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An animal model to evaluate skin–implant–bone integration and gait with a prosthesis directly attached to the residual limb

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ABSTRACT

Background: Despite the number of advantages of bone-anchored prostheses, their use in patients is limited due to the lack of complete skin–implant integration. The objective of the present study was to develop an animal model that would permit both detailed investigations of gait with a bone-anchored limb prosthesis and histological analysis of the skin–implant–bone interface after physiological loading of the implant during standing and walking.

Methods: Full-body mechanics of walking in two cats were recorded and analyzed before and after implantation of a percutaneous porous titanium pylon into the right tibia and attachment of a prosthesis. The rehabilitation procedures included initial limb casting, progressively increasing loading on the implant, and standing and locomotor training. Detailed histological analysis of bone and skin ingrowth into implant was performed at the end of the study.

Findings: The two animals adopted the bone-anchored prosthesis for standing and locomotion, although loads on the prosthetic limb during walking decreased by 22% and 62%, respectively, 4 months after implantation. The animals shifted body weight to the contralateral side and increased propulsion forces by the contralateral hindlimb. Histological analysis of the limb implants demonstrated bone and skin ingrowth.

Interpretation: The developed animal model to study prosthetic gait and tissue integration with the implant demonstrated that porous titanium implants may permit bone and skin integration and prosthetic gait with a bone-anchored prosthesis. Future studies with this model will help optimize the implant and prosthesis properties.

1. Introduction

Several types of bone-anchored (or osseointegrated) limb prostheses have been developed and evaluated in individuals with amputation (Rancho Los Amigos Hospital Implantation System (Mooney et al., 1977), Osseointegrated Prostheses for Rehabilitation of Amputees (Hagberg and Branemark, 2009), Endo–Exo Femoral Prosthesis (Aschoff et al., 2010), Intraosseous Transcutaneous Amputation Prosthesis (Pendegrass et al., 2006a)) and in animal studies (Percutaneous Osseointegrated Prosthesis (Shelton et al., 2011), Skin and Bone Integrated Prosthesis (Pitkin et al., 2006), University of Akron System (Saunders et al., 2012)). These prostheses are rigidly attached to the bone via a solid titanium implant in the marrow cavity and protrude through the skin (Branemark, 1983). Prostheses with a direct skeletal attachment (DSA) eliminate limitations of traditional socket prostheses including difficulties fitting the socket onto the residual limb, discomfort and pain due to skin irritation, development of pressure sores, sitting discomfort, limited range of motion, and transmission of external loads to the limb via soft tissues (Hagberg et al., 2005; Pezzin, 2004). In addition, the conventional socket prostheses provide little or no normal proprioceptive feedback thus, visual feedback with a relatively long delay becomes critical for successful performance of complex motor tasks (Barnett et al., 2013; Glencross, 1977). The lack of normal sensory feedback from the residual limb affects the control of balance and placement of the sound and prosthetic foot during standing and locomotion particularly on complex terrains (Buckley et al., 2002; Curtze et al., 2011, 2012; Hof et al., 2007; Segal et al., 2010). DSA prostheses might have certain advantages over traditional socket prostheses during standing and locomotion: (i) ground reaction forces are transmitted directly to the bone of the residual limb compared to indirect force transmission through soft tissues and (ii) the amputee has a better sense of load on and position of the prosthesis due to osseoperception (Jacobs et al., 2000).

Despite the number of advantages of DSA prostheses, their use in many countries, including the US, is limited or prohibited due to the

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lack of complete skin–implant integration. As a result amputees with DSA prostheses have a rather high skin infection rate (13%–30% (Aschoff and Juhnke, 2012; Aschoff et al., 2010)), 18%–23% (Hagberg and Brånemark, 2009; Tillander et al., 2010), which can lead to implant loosening, revision and/or removal. The majority of current DSA prostheses utilize intramedullary titanium implants with a solid percutaneous portion that has a smooth or partially modified surface (Aschoff et al., 2010; Hagberg and Brånemark, 2009; Jonsson et al., 2011). Since solid percutaneous implants do not completely eliminate skin infection problems, researchers have tried to improve the skin–implant integration through the use of porous implants (Pitkin et al., 2004, 2006), or implants with a perforated flange, imitating natural percutaneous structures such as the deer antler (Pendegrass et al., 2006b). Recent in vitro and in vivo studies of porous implants have demonstrated a potential for a better skin–implant integration and the possibility of developing a robust skin barrier to bacteria and other pathogens (Chou et al., 2010; Farrell et al., 2013b; Jeyapalina et al., 2012; Pendegrass et al., 2006b, 2008; Pitkin et al., 2006, 2007, 2009; Shelton et al., 2011).

Gait analysis in individuals with amputation who have prostheses directly attached to their residuum, has had the following principal aims (D'Angeli et al., 2013; Frossard, 2010; Frossard et al., 2008, 2009, 2010b, 2010c, 2013; Isackson et al., 2011; Lee et al., 2007, 2008; Tranberg et al., 2011; Van de Meent et al., 2013): to optimize the mechanical design of the fixation, to refine the rehabilitation program, to compare the performance of the osseointegrated prostheses with socket prostheses, and to evaluate walking ability, effect of falls and prosthetic components. Such gait studies have been conducted with the two commercially available DSA systems: OPRA—Osseointegrated Prosthesis for the Rehabilitation of Amputees (Brånemark et al., 2001) and EEFP/ILP—Endo–Exo-Femur Prosthesis/Integral Leg Prosthesis (Aschoff et al., 2010). As new experimental DSA systems emerge (Pitkin, 2013), a need exists for adequate animal models, which through gait studies will help in selecting the best technologies without compromising the safety of human subjects.

