EVALUATION OF MECHANICAL STABILITY FOR A PATENT DUCTUS ARTERIOSUS DEVICE

An Undergraduate Research Scholars Thesis

by

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ABSTRACT

Evaluation of Mechanical Stability for a Patent Ductus Arteriosus Device

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Patent ductus arteriosus (PDA) is a condition that occurs when the ductus arteriosus vessel, a vessel connecting the aorta to the main pulmonary artery, does not close after birth, causing irregularities in blood flow. A nitinol cage device has been created to address this pathology by straddling this opening and occluding it with a polymeric foam placed in the center of the device. As the pulsating high flow environment may contribute to unwanted device migration [1], stability testing for extraction is required to ensure the device has appropriate mechanical strength to withstand physiological conditions. Dislocation force testing was performed to evaluate device stability using an Instron 5965 test-frame (Instron, Norwood, MA) on bare foams (small and large pores) and hydrogel-clotted foams, i.e. foams covered in a gel that simulates conditions once a clot has formed within the prototype PDA device. The dislocation force provides the maximum force required to dislodge the prototype PDA device once positioned inside the PDA immediately after deployment (bare foam) and once clotted (hydrogel foam) to determine changes in stability as compared with the current clinical gold standard, the Amplatz Canine Ductal Occluder.

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CHAPTER I

INTRODUCTION

The patent ductus arteriosus (PDA) is a structure near the heart that connects the aorta to the main pulmonary artery [2]. Under normal conditions, the vessel pathway spontaneously closes following birth [3]. However, when the ductus arteriosus does not close and remains patent, variations in morphological openings create a shunt, which allows blood to flow from the aorta to the pulmonary artery. This pattern of blood flow causes a buildup of fluid in the lungs, increasing pressure and ultimately leading to congestive heart failure and death in serious cases [5]. Though this condition can occur in both humans and animals, the focus of this study is for veterinary applications, as 70% of affected animals die without treatment [4].

The conventional method to treat PDA is through highly invasive techniques, such as surgical ligation via thoracotomy. In this procedure, the chest cavity is opened to gain direct access to vessels. However, less invasive procedures can be performed using catheter based delivery of commercial devices such as the Amplatz Canine Ductal Occluder (ACDO), a device composed of a nitinol mesh used to occlude the defect [5]. Catheter-based delivery of devices begins with insertion of the device and catheter through the femoral artery. Attached to a delivery cable, the device can then be guided through the aorta to the PDA where the device can then be deployed across the vessel opening (Figure 2) [6]. Catheter delivery procedures improve recovery time and minimize risks associated with surgical ligation due to the smaller incision [7].

A prototype PDA occlusion device has been developed as an alternative method for device occlusion to address limitations of the ACDO, including device cost and the relatively large delivery system size. The prototype PDA device consists of a monolithic cage with ten

struts formed from a single piece of nickel titanium (nitinol) tubing and a shape memory polymer (SMP) foam positioned within the cage, which is placed across the MDD (Figure 2). In contrast to the ACDO's use of a nitinol mesh as an occlusion medium, the prototype aims to occlude the PDA with a SMP foam placed directly into the center of the cage. The foam is delivered in a compressed form and expands upon placement in the body, due to heat activation at body temperature, initiating a clotting and tissue healing response [8]. Utilizing the SMP foam as an occlusion mechanism instead of a dense nitinol mesh allows for a reduction of material used in the device, which could reduce the cost to manufacture. Furthermore, the overall compressed diameter has the potential to be reduced, as the minimal diameter of the prototype is dictated by the compressed diameter of the foam and outer diameter of the nitinol tubing. The size reduction allows for treatment in smaller dogs whose vascular system may be too narrow for the less compressible ACDO [6]. The prototype device is shape-set, which allows for flexible manipulation without sacrificing the shape and/or strength of the device. Therefore, once removed from the catheter, the prototype is expected to expand to conform to the PDA morphology. Despite the properties of a shape set frame, a concern with reducing the amount of material used is that the prototype may be less stable once positioned and could be prone to dislocation.

