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An experimental canine patent ductus arteriosus occlusion device based on shape memory polymer foam in a nitinol cage

Mark A. Wierzbicki[a], Sarah B. Raines[b], Sonya G. Gordon[c], John C. Criscione[a], Ashley B. Saunders[c], Scott Birch[d], Bradley Due[a], Brandis Keller[a], Landon D. Nash[a], Matthew W. Miller[e], Duncan J. Maitland[a,*]

[a] Department of Biomedical Engineering, Texas A & M University, MS 3120, 5045 Emerging Technologies Building, College Station, TX 77843, USA
[b] Department of Electrical Engineering, Texas A & M University, USA
[c] Department of Small Animal Clinical Sciences of Veterinary Medicine and Biomedical Sciences, Texas A & M University, USA
[d] The Center for Educational Technologies, College of Veterinary Medicine and Biomedical Sciences, Texas A & M University, USA
[e] Texas Institute for Preclinical Studies, Texas A & M University, MS 4478, College Station, TX 77845, USA

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ABSTRACT

Patent ductus arteriosus (PDA) is a congenital cardiovascular defect in which a fetal connection between the aorta and pulmonary artery does not spontaneously close shortly after birth. If left uncorrected serious complications and even death can occur. Surgical ligation is the traditional treatment method; however, it is an invasive procedure, that motivates development of a minimally invasive option. Shape memory polymer (SMP) foams are unique materials that hold promise in the field of minimally invasive occlusion devices. In this work, a prototype nitinol foam cage (NFC) incorporating SMP foams has been designed and evaluated in multiple mechanical and *in vitro* verification tests. The NFC demonstrated acceptable fatigue resistance in a preliminary strut integrity test, withstanding one million cycles without complete strut fracture. Radial force analysis of both thick- and thin-walled prototype variations generated less vessel distension and wall tension in a vessel mimic compared to a commercial device. The NFCs exhibited negligible *in vitro* migration, comparable to that of a commercial device, using simplified, ideal models of PDA. Deployment characteristics of the prototypes were evaluated and compared to that of a commercial device when delivered into physiological models of PDA. During mock deployments, a veterinary cardiologist noted that, while deliverable, the thin-walled NFC prototype exhibited poor deployment characteristics, however the thick-walled NFC had deployment characteristics comparable to that of a commercial device. The promising results of this study warrant further investigation of the NFC device for canine PDA closure.

1. Introduction

Patent ductus arteriosus (PDA) occurs when a normal fetal connection between the aorta and pulmonary artery does not close shortly after birth, leading to a continuous left-to-right side shunting of blood. When left uncorrected, the PDA leads to many complications including, congestive heart failure and even death (Buchanan, 2001; Nguyenba and Tobias, 2008)

PDA is the most common congenital cardiovascular defect that occurs in canines, manifesting in 6.8 out of 1000 live births and comprising approximately 28% of all congenital cardiovascular defects (Patterson, 1968). PDA has been traditionally treated *via* surgical ligation, in which the chest cavity of the dog is opened *via* thoracotomy and the ductus is ligated (Birchard et al., 1990; Eyster, 1976; Jackson and Henderson, 1979; Nguyenba and Tobias, 2008). While effective, surgical ligation is invasive, and carries non-trivial operative risks including, nonfatal hemorrhage, pneumothorax, and chylothorax as reported in 11–15% of cases (Bureau et al., 2005; Goodrich et al., 2007; Stanley et al., 2003; Van Israel et al., 2002) and operative mortality in up to 11% of cases (Birchard et al., 1990; Bureau et al., 2005; Eyster,

Abbreviations: PDA, Patent ductus arteriosus; ADO, Amplatzer™ Duct Occluder; AVP, Amplatzer™ Vascular Plug; ACDO, Amplatz® Canine Ductal Occluder; NFC, Nitinol foam cage; SMP, Shape memory polymer; T_g, Glass Transition Temperature; MDD, Minimal ductal diameter; MPA, Main pulmonary artery; NFC_{Tn}, Thin-walled nitinol foam cage; NFC_{Tk}, Thick-walled nitinol foam cage; NFC_{TkEP}, Electropolished thick-walled nitinol foam cage; WA, Wide ampulla

* Correspondence to: Department of Biomedical Engineering, Texas A & M University, MS 3120, 5057 Emerging Technologies Building, College Station, TX, 77843, College Station, TX, 7784, USA.
E-mail address: djmaitland@tamu.edu (D.J. Maitland).