The effects of porous or porous-coated implant properties on skin and bone integration have been studied in animal models: rats (Ysander et al., 2001), guinea pigs, rabbits (Jansen and de Groot, 1988; Jansen et al., 1994; Pitkin et al., 2006), cats (Pitkin et al., 2009), dogs (Drygas et al., 2008; Murphy, 1973), pigs (Fernie et al., 1977), goats (Hall, 1974) and sheep (Shelton et al., 2011; Williams et al., 2010); with few of these studies involving any gait analysis. A recent study in sheep showed that loading on the implanted limb decreased to approximately 74% of the pre-implantation load 12 months after implantation of a percutaneous osseointegrated prosthesis with porous skin–implant interface into the third metacarpal bone (Shelton et al., 2011). The limited data on reduced load on DSA prostheses attached through porous percutaneous implants during gait might indicate potential problems with integration between the implant and residual limb. This warrants further investigation and development of an animal model that permits detailed histological investigations of skin and bone integration, as well as detailed biomechanical analysis of gait with DSA prostheses.

A feline model appears to be well suited for this purpose. It has been the model of choice in studies of the neural control and biomechanics of posture and locomotion (Beloozerova et al., 2010; Brown, 1914; Honeycutt and Nichols, 2010; Musienko et al., 2012; Rossignol, 2006; Sherrington, 1910; Shik et al., 1966). The advantage of the cat model compared to a rodent model is that the cat has highly developed locomotor abilities, it maintains the upright posture, and the loads experienced by the hindlimbs during locomotion are larger than those in rodents and have similar patterns to human ground reaction forces during walking. Loading on the implant is especially important because the degree of osseointegration has been shown to be load dependent (Torcasio et al., 2008). Furthermore, cat limb inertial properties have been determined (Hoy and Zernicke, 1985), which permits calculations of forces and moments at the joints and the prosthesis interface with the residual limb by means of inverse dynamics analysis (Gregor et al., 2006; Hoy and Zernicke, 1985; Manter, 1938; Prilutsky et al., 2005). Larger animal models (e.g., large dogs, sheep) have also been used to study DSA prostheses (Shelton et al., 2011), however lab settings for a detailed biomechanical analysis of prosthetic gaits in these models are not readily available.

The objective of the present study was to develop a feline prosthetic gait model for evaluating locomotion with the DSA prostheses attached via porous titanium implants (Farrell et al., 2013b; Pitkin et al., 2009) and for testing skin–implant–bone integration of these implants. This model would permit both a detailed histological analysis of the skin–implant–bone interface after physiological loading of the implant during standing and walking and investigations of prosthetic gait adaptations. Based on data available (Farrell et al., 2013b; Jeyapalina et al., 2012; Pitkin et al., 2007, 2009; Shelton et al., 2011) we hypothesize that (1) the animals will adopt the prosthesis for standing and walking, although gait mechanics would change and (2) skin and bone tissue will be present inside the porous titanium implants after mechanical loading of implant during normal physiological activities such as standing and walking. The preliminary results of the study have been published in abstract form (Farrell et al., 2012, 2013a).

2. Methods

2.1. Animal model and study design

All experimental procedures in this study were in agreement with the US Public Health Service Policy on Humane Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committees of Georgia Institute of Technology and Saint Joseph's Translational Research Institute. Two adult purposely bred cats (mass 3.2 and 3.0 kg) were selected for this study. They were trained daily for two weeks to walk across an enclosed walkway with embedded force platforms for food reward. After completion of training, full body walking mechanics were recorded (see Subsection 2.8) for another two weeks (for time line of study see Fig. 1A). X-ray images were taken prior to surgery to measure the dimensions and geometry of the tibia marrow cavity, and after implantation to monitor healing and possible bone lysis or fracture (Fig. 1B). After implantation of the implant into the tibial medullary cavity (see Fig. 1), a cast was placed on the residual limb to prevent premature loading of the implant (Fig. 1B,C). Starting at week 6 after implantation, the protruding end of the implant was progressively loaded (Fig. 1D) to promote bone–implant integration (Frossard et al., 2008; Torcasio et al., 2008). At the end of week 10 the cast was removed and a standing prosthesis (Fig. 2A) was attached to the protruding implant 2–3 times a day to train the animal to use the prosthesis for standing. After initial training for 1 week, the animals started wearing the standing prosthesis continuously. Starting at weeks 12–14, a J-shape walking prosthesis was attached (Fig. 2B, C), and the animals were retrained to walk along the walkway using food as a reward. Training lasted for 4–6 weeks until the animals started repeatedly crossing the walkway (at least 15–20 times in a recording session) with loading the prosthetic leg. Walking mechanics were recorded for several weeks. At week 21 the animals were euthanized using deep anesthesia and the limb with implant was harvested for histological analysis (see Subsection 2.9).

2.2. Implants

Porous titanium implants were obtained from Poly-Orth International (Sharon, MA, USA). The manufacturing technology for these implants has been described elsewhere (e.g. (Pitkin et al., 2012; Pitkin et al., 2009)). Porous composite implants called Skin and Bone Integrated Pylons (SBIPs) were sintered from titanium particles and solid inserts. The inserts were included to provide required strength, and were perforated to promote the ingrowth of cells throughout the entire volume of the device. The SBIPs had a patented combination of four