A unique embolic protection device to mitigate circulating debris generated during cardiac surgeries

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Abstract

Postoperative cerebral injuries due to debris traveling up the carotid arteries can be a devastating complications of open-heart surgeries. While the benchmark medical device manufacturers sought to address the problem with embolic protection devices, so far, clinical outcomes have not improved. This study builds on a solution proposed by demonstrates the feasibility to use a double-layered, pocketed medical grade mesh, with a conical Nitinol frame. To conduct preliminary tests for capture efficiency and the design's effect on blood flow, planar and conical mesh structures were built (PMSs, CMSs). Each structures were either single layered (SL) (100 μm pore size), double layered (DL) (350 μm pore size mesh on the inner layer), small pocketed double layered (SP DL) or large pocketed double layered (LP DL). PMSs were tested for their capture efficiency and on average caught 92.47 ∓2.02% of the introduced debris. CMSs were placed in an aortic model and were tested for their capture efficiency as they were being retrieved. SP DL CMSs caught significantly more debris than the rest (*P>0.05*) with an average of 96.67∓8.09%. Furthermore, preliminary modeling of fluid dynamics shows a 36-fold drop in velocity across the CMSs of the water exiting a cannula with an average velocity of 225.08 ∓ 1.40 cm/s. Future studies will account for and include the use of blood both for computational modeling and for a flow profile analysis of blood as it flows through the EPD, with Doppler ultrasound imaging. The verification tests presented in this study were promising in terms of the debris capture of the proposed EPD. With the conceptual framework that this study has built, and with the identified limitations, future verification experiments will aim to ensure and underscore the safety of use of the proposed EPD. These preliminary results and the next set of verification experiments should lead to validation studies in animal models for an extensive preclinical trial. Eventually, the iterative design process and early adaptation to challenges ahead will result in a product that would protect open-heart surgery patients from cerebral-injury, all around the world.

I. INTRODUCTION

A. The Need to Mitigate Debris Release to Prevent Cerebral Injury Related to Cardiac Surgeries

As life-saving as they may be, cardiac surgeries put patients under a documented risk of cerebral injury. Debris traveling up the carotid arteries during surgery often causes postoperative stroke (PS) and cognitive decline (CD) – devastating complications for patients and their families. The incidence of these procedures averages more than 290,000 every year in the US [1], and is likely to increase as the population ages. 50% of all heart failure diagnosis, and 90% of all heart failure deaths occur for patients over the age of 70 [2]; and the population over the age of 65 in the US is expected to double in the next 40 years [3]. Studies have demonstrated that permanent cerebral injury not only is the leading cause of disability in the US, [4] occuring in as many as 6% of the cardiac surgical patients, [5] but also increases the mortality rates significantly, doubles the cost of care [6], and lengthens the time of stay in the ICU, burdening both the families and the hospitals. There is an unmet clinical need to mitigate debris release in patients undergoing open-heart surgeries in order to reduce postoperative ischemic events.

B. Cerebrovascular Disease and Cardiopulmonary Bypass

Cerebrovascular disease is the fourth leading cause of death and the leading cause of disability in the US[4]. Transient ischemic attacks (TIA) and ischemic strokes are common results of a single and prevalent pathological mechanical pathway: vascular occlusion in the cerebellum. The diagnosis of stroke versus TIA is based on the presence of an infarct with the former. The duration of symptoms is no longer a distinguishing criterion. A TIA is considered to be the precursor of an ischemic stroke and conveys a high risk of recurrent stroke within 90

days [4] as well as a 5% risk within 24 hours [7] of the first event. In both stroke and TIA, cerebral vessel occlusion prevents natural blood flow to the brain and causes hypoxia and eventual cell death in the post-occlusion cerebral areas. If the debris that clogs vessels is too fine to cause stroke or TIA, it is hypothesized that (micro)occlusions can still affect smaller and undetected areas in the brain resulting in CD, also known as “Pump Head Syndrome.”[29] While a quantitative measure is difficult to provide, CD is often distinguished when patients, relatives or caregivers observe a notable decline in cognitive performance of the patients.

