

# ***Pre-Clinical Research Services, Inc.***

## **Publications on Osteoarthritis Animal Model**

Below are three references that Alison Bendele of Pre-Clinical Research Services, Inc. has published about osteoarthritis animal models.

Study using a cranial cruciate ligament transection procedure in hounds - Don Maul and Alison Bendele

### **Evaluation of changes in vertical ground reaction forces as indicators of meniscal damage after transection of the cranial cruciate ligament in dogs.**

**Bendele AM, Trumble TN, Billingham RC, McIlwraith CW.** Orthopedic Research Center, Department of Clinical Sciences, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, CO 80523, USA.

**OBJECTIVE:** To determine whether decreases in peak vertical force of the hind limb after transection of the cranial cruciate ligament (CrCL) would be indicative of medial meniscal damage in dogs. **ANIMALS:** 39 purpose-bred adult male Walker Hounds. **PROCEDURE:** The right CrCL was transected arthroscopically. Force plate measurements of the right hind limb were made prior to and 2, 4, 10, and 18 weeks after transection of the CrCL. Only dogs with > or =10% decreases in peak vertical force after week 2 were considered to have potential meniscal damage. Dogs that did not have > or =10% decreases in peak vertical force at any time point after week 2 were assigned to group 1. Group 2 dogs had > or =10% decreases in peak vertical force from weeks 2 to 4 only. Group 3 and 4 dogs had > or =10% decreases in peak vertical force from weeks 4 to 10 only or from weeks 10 to 18 only, respectively. Damage to menisci and articular cartilage was graded at week 18, and grades for groups 2 to 4 were compared with those of group 1. **RESULTS:** The percentage change in peak vertical force and impulse area was significantly different in groups 2 (n = 4), 3 (4), and 4 (4) at the end of each measurement period (weeks 4, 10, and 18, respectively) than in group 1 (27). The meniscal grade for groups 2 to 4 was significantly higher than for group 1. A > or =10% decrease in peak vertical force had sensitivity of 52% and accuracy of 72% for identifying dogs with moderate to severe medial meniscal damage. **CONCLUSIONS AND CLINICAL RELEVANCE:** In dogs with transected or ruptured CrCLs, force plate analysis can detect acute exacerbation of lameness, which may be the result of secondary meniscal damage, and provide an objective noninvasive technique that delineates the temporal pattern of medial meniscal injury.

Am J Vet Res. 2005 Jan;66(1):156-63.

PMID: 15691052 [PubMed - indexed for MEDLINE]

### **Animal models of osteoarthritis.**

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Animal models of osteoarthritis are used to study the pathogenesis of cartilage degeneration and to evaluate potential antiarthritic drugs for clinical use. Animal models of naturally occurring osteoarthritis (OA) occur in knee joints of guinea pigs, mice and other laboratory animal species. Transgenic models have been developed in mice. Commonly utilized surgical instability models include medial meniscal tear in guinea pigs and rats, medial or lateral partial meniscectomy in rabbits, medial partial or total meniscectomy or anterior cruciate transection in dogs. Additional models of cartilage degeneration can be induced by intra-articular iodoacetate injection or by administration of oral or parenteral quinolone antibiotics. None of these models have a proven track record of predicting efficacy in human disease since there are no agents that have been proven to provide anything other than symptomatic relief in human OA. However, agents that are active in these models are currently in clinical trials. Methodologies, gross and histopathologic features and comparisons to human disease will be discussed for the various models.

PMID: 15758487 [PubMed]

### **Animal models of osteoarthritis in an era of molecular biology.**

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Animal models of osteoarthritis (OA) are used to study the pathogenesis of cartilage degeneration and to evaluate potential anti-arthritis drugs for clinical use. In general, these models fall into 2 categories, spontaneous and induced (surgical instability or genetic manipulation). Animal models of naturally occurring OA occur in knee joints of guinea

pigs, mice and Syrian hamsters. Commonly utilized surgical instability models include medial meniscal tear in guinea pigs and rats, medial or lateral partial meniscectomy in rabbits, medial partial or total meniscectomy or anterior cruciate transection in dogs. Transgenic models have been developed in mice. These models all have potential use in the study of molecular mechanisms associated with OA development via use of immunohistochemistry, biochemistry and molecular probes to identify altered matrix molecules at different stages in disease progression. Testing of specific types of inhibitors developed through evaluation of matrix changes in the disease process will ultimately help identify key processes which initiate and perpetuate the disease and will lead to discovery of new disease modifying pharmaceutical agents for OA patients. This paper will focus on the discussion of several models which are likely to be useful in the molecular dissection of processes involved in cartilage degeneration.

PMID: 15758375 [PubMed]

We use the partial medial meniscectomy model in beagles. We do the partial meniscectomy in the left knee only. The studies we have typically run are between 28 and 42 days in duration after surgery. We have done oral gavage or capsule test article administration up to 2 times daily for the duration of the study. We are currently doing a study that requires intra-articular injection of test article 2 times per week for the 42 day study. We have another study where we are going to follow the dogs for 1 year post op with IA injections 2x per week for 3 weeks and that is repeated once every 3 months. For that study we are also doing 1 pre-op and 4 post-op MRI scans of the knee joint as well as the force plate testing once every 3 months post-op.

For clinical lameness we have a lameness evaluation scale that we use to monitor clinically evident lameness, but typically on the short studies the dogs are somewhat lame for the first 4-7 days post-op and then not much lameness after that which at least isn't obvious when you watch them walk in the 28 day studies. I expect in the longer studies (i.e 42 days or longer) we will see some clinical lameness. We hope to be able to detect more subtle lameness using the force plate. The year-long study we are doing now is having force plate analysis done 1 time pre-op and 4 times post op in the year-long study. Here is what we will evaluate by force plate.

