, Evan et al. 1996) just after treatment with SWL show that the damage is extensive and occurs during treatment rather than from longer-term hypoxia resulting from vascular damage (Shao et al. 2003). It appears that as they are delivered, the shock waves rupture the basement membranes of vessels and tubules and destroy cells (Shao et al. 2003).

Inertial cavitation is thought to be the mechanism responsible for the greatest part of the observed damage (Bailey et al. 2003). The precise mechanism(s) of bubble action in vascular injury, however, are not known, but bubble expansion or bubble collapse and rebound may all be involved. The rapid collapse and rebound of bubbles is known to be potentially destructive to surrounding material (Sturtevant 1996; Zhong et al. 2001). The importance of cavitation in renal injury is supported by results for inverted shock waves, which are generated *via* a pressure release reflector. These are significantly less destructive (Evan et al. 2002), presumably because the trailing wave is compressive and therefore suppresses cavitation. Inverted shock waves have also been shown to reduce hemolysis relative to the

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standard lithotripter shocks when directed at *in-vitro* samples of red blood cells (Evan et al. 2002). The acoustic signature of inertial cavitation has been observed in pig kidney tissue after ~1000 shocks (Bailey et al. 2005), which is comparable to the number necessary for significant tissue injury (Evan et al. 1998), although specific thresholds have not yet been determined.

Questions remain, however, as to how cavitation and cavitation damage are initiated. For example, why are so many (~1000) shock waves necessary before cavitation signatures and significant injury are observed in kidney tissue (Bailey et al. 2005)? It has been suggested that bleeding is a necessary prelude to extensive cavitation (Shao et al. 2003). In this view, the accumulation of noncirculating blood in the lesion would provide favorable conditions for extensive and spreading cavitation damage. At normal physiological conditions, blood flow speeds, which are estimated to be ~0.5 mm/s in the vasa recta (Jamison and Kriz 1982) and would probably have a similar speed in the capillaries, seem fast enough to remove nucleation sites before more than a few shocks could grow them into damaging cavitation bubbles. It has been proposed in conjunction with *in-vitro* models that the initial rupture might be caused by expanding cavitation bubbles (Zhong et al. 2001), although this has not yet been observed *in vivo*.

It is also possible that the initial hemorrhage does not involve bubbles at all. Although damage was modest and localized, inverted wave studies still showed hemorrhaging near the papilla tip (Evan et al. 2002). Shock wave–induced shearing is another proposed injury mechanism, but as we discuss in more detail in following sections, the shear due to a single shock is estimated to be insufficient to tear basement membranes. It has been proposed that the renal papilla structure makes it particularly prone to the focusing of shock waves scattered by its acoustic inhomogeneities (Howard and Sturtevant 1997). However, based on the speed of sound in its constituent components, the papilla is not expected to be significantly more acoustically inhomogeneous than other parts of the kidney that seem to be less susceptible to damage in the absence of cavitation (Evan et al. 2002).

In this paper we investigate the possibility that the greater interstitial volume near the papilla tip makes it particularly susceptible to shear accumulation during repeated shock applications, leading eventually to damage and hemorrhage. Once hemorrhage has occurred, pooled blood could then give rise to more extensive cavitation damage as previously discussed. The net shear displacement that remains after the passing of the focused wave is computed from the simulation results of Tanguay and Colonius (2003). A simulation model of the inner medulla, which is constructed based on its known structure and estimates of the material properties of its components, suggests that shear strain can indeed accumulate near the papilla tip.

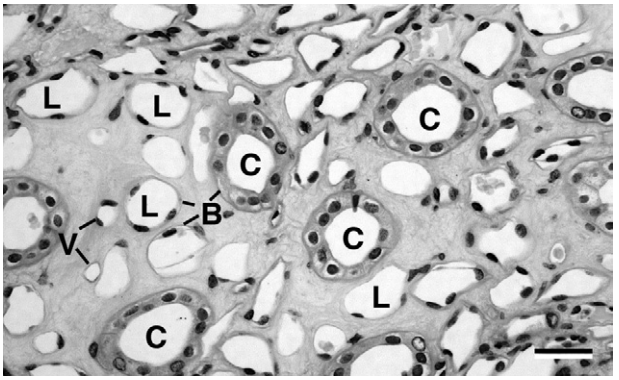

Fig. 1. A light micrograph of a transverse cross section of an inner medulla near the papilla tip (human): collecting ducts (C), loop limbs (L) and blood vessels (V). Each tubule is defined by a basement membrane (B) as discussed in the text. The scale bar is ~40 μm.

MATERIALS AND METHODS

Tissue: structure and approximate properties

The structural properties of the tissue of the inner medulla (Fig. 1) appear to be set by the relatively stiff and strong basement membranes of the thin limbs of the loops of Henle, larger collecting ducts and small blood vessels (vasa recta and capillaries). Collectively, we refer to these simply as tubes. Although there are a few branch points, these tubes are generally aligned in parallel (Jamison and Kriz 1982). The interstitial space between the tubes in the inner medulla is filled with interstitial cells surrounded by extracellular matrix material referred to here as an interstitial gel. The cells typically span between two or more tubes or vessels, suggesting a structural role (Madsen and Tisher 2004). Higher in the medulla and the cortex, they are less ordered and resemble typical fibroblasts (Jamison and Kriz 1982). The interstitial gel is made of a flocculent polysaccharide material (Madsen and Tisher 2004). The fraction of the inner medulla that is interstitial space increases into the papilla and toward its tip as discussed in the following, where we discuss our model's geometric parameterization.

The pressure-diameter relation of rabbit renal tubule basement membranes has been measured by Welling et al. (1995), with additional references therein. These were found to be similar to properties of the basement membranes of frog capillaries and rat venules (Swane et al. 1989), which suggests at least a degree of universality to basement membrane properties. They are surprisingly stiff, with elasticity comparable to that of tendon (Welling et al. 1995). A luminal pressure increase of as much