Cardiopulmonary bypass is a common and essential method of redirecting blood flow to a heart-lung machine (HLM) in order to stop and subsequently operate on the heart. The procedure procures pressure drive and oxygenation during the open-heart surgery, mimicking the functions of the heart and lungs. The oxygenated blood flowing from the HLM returns through an aortic cannula that is surgically inserted into the ascending aorta through a incision hole of 15 mm **(Figure 1)**. The inner linings of the aorta consist of cholesterol and fatty tissue. It is hypothesized that physical disturbances such as clamping and unclamping, incisions, and the blood exiting the aortic cannula with high velocity hitting the inner walls (the sandblasting effect) cause debris to be dislocated and join the circulation. When the debris travels up the carotid arteries, it blocks arteries or capillaries in the brain, causing ischemic strokes, TIA, or CD.

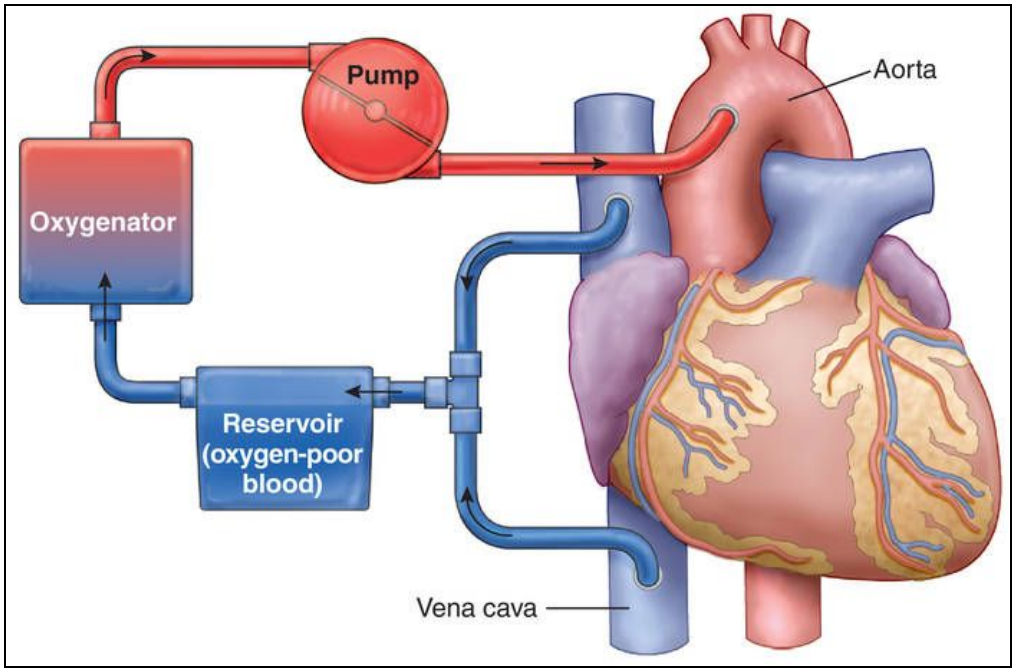


Figure 1: **Heart-Lung Machine diagram** (courtesy of Medical Dictionary, © 2009 Farlex and Partners). After the heart is stopped and the aorta is clamped, the deoxygenated blood is collected through vena cavae and flows through an oxygenator and gets pumped back into circulation through the tip of an aortic cannula inserted into the aorta. In the meanwhile the aorta gets clamped as well. This procedure exacerbates the risk of debris release due to the clamping of the aorta, the incision in the aorta, and the impact of high velocity blood exiting the cannula has on the inner aortic walls.