While catheter based delivery proves to be a more advantageous alternative to the aforementioned invasive surgical techniques, a major complication from this option is migration of the implanted device, which occurs in 3% of cases [4]. A dislodged device may be difficult to recover and in some cases, is left in place due to the risk involved in removing the device, though this has not been reported to create serious complications [1, 9]. Migration can be due to incorrect sizing of the device relative to the minimal ductal diameter (MDD) of the PDA or ill-

advised activity post-surgery [10]. Thus, in this work, we measure the force required to dislodge the prototype and ACDO from their deployed positions (dislocation force) in multiple models of PDA morphologies. Additionally, the dislocation force of the prototype is measured with SMPs of two different pore sizes and with SMP-hydrogel blood-clot mimics.

CHAPTER II

METHODS

PDA Model Fabrication

While the PDA morphology varies from animal to animal, there are three basic morphologies that the ductus arteriosus may manifest that vary in size and shape and affect blood flow [2]. These structures include the cylindrical ampulla (IIA), the conical ampulla (IIB), and the wide ampulla (WA), for cases in which the ampulla size may have swelled (Figure 1). Thin-walled silicon models of these morphologies with 3 and 5 mm MDDs were fabricated for *in vitro* testing to evaluate the influences of the PDA shape and MDD size on dislocation force. Setting the device waist to be two times the diameter of the MDD of the vessel is the clinical practice of oversizing a device and can be crucial in preventing a device from dislodging if sized correctly. The 3 mm MDD is used to represent the case of an appropriately sized device, as the PDA waist is 6 mm in diameter. The 5 mm MDD is used to represent the case in which the devise is undersized. For each model and MDD, three prototypes were tested up to three times each.

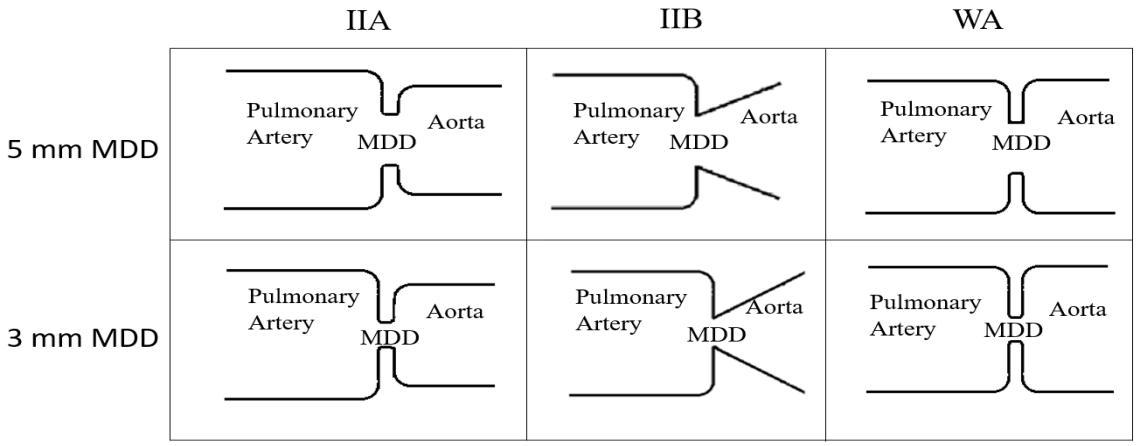

Figure 1: Model Diagram for IIA, IIB, and WA morphologies.

Foam Preparation

As mentioned previously, the prototype PDA device consists of a monolithic cage with ten struts formed from a single piece of nitinol tubing and a SMP foam positioned within the cage. The nitinol frame is shape set into three main sections - the proximal cage placed on the aortic side of the PDA, the distal cage placed on the pulmonary artery side, and the waist, which connects the proximal and distal cages and applies pressure to the wall of the MDD (Figure 2).