Vertical force measurements that will be used are peak vertical ground reaction force and associated vertical impulse normalized to the animal's body weight. Numerous studies have shown that these two variables are the most reliable when evaluating the effect of treatment (surgical or medical) on limb function[1]<sup>3</sup>. Accordingly, we recommend that statistical analysis be performed primarily on PVGRF and AVI. Based on a recent publication from Budsberg<sup>4</sup>, a 20% decrease in PVGRF of the affected leg (and a 5% change in PVGRF of the sound, contra-lateral limb) may be expected in chronic hind limb lameness secondary to CCL rupture (Fig. 2).

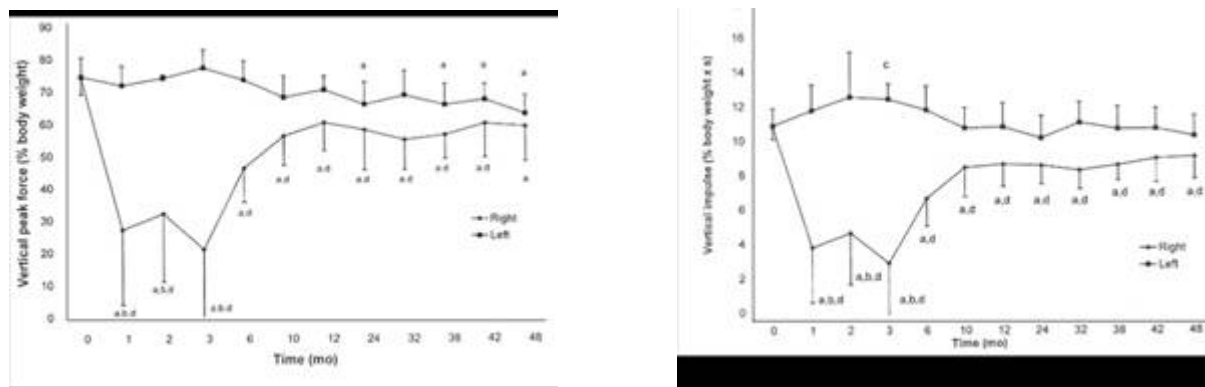


Figure 2 – Mean +/- SD of PVGRF (left) & AVI (right) after surgical transection of the CCL (12 dogs). a = significantly different from base line value (same leg). b = significantly lower than values obtained at all later time points (same leg). c = significantly greater than base line value (same leg). d = significantly different between limbs.

Cranio-caudal force (divided into braking and propulsion, with both peak force and impulse measurements being collected) will be provided and may also be evaluated.

[1] Rumph PF, Kinkaid SA, Visco DM, et al: Redistribution of vertical reaction force in dogs with experimentally induced chronic hind limb lameness. Vet Surg, 24:383-389, 1995.

<sup>2</sup> Jevens DJ, DeCamp CE, Hauptman J et al: Use of force plate analysis of gait to compare two surgical techniques for the treatment of cranial cruciate ligament rupture in dogs. AJVR, 57(3):389-393, 1996.

**MRI analysis will be as follows:**

We can do MRI imaging of the operated stifle joint. The MRI Image analysis endpoints will include cartilage volume and thickness, dGEMRIC (T1) analysis, T2 analysis, analysis of local/focal morphological changes, fluid analysis and bone marrow edema volume. Endpoints will be defined by region of the joint. We use a commercial image analysis company that can do 3-D renderings of the MRI scan images to aid in the analysis of morphologic changes in the tibial and femoral cartilage as well as in the subchondral bone to assess bone edema or other changes. The MRI that we have been using for our dog OA studies has the following specs.

GE 1.5 Signa Hi Speed Plus MR  
Bore Size: 70cmX60cmX60cm ( LxWxH)  
Mobile Patient Table  
Wt limit 350 lbs  
Minimum slice thickness in 2D .7 mm  
Minimum slice thickness in 3D .1 mm  
Maximum FOV 48 cm  
Maximum Amplitude/Strength of 33m/jTm  
Slew Rate of 77 T/M/s  
Active Shielding Gradient System  
Research Key Capabilities  
Medrad MRI power injector.

For the dog OA studies we have special coils made specific for the knee joint of the beagle. For image analysis we contract with a company that has specialize software to analyze the image and can do image enhancements such as measuring cartilage depth in a 3 dimensional image. If you are interested I can provide additional information about the image analysis.

The MRI scans and the Force Plate testing are optional based on the sponsor's request and interest. For all of the dog OA studies the final and definitive evaluation of the joint changes is done by the pathologist as follows:

**Gross and Histopathology:**

We do gross lesion analysis with photography of the tibial and femoral lesion, and collect that for histopathology evaluation. My colleague, Alison Bendele, has a full panel of histopathology evaluation parameters that she does including:

**Gross Evaluation of lesions include:**

Gross cartilage lesion measurements  
Gross Cartilage degeneration scores  
Gross appearance of osteophytes or peripheral fibrous tissue proliferation  
Gross synovial reaction

**Histopathology evaluation includes:**

Depth of chondrocyte and proteoglycan loss with fibrillation  
Measurements of width and depth of lesion  
Osteophyte measurement  
Synovial pathology  
Sclerosis of subchondral bone  
Histology image analysis to quantitate and compare cartilage matrix preservation.