C. Risk Factors

Literature shows that most of the risk factors for PS are nonmodifiable, although there is conflicting evidence within the field. For instance, age often is considered to be a risk factor for PS, and according to Cropley *et al*. the likelihood of PS is twice in octogenarians compared to younger patients [7]. However, a retrospective study by Carrascal et al. compared the postoperative stroke incident rates of 418 patients over the age of 80 and 426 younger patients and found no significant difference (4.1% and 3.6% incidence rates, respectively) [8]. Moreover, in the older cohort, a multivariate analysis demonstrated that preoperative anemia was the leading risk factor and factors related to intraoperative brain oxygenation were the second most critical determinants. For the younger cohort, preoperative peripheral vascular disease and

postoperative atrial fibrillation were found to be risk factors [7], in parallel with previously published studies.

Another retrospective study, conducted by Bucerius *et al,* includes 16,184 patients undergoing cardiac surgery in order to identify the risk factors. While the study showed that the overall incidence rate of stroke was 4.6%, the rate varied across the type of surgeries (Coronary artery bypass grafting (CABG): 3.8%; beating-heart CABG: 1.9%; aortic valve surgery (VS): 4.8%; mitral VS: 8.8%; double or triple VS: 9.7%; CABG & VS: 7.4%)[5]. An important finding that Bucerius *et al.* shared was that the duration of CPB was also a risk factor: CPB time longer than two hours often indicates a technical difficulty due to unfavorable anatomy or intraoperative complications, thus making it an important risk factor [5].

Another risk factor is atheroma in the ascending aorta [9]. An atheromatous aorta comprehends abnormal plaque accumulation on the inner linings of the aorta. Atheroma can be assessed by surgical palpation, or through newer techniques such as epiaortic ultrasound and transesophageal echocardiography [7]; however, the diagnosis often fails to be reliable. Considering that it increases the likelihood of PS three- to four-fold, a better diagnosis is imperative [9].

The literature suggests that the most feasible ways of preventing the harms of strokes are preoperative risk factor modification (such as exercise and healthy diet), early recognition and management [7]. Nevertheless, there is currently no technology that have met the important clinical primary endpoints such as decreased mortality rate and decreased incidence rate of strokes.

The risk factors of CD, likewise, have not been clearly identified. Although some promising approaches have been proposed by researchers, there is no clear guideline on prevention. A Revascularization On versus Off Bypass (ROOBY) trial evaluated the effect of

on-pump versus off-pump CABG on cognitive impairment with 581 on-pump and 575 off-pump patients, and no significant difference in the level of cognitive impairment between the two method was found [10]. Following up on the ROOBY trial, Kozora *et al.* found that among the 1,156 patients studied, lower cognitive function, age, education level, and ethnicity were predictive factors of CD rather than the on- vs. off-pump procedure.

Intraoperative cerebral ischemia and cerebral oxygen desaturation (hypoxia) are thought to be risk factors as well. In a cohort of primary CABG patients (either prospectively randomized blinded control group or an unblinded intervention group), Slater *et al.* monitored intraoperative regional cerebral oxygen saturation (rSo_2) and assessed cognitive function preoperatively and postoperatively. Calculating rSo_2 desaturation score by multiplying the amount of time in seconds that rSo_2 was below %50 with the rSo_2 below 50%, Kozora *et al.* found that patients with rSo_2 desaturation score larger than 3000%-seconds were under significantly higher risk of cognitive impairment [11]. The study concludes that oxygen desaturation is an important risk factor for cognitive impairment, hence attempts at preventing vessel occlusion and consequent cerebral hypoxia can protect the cerebellum from injuries.

D. Epidemiology

The incidence rate of stroke is not a readily available number. However, studies summarized in Table 1 demonstrate that the incidence rate had been around 3.0-4.0% since 2001. Furthermore, a simple calculation of total patients and total stroke patients in all the studies reveal a solid 4.00% stroke incident rate. The same calculation, however, cannot be done for the mortality rates, for that the clinical endpoint time vary from study to study (24 hours, 30 days, 1 year etc.).