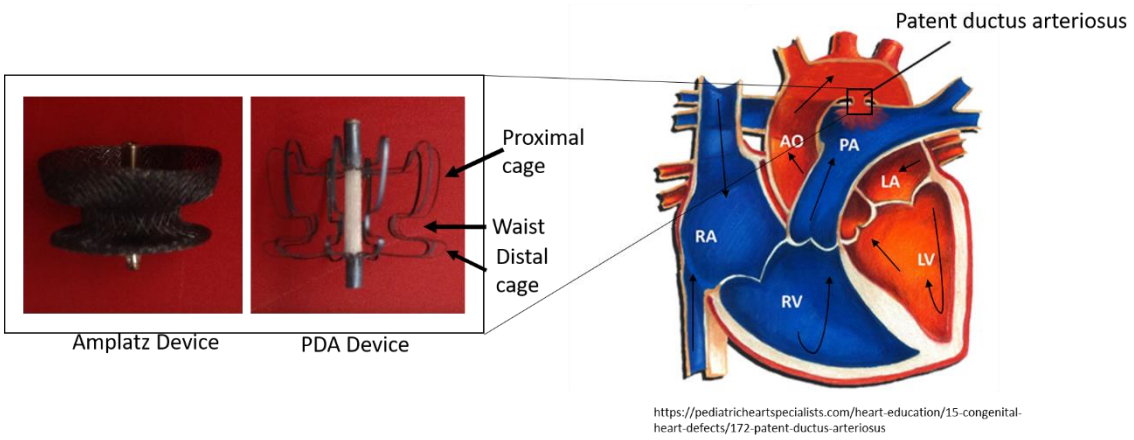

Figure 2: The ACDO and prototype placement in the PDA.

SMP foams were fabricated as previously described [11]. Briefly, a 100% hexameththylene diisocyanate (HDI) with 67% *N*,*N*,*N*′,*N*′-tetrakis(2-hydroxypropyl) ethylenediamine/33% triethanolamine (TEA) foam composition was synthesized via gas foaming techniques to result in two transverse pore sizes: small (650 ± 130 µm) and large (1970 ± 240 µm) pores [12]. In total, four types of foams were used for dislocation force testing: small pore bare (SPB), large pore bare (LPB), small pore hydrogel-clotted (SPH), and large pore hydrogel-clotted (LPH) foam configurations. Each foam was cut initially in the bare foam configuration using a hot wire, reticulated, and biopsy punched into an 8 mm diameter foam cylinder. Each bare punched foam was then cut to a height of approximately 6.6 – 6.9 mm and used for testing. Foams were heated and compressed using a stent crimper (Machine Solutions, Inc) to reduce their size and allow for

placement into the prototype. Compressed foams were attached to the prototype nitinol frame by supergluing foams to the inner proximal end of the device. Alternatively, the hydrogel-clotted foams were freeze dried prior to crimping. Once crimped, the clotted foams were ready to be inserted into the device after shaving one end of the foam down to a fine point to enable gluing to the proximal end of the device.

Blood Clot Mimics

A separate study was conducted to determine the correct hydrogel solution that could mimic the effects of blood clotting when added to bare foams. Polyacrylamide hydrogels were used in this study due to their use for similar applications in published studies (Jaeger et al.) [13] and their easily tailorable modulus. The study was conducted on 1 cm diameter bare, bovine blood-clotted, and hydrogel-clotted foams (Figure 3). A microscope (Leica, Wetzlar, Germany) camera (Jenoptik, Jena, Germany) was used to capture the image of the blood-clotted foams and a VHX 5000 digital microscope (Keyence, Osaka, Japan) was used to photograph the bare foams and hydrogel-clotted foams for greater image contrast.

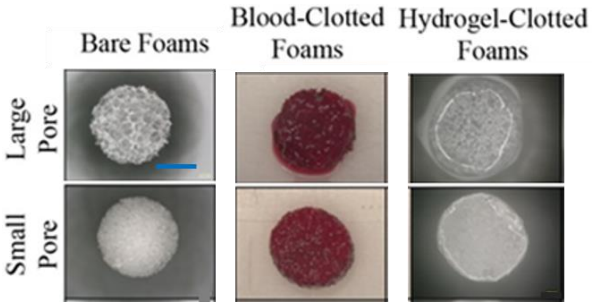

Figure 3: Images of large pore and small pore, bare, blood-clotted, and hydrogel clotted foams. The halos are an artifact of the lighting used to illuminate the foam struts. The 5 mm scale bar in the top left image is the same in all images.

Bovine blood was obtained as part of a tissue share program with the Rosenthal Meat Science and Technology Center at Texas A&M University in College Station, TX. All blood in

this study was obtained from animals sacrificed for purposes unrelated to this research. Polyacrylamide hydrogel solutions were manufactured following the protocols given by Tse et al. [14], and a series of compositions using varying amounts of acrylamide (Sigma-Aldrich) and bis-acrylamide (Sigma-Aldrich) was formulated to find the hydrogel composition with the closest match to the blood clotted foams using dynamic mechanical analysis (DMA, TA Instruments). The storage moduli for six foams of each foam composition were recorded and compared to determine the ideal hydrogel composition.