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1976; Goodrich et al., 2007; Stanley et al., 2003; Van Israel et al., 2002). These complications motivate the development of improved minimally invasive closure techniques (Tobias and Stauthammer, 2010).

Many endovascular devices intended for human PDA and peripheral occlusion, such as embolization coils, the Amplatzer™ duct occluder (ADO), and the Amplatzer™ vascular plug (AVP), have been investigated as options to treat the canine PDA. While there has been moderate success using human devices within the canine anatomy, limitations such as incompleteness of occlusion, device migration, delivery system size, and ease of delivery have prevented widespread use (Achen et al., 2008; Campbell et al., 2006; Glaus et al., 2002; Gordon and Miller, 2005; Hogan et al., 2006; Singh et al., 2012; Sisson, 2003; Tanaka et al., 2007; Tobias and Stauthammer, 2010) and led to the development of the Amplatz® canine ductal occluder (ACDO) (Nguyenba and Tobias, 2007, 2008). The ACDO is very successful in PDA closure, yet is still limited by cost and its relatively large delivery system profile. While some advances have been made to reduce the profile (Stauthammer et al., 2015), the smallest sheath that current commercial devices can be delivered through is a 4 Fr sheath, restricting the range of dogs that can be treated.

A prototype nitinol foam cage (NFC) device that utilizes shape memory polymer (SMP) foams has been developed as previously described in Wierzbicki et al. (Wierzbicki et al., 2016) with design modifications to the shape for improved stability and increased foam capacity. The NFC prototype utilizes an SMP polyurethane foam, rather than a dense nitinol mesh to occlude flow. SMPs are a unique class of materials that can be heated above a characteristic glass transition temperature (T_g) and when deformed and cooled below the T_g, hold a secondary shape. The polymer can then be actuated back to its original configuration through an entropy driven process by increasing the temperature of the polymer above its T_g *via* an external stimulus such as heat or contact with body temperature blood (Lendlein and Kelch, 2002). The unique mechanical and embolic properties of these materials have led to the investigation of multiple biomedical embolic device applications for endovascular occlusion (Maitland et al., 2007; Small et al., 2010). Multiple *in vitro* and *in vivo* studies have been conducted demonstrating the favorable occlusion and biocompatible properties of these materials, as shown through occlusion within two minutes once implanted (Rodriguez et al., 2014b) and minimal inflammation characterized by dense tissue growth and collagen deposition at 90 days post-implant, prompting investigation for their use in other embolization applications (Rodriguez et al., 2014a).

The prototype NFC discussed herein is constructed from one continuous nitinol conduit comprising three sections: the proximal cage, waist, and distal cage, and an SMP foam. In endovascular deliveries, the distal cage is advanced out of the catheter first and pulled against the pulmonary artery wall, serving as an anchor point and landmark for the device and clinician, respectively. The waist is designed to be 2x oversized relative to the minimal ductal diameter (MDD), such that it will apply an outward force to the ductus, aiding in stability. The proximal cage expands to apply pressure to the ampulla wall. The SMP foam is anchored within the proximal cage and spans all three sections of the frame to volumetrically fill the PDA.

Through discussions with clinicians, multiple design criteria were defined to determine device success. First, the device must be deliverable through a 4 Fr sheath having an internal diameter of 1.3 mm or smaller, as larger sheaths and catheters exclude small dogs, an important subset of the canine population that cannot currently be treated with minimally invasive devices. Additionally, the prototype must be retractable into the sheath in the event of an improper deployment or sizing, be visible under fluoroscopy following delivery, and remain stable once deployed at physiological and elevated pressures. Fabricated NFC prototypes were tested against ACDO performance in multiple verification tests to evaluate strut integrity and nitinol frame radial forces, as well as stability and deployment characteristics in simplified and physiological PDA models, respectively, under experimental flow conditions.

