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● *Original Contribution*

POTENTIAL FEMORAL HEAD OSTEONECROSIS MODEL INDUCED BY HIGH-INTENSITY FOCUSED ULTRASOUND

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Abstract—Osteonecrosis of the femoral head is a common disease that can result in complex hip replacement. To evaluate potential treatments, a model that consistently creates osteonecrosis is needed. We studied and demonstrated the possibility of developing an osteonecrosis model using high-intensity focused ultrasound (HIFU) on canine femora *in vitro*. To achieve these goals, the temperature in the medullary cavity of the femoral head was measured. A phenomenological model was developed to fit the measured temperature variations with the HIFU parameters for similar HIFU experiments on femoral heads. The average temperature discrepancy between model and measured values was less than 0.83°C. Histology confirmed that the temperature in the medullary cavity can be elevated to a level at which an acute thermal injury is created. HIFU has the potential to be used in a non-invasive model of osteonecrosis. (E-mail: mcclures@iastate.edu) © 2013 World Federation for Ultrasound in Medicine & Biology.

Key Words: **High-intensity focused ultrasound, Osteonecrosis, Canine femoral head, Mathematical models.**

INTRODUCTION

Osteonecrosis of the femoral head affects more than 20,000 people in the United States yearly (Lavernia et al. 1999). Its development can be attributed to a number of disease pathways (Pavelka 2000). For example, multiple pre-disposing factors, including chronic steroid administration, alcoholism and trauma, can all contribute to the development of osteonecrosis. There are also a large number of cases that are idiopathic (Pavelka 2000). The objective of treatment is to arrest the disease in its early stages to stop progression prior to femoral head collapse and resultant osteoarthritis of the coxofemoral joint (Pavelka 2000). Once the latter have occurred, the condition is no longer considered reversible and often results in the need for total hip replacement (Steinberg et al. 1995).

Although the pathogenesis of osteonecrosis of the femoral head is not fully understood, there are some common histologic findings including decreased blood flow with fibrin thrombi in arterioles with subsequent ischemic damage, osteonecrosis and limited ability to regenerate (Inoue and Ono 1979, Kerachian et al. 2006). Evaluation of therapeutic modalities for treatment of osteonecrosis in humans requires a suitable experimental model that can induce a similar histologic and temporal osteonecrosis. Numerous models in multiple species have been used (Boss and Misselevich 2003; Conzemius et al. 2002; Fan et al. 2011). Commonly, drugs and surgical intervention are used to develop such models. Corticosteroids, lipopolysaccharide and alcohol have been administered systemically to induce osteonecrotic changes. However, these substances also induce other unwanted systemic changes similar to naturally occurring diseases such as hyperadrenocorticism and endotoxemia. Surgical approaches to disrupt the vascular supply and collateral circulation around the joint capsule have been used in multiple laboratory species (Bejar et al. 2005; Fan et al. 2011). For example, surgical approaches that might induce physical insult by cryotherapy are frequently used and have been employed in emus to simulate a bipedal model (Conzemius et al. 2002). The morbidity associated with current osteonecrosis models is undesirable because of the systemic effects of drugs and the need for invasive procedures. An ideal alternative method would induce ischemia with osteonecrosis without the side effects of drugs and surgical approaches.

High-intensity focused ultrasound (HIFU) has the potential to non-invasively induce osteonecrosis by

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thermally inducing osteocyte damage and vascular thrombosis.

This combination may closely mimic clinical osteonecrosis, which is characterized by ischemia and a lack of a reparative response (Lavernia et al. 1999). The hyperthermia induces the osteonecrosis, and the vascular insult results in the ischemia and lack of reparative response.