Dislocation Force Testing

Dislocation force testing was conducted using an Instron test frame with a 500 N load cell (Figure 4). The rod holding the device was centered in the Instron clamp and secured.

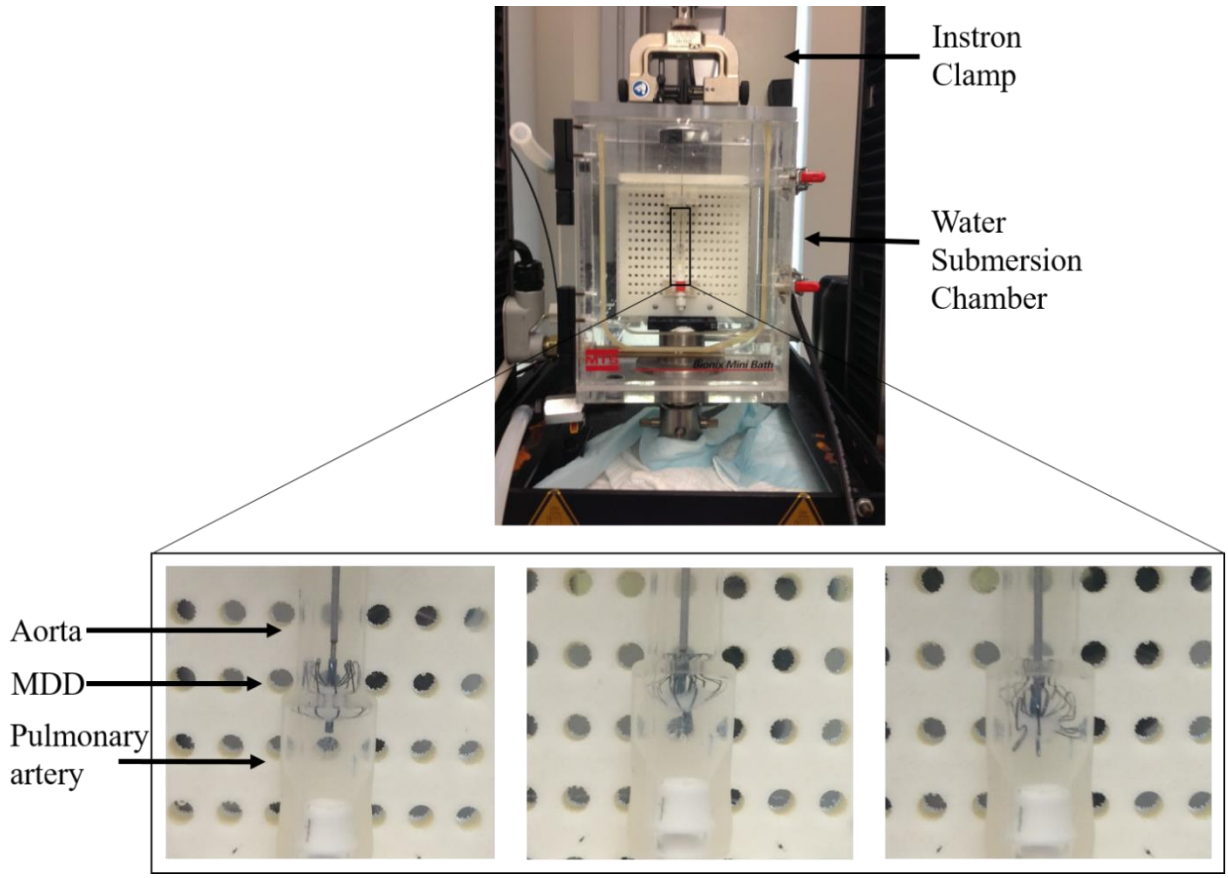

Figure 4: Instron Test Frame and water submersion chamber with test progression for the IIA 5 mm model small pore trial, (left to right) at 0 mm, 6 mm (max force), 6.74 mm extension.