2. Methods

2.1. Device fabrication

NFC prototypes were fabricated in a similar way to those described in Wierzbicki et al. (Wierzbicki et al., 2016); however, two variations in wall-thickness were used to assess differences regarding the effects of strut stiffness on the prototype's deployment characteristics. Briefly, the NFC prototypes were fabricated by cutting ten equally spaced slots radially into a straight, superelastic, nickel titanium alloy (nitinol) tubing using an excimer laser (Resonetics, Nashua, NH). The thin-walled prototypes (NFC_{Tn}) were constructed using 1.12 mm (0.044″) outer diameter (OD) and 1.04 mm (0.041″) inner diameter (ID) (NDC, Fremont, CA) tubing (0.038 mm (0.0015″) wall thickness), while the thick-walled prototypes (NFC_{Tk}) were constructed using 1.12 mm OD and 1.00 mm ID (Vascotube, Birkenfeld, Germany) tubing (0.06 mm wall thickness). The austenite finish temperature (A_f) of the thick-walled material was approximately −11 °C prior to shape setting. The A_f of the thin-walled material following shape setting was approximately ~11 °C as determined by a bend and free recovery test based upon ASTM F2082 in which the NFC_{Tn} prototypes were submerged within a −20 °C water/ethanol solution, elongated to a maximal length and imaged in 0.5–1 °C intervals as the solution was slowly heated. Axial device length was measured from the images and plotted against temperature. The A_f was estimated from the generated curves. The laser cut nitinol tubes were deburred using abrasive paper and sonicated in isopropyl alcohol. Custom fixturing compressed the tubing, while allowing the struts to expand to the desired shape with a waist of 6 mm OD, shown in Fig. 1. All material deformations when preparing the devices for shape setting were conducted at room temperature, when the nitinol was superelastic. The final shape was defined by annealing the nitinol frame and fixture within a furnace held at 550 °C for twenty-five minutes, followed by quenching in water. A threaded release mechanism was laser welded to the proximal end of the device and an 8 mm OD, 5 mm length SMP foam was compressed to a minimal diameter and epoxied into the lumen of the proximal portion of the device. Fig. 2 illustrates a comparison between the ACDO and the NFC_{Tn} prototype with a compressed and expanded foam insert. Additionally, a subset of thick-walled prototypes (NFC_{Tk}) were electropolished (NFC_{TkEP}) (Able Electropolishing, Chicago, Il) to a wall thickness of approximately 0.038 mm (0.0015″) to evaluate how electropolishing influenced frame durability and strut integrity.

2.2. PDA model fabrication

While the PDA morphology varies from animal to animal, there are three basic morphologies that the ductus arteriosus may manifest which vary in size and shape (Miller et al., 2006). Simplified thin-walled silicone models were fabricated with shapes based on those described by Miller et al. (Miller et al., 2006), including the cylindrical (IIA) and elliptical ampulla (IIA ovular), conical ampulla (IIB), and a wide ampulla (WA) models with 3 mm and 5 mm minimal ductal diameters (MDD) (Fig. 3). Dimensions of all simplified models are detailed in Table 1. The WA model simulates conditions in which the device struts do not contact the ampulla walls, as could occur shortly after occlusion due to systemic hypertension and a reflex bradycardia (Branham reflex) (Achen et al., 2008; Franks, 2004). The 6 mm waist of the NFC prototype is designed to be twice the diameter of the 3 mm PDA MDD. Model MDDs were designed such that the prototypes would evaluate 2x and 1.2x oversizing to serve as a safety factor for clinician device sizing. Additionally, elliptical morphology dimensions were applied for the IIA ovular model to account for irregularly shaped PDAs that occur *in vivo* (Saunders et al., 2010).