The use of HIFU to induce osteonecrosis does pose some uncertainties and challenges. HIFU was initially developed and used for hyperthermic therapy of neoplasia and soft tissue pathology of, among other tissues, the breast (Wu et al. 2003), prostate (Souchon et al. 2003) and liver (Shen et al. 2011). Exposure to HIFU in or through the bone tissue has been complicated by the highly reflective interface between the soft and bone tissues resulting from the drastic acoustic impedance difference (Nell and Myers 2010; Tanter et al. 2007). Several research groups have evaluated the viability of delivering HIFU into regions where bone is involved or is in the treatment field (Civale et al. 2006; Persson et al. 2005; Pinton et al. 2011). A set of HIFU parameters have been established for proper application to osseous neoplasms (Li et al. 2010).

The primary mechanism by which HIFU induces osteonecrosis is heating. High-power acoustic energy is transmitted and focused on small target areas, up to 1000 W/cm^2 in our experimental setting (Long et al. 2008). In the overlying tissues between the HIFU transducer and its focus, acoustic energy is transmitted over a large area, resulting in minimal effects on the tissue. Depending on the HIFU parameter settings and target tissue characteristics, the effects of HIFU are commonly heating and mechanical disruption (histotripsy) (Xu et al. 2011). In this study, we were interested primarily in investigating heating as it can non-invasively induce osteocyte death.

Previous studies have provided insight into appropriate temperature thresholds for this study. At temperatures less than approximately 42.5°C, cells become resistant to heat (Field and Morris 1985). As the temperature rises beyond 43°C, there is a direct relationship between duration of exposure and temperature with respect to thermal damage of the bone; specifically, increasing the temperature 1°C is equivalent to cutting the time by approximately half (Field and Morris 1983). Further increasing the temperature to 47°C for 1 min causes bone resorption (Eriksson et al. 1984a). At this temperature, slow osteocyte death starts to occur and may not be seen until 3 wk or longer after the thermal exposure (Eriksson et al. 1984b). In a rabbit femoral head model of osteonecrosis, microwave heating of the femoral heads to 55°C for 10 min induced osteonecrosis (Li et al. 2009).

High-intensity focused ultrasound can induce hemostasis and thrombosis, which can limit the reparative response when temperatures exceed 45°C (Delon-Martin et al. 1995; Deng et al. 2004; Ishikawa et al. 2003). Femoral vein thromboses were present in rats 2 d after HIFU treatment (Delon-Martin et al. 1995). Thermally induced osteonecrosis is increased by the addition of vascular thrombosis (Morris and Field 1985).

The objective of this study was to evaluate the potential of HIFU to induce osteonecrosis of the femoral head and neck. The two specific aims of this study using canine femora *in vitro* were to evaluate the ability to develop a valid osteonecrosis model in the medullary cavity and to produce a mathematical model that correlates the temperature rise during HIFU exposure with HIFU parameters and femoral head geometry.

METHODS

Phenomenological model

Basic assumptions. The objective of this study was to heat the target area in the medullary cavity of the femoral head to induce hyperthermia-induced osteonecrosis. The exact temperature and duration of exposure combination required to accomplish this aim is not known; therefore, the goal was to increase the temperature in the medullary cavity to a range that would be expected to induce osteonecrosis (>45°C). To this end, a model of temperature inside the medullary cavity was used to account for, first, the temperature increase caused by HIFU power and, second, the temperature decrease caused by heat dissipation through the surrounding tissues, which would have a constant temperature. The specific assumptions for the model are as follows:

1. The target medullary cavity is modeled as a uniform thermal entity. That is, heat distribution inside the medullary cavity is not modeled; only gross temperature T measurable with a simple implanted thermocouple is modeled.
2. High-intensity focused ultrasound as a heat source constantly deposits heat in the medullary cavity at a uniform rate, which increases T at the constant rate k_1, which depends on the geometry of the medullary cavity and HIFU parameter settings.
3. Surrounding tissue (in this case, a water bath) is held at constant temperature T_{base}; when $T > T_{base}$, heat is lost from the medullary cavity through dissipation, which causes the temperature to fall at the rate of $k_2(T–T_{base})$.

Differential equations. On the basis of these assumptions, the temperature when HIFU is turned on, is modeled as

$$\frac{dT}{dt} = k_1 - k_2(T - T_{base}) \quad (1)$$