At the start of each test, the Instron load cell was balanced prior to advancing the device through the MDD at a rate of 2 mm/minute. The devices were inserted into each of the models by placing the waist of the prototype across the MDD of the model. This placement was done in every case except for the IIB 3 mm model with hydrogel-clotted foams. The hydrogel-clotted foam diameter was approximately equal to the MDD of the IIB 3 mm model, and the prototype could not be positioned normally without distorting its shape. Thus, for the IIB model, the MDD and waist diameters matched, and the proximal cage was left elongated with the foam only on the aortic side (Figure 5).

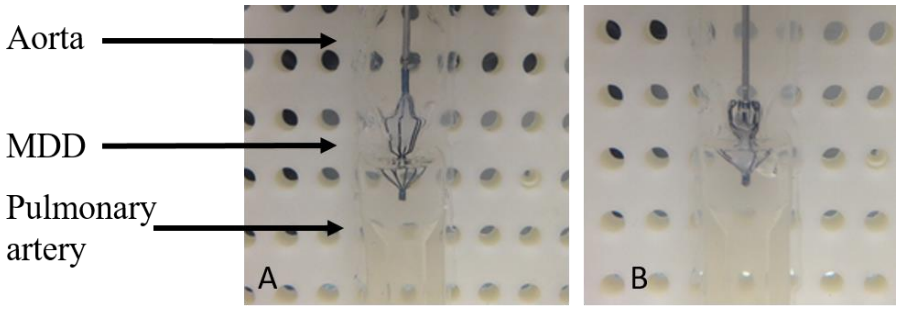

Figure 5: Device placement in IIB 3 mm model with (A) small pore hydrogel foam and (B) large pore bare foam.

Once inserted into the prototype and model, all foams were placed in a 50˚C water bath, and expanded to their original size. After the foams were fully expanded, models containing the prototypes were submerged in a 35 – 36˚C water chamber, simulating physiological conditions. Luer fittings placed at each end of the model were inserted into the clamps of a board holding the model, and a rod was attached to the device (Figure 4).

The test was stopped once all ten struts of the prototype were pushed through the model into the pulmonary artery side of the model (Figure 4). In all, each model and foam combination was tested with three separate prototype devices and one ACDO. The dislocation force was recorded and averaged to compare results between sample types.

Statistical Analysis

The mean dislocation forces of all foam compositions and model types were compared using two sided analysis of variance (ANOVA) with Tukey multiple comparisons. This analysis was utilized to evaluate differences in dislocation force between each comparison ($p - value < 0.05$). Two sets of analysis were run. One set compared each foam composition, small and large pore, and bare and hydrogel foams, within a single model type. The other analysis set compared each model type using a single foam composition. Two sided ANOVA with Tukey multiple comparison was also used to compare the mean storage moduli for DMA results.

CHAPTER III

RESULTS

Blood Clot Mimic Composition

The storage moduli for three hydrogel compositions, bare foams, and blood-clotted foams were compared with one another, as shown in Figure 6.