Incidence Rate of Stroke According to Various Studies			
Study	**Cohort**	**Stroke Incidence Rate**	**Perioperative Stroke-caused Mortality Rate**
Carrascal *et al.* "Postoperative stroke related to cardiac surgery in octogenarians" 2014 [8]	**Group A**: 418 patients over 80 **Group B**: 426 patients younger than 80	**Group A**: 4.1% **Group B**: 3.6%	**Group A**: 41.2% **Group B**: 26.7%
Anyanwu *et al.* "Epidemiology of stroke after cardiac surgery in the current era" 2007 [12]	5,085 patients	2.6%	32.8%
Bucerius *et al.* "Stroke after cardiac surgery: a risk factor analysis of 16,184 consecutive adult patients" 2003 [5]	16,184 patients	4.6%	22.2% at 30 days
Salazar *et al.* "Stroke after cardiac surgery: short- and long-term outcomes" 2001 [6]	5,971 patients	3.6%	33% at 1 year 53% at 5 years

Table 1: A comparative table summarizing four studies and their findings on the incidence rate of perioperative strokes and related mortality rates

In 2014, over 210,000 patients underwent CAB and over 155,000 patients underwent isolated valve operations, both of which need a CPB procedure [13]. According to Table 1 and overall stroke incidence rate calculated above, out of 365,000 patients, 14,600 patients developed perioperative stroke in 2014 in the US alone.

With a variety of risk factors and disparate cohort characteristics, Table 2 demonstrates the overall challenge to understand the uncertainty of underlying risks for postoperative CD. Both the level and persistence of CD varies across different cohorts and characteristics. In any

case, CD has been proven to be associated with cardiac surgeries and affecting more than at least 10% of the patients postoperatively.

Incidence Rate of CD According to Various Studies			
Study	**Cohort**	**CD Incidence Rate**	**Method of Cognitive Test**
Kozora *et al.* "Cognitive Outcomes After On-Versus Off-Pump Coronary Artery Bypass Surgery" 2010 [10]	1,156 patients **On-pump:** 581 **Off-pump:** 575	**On-pump:** 12.0% **Off-pump:** 13.2%	Combination of subtests from: -Wechsler Memory Scale -Wechsler Adult Intelligence Scale -Trail Making Test A and B -Clock Drawing
Cook *et al.* "Postcardiac Surgical Cognitive Impairment in the Aged Using Diffusion-Weighted Magnetic Resonance Imaging" 2007 [14]	50 patients over 65	30%	Standardized 10-test neurocognitive battery
Newman *et al.* "Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery" 2001 [15]	261 patients who underwent CABG	53% at discharge 36% at 6 weeks 24% at 6 months 42% at 5 years	Standardized 5-test neurocognitive battery
Shaw *et al.* "Long-Term Intellectual Dysfunction Following Coronary Artery Bypass Graft Surgery: A Six Month Follow-Up Study" 1987 [16]	259 patients	88% mild cognitive dysfunction 12% moderate or severe impairment	Standardized 10-test neurocognitive battery

Table 2: A comparative table summarizing four studies and their findings on the incidence rate of perioperative CD and methods of cognition assessment

The PS and CD distribution and prevalence in cardiac patients are high, and expected to rise with the aging population. Although the studies have shown that the risk factors vary, it is unarguably clear that this devastating clinical problem stems from cerebral hypoxia and no efficient prevention method has been devised yet.

E. Economic Impact

The economic burden of postoperative neurovascular diseases is remarkable. A study conducted in 2001 by Salazar *et al.* estimates a 15-day increase in the postoperative length of stay for the perioperative stroke patients, which raises the hospital cost about $30,000 [6]. A more recent study conducted by Stamou *et al.* shows that as many as 35,000 perioperative strokes occur per year [17]. Furthermore Anyanwu *et al.* calculates that PS causes an incremental increase of 30 days in the length of stay in PS patients and with a conservative cost of $1000 per day (an average of $30,000 per patient per overall prolonged hospital stay, in parallel with the foundings of Salazar *et al.*), the cost of healthcare related to PS may surpass $1bil annually in the US [12].

While the disease puts patients and their families under great strain, its prevalence burdens the healthcare system significantly. Considering the studies by Salazar *et al.* and Anyanwu *et al.* were conducted in early 2000s, in over a decade both the cost of care, and the number of patients must have increased, exceeding $1bil significantly as of today.