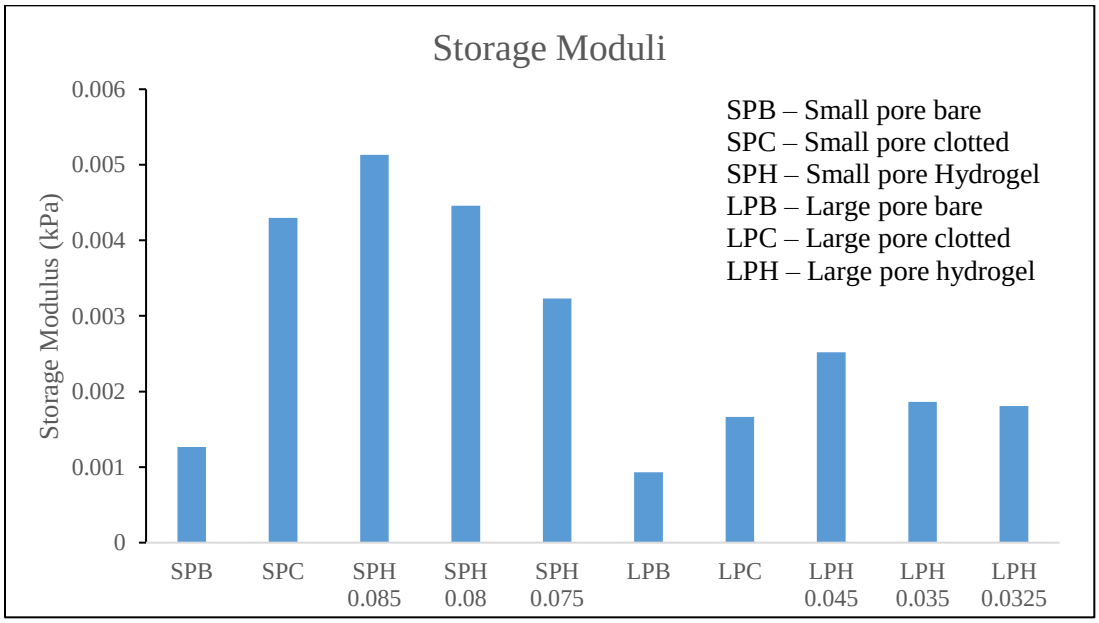

Figure 6: Storage moduli for small pore bare, small pore clotted, small pore hydrogel, large pore bare, large pore clotted, and large pore hydrogel foams. Hydrogel foams were fabricated with 3.0% acrylamide and varying bis-acrylamide concentrations (0.0325-0.085%), as shown below each bar.

From preliminary tests, it was determined that 3.0% acrylamide compositions should be used in all hydrogel compositions. The difference between the blood-clotted foams and all three of the hydrogel foam compositions for both small pore and large pore foams was not statistically significant. Therefore, the composition with the average that most closely resembled the average

of the blood clotted foam was selected. Based on these averages, the selected hydrogel compositions were 3.0% acrylamide with 0.08% bis-acrylamide for small pore foams and 3.0% acrylamide with 0.0325% bis-acrylamide for large pore foams (Figure 6).

Influence of MDD Size and Pore Size on Dislocation Force

The MDD size can play a crucial role on the dislocation force on each of the foams types. The smaller 3 mm MDD models provide more resistance, resulting in a higher dislocation force for all foam compositions compared to the larger 5 mm MDD models, as shown in Figure 7 and Table 1. Due to the lack of resistance in the 5 mm MDD, differences in foam compositions play a lesser role in dislocation force compared to the 3 mm MDD, demonstrating the effects that oversizing the device within the MDD can have on the dislocation force.

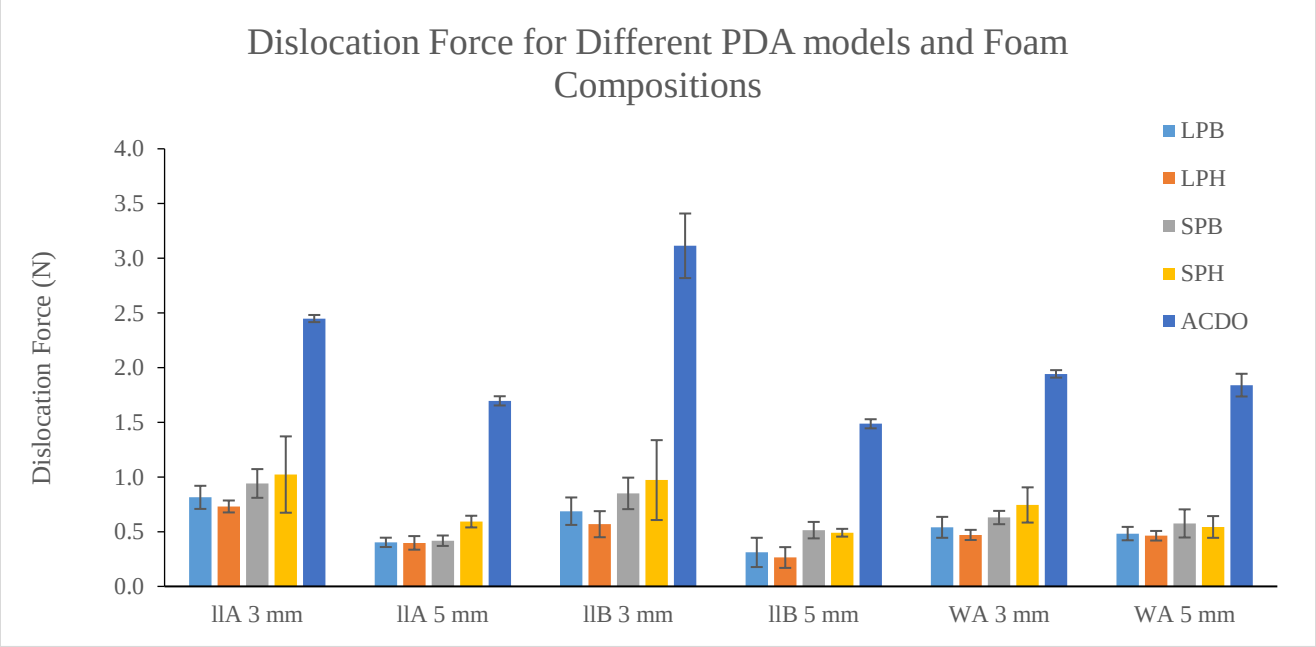

Figure 7: Dislocation force for different PDA models and foam compositions. LPB – Large pore bare foams; LPH – Large pore hydrogel-clotted foams; SPB – Small pore bare foams; SPH – Small pore hydrogel-clotted foams; ACDO – Amplatz Canine Ductal Occluder.

Table 1: Average dislocation force (N) and standard deviations for devices in IIA, IIB, and WA PDA models.

PDA Model (MDD)[1]	Dislocation Force (N) for Device Configuration				
	LPB	LPH	SPB	SPH	ACDO
IIA (3mm)	0.814 ± 0.106	0.731± 0.055	0.941 ± 0.131	1.023 ± 0.349	2.448 ± 0.033
IIA (5 mm)	0.403 ± 0.043	0.398 ± 0.062	0.418 ± 0.048	0.593 ± 0.053	1.696 ± 0.042
IIB (3 mm)	0.688 ± 0.125	0.569 ± 0.119	0.850 ± 0.144	0.972 ± 0.365	3.114 ± 0.295
IIB (5 mm)	0.311 ± 0.134	0.264 ± 0.095	0.514 ± 0.075	0.491 ± 0.036	1.487 ± 0.042
WA (3 mm)	0.540 ± 0.096	0.471 ± 0.046	0.630 ± 0.061	0.745 ± 0.161	1.943 ± 0.034
WA (5 mm)	0.483 ± 0.061	0.463 ± 0.044	0.576 ± 0.129	0.544 ± 0.099	1.840 ± 0.104

[1] MDD – Minimal Ductal Diameter; LPB – Large pore bare foams; LPH – Large pore hydrogel-clotted foams; SPB – Small pore bare foams; SPH – Small pore hydrogel-clotted foams; ACDO – Amplatz Canine Ductal Occluder

Small and large pore foams were studied, as different pore morphologies are necessary for different applications. For each model used, the LPB foams displayed lower dislocation forces than the SPB foams. This could be expected since, as mentioned previously, small pore foams are denser, providing more resistance to removal. The lower density composition of the LPB foams allows for easier removal within a given model. The same can be said for SPH and LPH in the same model, where LPH foams have a lower dislocation force compared to the denser SPH foams. While small differences are observed, the statistical analysis indicates that the variations were not significant.

Comparison of Bare and Hydrogel-Clotted Foams

Bare and hydrogel foams were compared to demonstrate the change in dislocation force of a device first inserted into the body and acutely when the foam has clotted with blood forming a thrombus. In most cases, the numerical differences in dislocation force between the bare foam and the hydrogel counterpart are very small and are also statistically insignificant. This observation indicates that the difference between the two foam compositions have little impact on dislocation force. However, in most foam compositions and model types, the bare foams do demonstrate a slightly larger dislocation force than the hydrogel foams, with the exception of

SPH foam in the 3 mm MDD models (Figure 7). The higher dislocation force of the hydrogel foams is expected due to the density of the small pore foams in combination with the hydrogel. This characteristic of the SPH composition, in addition to a smaller MDD, make the foams more constricted and result in a higher dislocation force. It is important to note that the increased thickness of the SPH foams compared to other foam compositions also makes it difficult to crimp hydrogel-clotted foams to a size that is small enough to fit through the MDD of the IIB 3 mm model. Due to the size of the crimped foams in combination with the angular morphology of the IIB 3 mm model, the SPH foams were placed only in the proximal end of the model (Figure 5). Typically, the foam is deployed across the MDD, however, the positioning of the foams in the IIB models require that they be fully compressed through the MDD increasing the dislocation force. In bare foams, the foams can be placed across the MDD reducing the amount of total force required to dislodge the prototype. Therefore, the SPH in the IIB model would be expected to display a higher dislocation force for the 3 mm MDD models. In general, the ACDO's uniform mesh provides fewer differences in the way the device interacts with each of the three models. In every case the only factor that influences the device dislocation force is the MDD of the model.

Comparison of Dislocation Force in All Models

When looking at the three models' dislocation forces, the WA model (Figure 7) noticeably demonstrates little variation between each foam composition. This is most likely due to the expanded ampulla that the WA model represents. The wider ampulla size provides less contact with the prototype device. Therefore, any changes in foam composition are less pronounced, since the prototype itself has a greater degree of mobility. In contrast, the IIA and IIB models have more contact with the prototype and have higher variations in dislocation forces

(Figure 7). For all three models, the ACDO had larger dislocation forces than the prototype device, and the dislocation force was larger for the 3 mm MDD models when compared to the 5 mm MDD models. Similarly to the prototype device dislocation forces, the ACDO device dislocation force was relatively unchanged for the WA model whereas a greater difference can be seen in the IIA and IIB models.

Implications for the ACDO and PDA Prototype

The differences in dislocation force between all foam compositions were minimal for each model tested (Figure 7). The insignificance of the of hydrogel-clotted foam and bare foam results show the device's relative stability, which is most crucial when the device is first deployed, can be expected to remain the same even after thrombus forms, potentially indicating long term stability. The minimal differences in dislocation force for small pore and large pore foams also indicate the viability in using either of the pore sizes for various applications. For example, if pore sizes can be made large enough to allow for smaller crimp diameters without affecting the dislocation force, then devices can be manufactured for even smaller animals.

The ACDO device is the current leading method for device occlusion. After analyzing the results of experiments with the ACDO and the PDA prototype, it is evident that the ACDO does demonstrate a higher dislocation force. However, this data does not discount the viability of the stability of the PDA porotype simply because the dislocation force is not as large. The device's stability in the vessel is not solely determined by the dislocation force. The dislocation force can provide valuable insight into the way the prototype may be influenced by changing foam compositions, though it is evident that foam composition plays a lesser role in the prototype dislocation force than the nitinol cage that comprises the device itself. Thus, dislocation force also demonstrates the ways different PDA morphologies may influence the stability of the device

based on the ways the prototype must change shape to conform to different models. More specifically, the way the device is deployed and positioned plays a large part in the device stability. This is most evident in the way the dislocation force results were influenced by positioning of the small pore hydrogel-clotted foam in the IIB 3 mm model, the MDD size, and the lack of ampulla-prototype contact in the WA models. Additionally, when deploying the device, surgeons perform a "push-pull test" where the delivery cable, still attached to the device, is gently pushed and pulled after positioning the device to determine if it is stable enough to deploy. Potentially, if the "push-pull test" exceeds the dislocation force, the device will be forced through to the distal side of the vessel and the surgeon will either need to recapture and reposition, or remove the device. Thus, the dislocation force can provide insight into the mechanical stability of the PDA prototype and the ACDO, though it is not the only factor to consider.

CHAPTER IV

CONCLUSION

In conclusion, the lack of variation in dislocation force due to foam composition can be a powerful asset in future device development while broadening the prototype uses and capabilities. Since the foam is specific to the prototype and not the ACDO, the prototype may prove more advantageous to use in certain future applications. In addition, the lack of significance in effects of foam compositions indicates that the placement of the nitinol frame of the prototype device is more influential in the device dislocation force. The strong influence of MDD size on dislocation force emphasizes how crucial it is to oversize devices in the vessel to maintain stability. Lastly, the dislocation force provides insight into the ways each of the devices can be affected by PDA morphology and how the prototype may also be affected by its use of SMP foams for occlusion. We now know the ACDO structure provides enough resistance to maintain a high dislocation force, and that the foam composition can be varied in the prototype device to fit the needs of the situation without compromising the device's potential stability. It is also possible to increase the prototype stability by increasing the length or width of the struts composing the nitinol frame. However, it is also important to note that in addition to dislocation force testing, more studies can be performed, such as flow driven tests, to further characterize the device's mechanical stability.

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