F. Prior-Art-Research

As the studies dating back to 1980s show, the clinical need for a solution had been present for a long time. Several medical device companies addressed the problem and designed, tested and released devices into the market to reduce the incidence rate of PS and CD. In that regard, there had been two major predicates identified:

1) CardioGard Embolic Protection Cannula (CEPC)
2) Embol-X (EX)
    a) Access Device / Aortic Cannula
    b) Intra-Aortic Filter

To date, CEPC and EX are few of the only embolic protection devices (EPD) intended to reduce emboli during cardiac surgery approved by the Food and Drug Administration (FDA).

Technical Comparison of Predicate Embolic Protection Devices [18]

	CEPC	EX Access Device / Aortic Cannula	EX Intra-Aortic Filter
Intended use	CEPC combines an aortic cannula with a suction cannula that allows for blood cells to pass and capture debris in the ascending aorta, during procedures that require CPB.	Intended for the perfusion of the ascending aorta for procedures which may require introduction and removal, in a hemostatic fashion, of compatible vascular devices, such as an EX Intra-Aortic Filter.	To be used with EX Access Device / Aortic Cannula, in non-emergent cardiac surgery procedures that require CPB and cross clamping of the aorta. EX Intra-Aortic Filter aims to capture and remove any debris from the ascending aorta in patients 18 and older.
Use duration	For the length of the surgery (<= six hours)	For the length of the surgery (<= six hours)	May remain *in situ* up to 60 minutes.
Design	Consists of two curved tips with two ports, one for the aortic perfusion of oxygenated blood, the other for suction of debris from the aortic arch.	Consists of two curved tips with two ports, one for the aortic perfusion of oxygenated blood, the other is an open hole for the insertion of EX Intra-Aortic Filter that would remove debris from the circulation.	Consists of a filter that fills the diameter of the aorta, and manufactured in five different sizes to conform patient anatomy. Also a cartridge that firmly connects to the open port of the EX Access Device / Aortic Cannula.
Dimensions	Cannula tip size: 24 Fr Main tube diameter: 3/8" Suction tube diameter: 1/4" Length of cannula: 30 cm	Cannula tip size: 24 Fr, with 20 Fr effective flow Main tube diameter: 3/8" Second port diameter: unknown Length of cannula: 28 cm	Filter opens to conform to the aortic size, from 2.2 cm to 4.0 cm, five sizes are available.

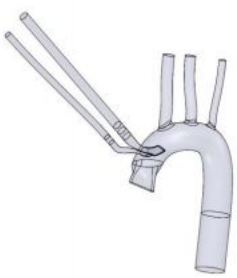
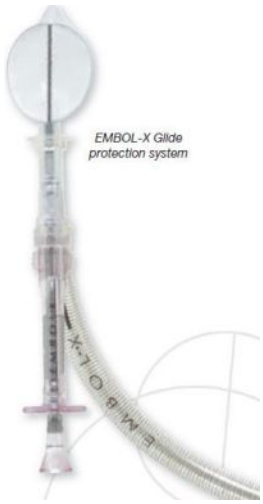
Schematic of device			
Biological Safety	Confirmed biocompatibility in accordance with testing under ISO-10993.	Biocompatible polymeric tubes	Biocompatible and traditional medical grade meshes

Table 3: Technical comparison of predicate embolic protection devices

Table 3 outlines the technical qualities of the predicate devices. CEPC (Cardiogard Medical, Or Yehuda, Israel, see **Table 3, Schematic of Device, CEPC**) is a medical device that combines a regular aortic cannula with a suction orifice at the tip of the cannula. It is intended to be used for the duration of the whole surgery and remove all the gaseous and solid emboli out of the blood flow. CEPC was tested for safety and efficacy in a small, randomized, controlled trial by comparing 24 CEPC patients with 27 control patients (no CEPC) undergoing aortic valve replacement with or without CABG. While the results showed a decrease of brain lesions for CEPC patients versus control patients, there was no significant difference between the two groups for the important clinical end-points of stroke, death, major adverse events, and Mini-Mental Examination Score [9].

EX, on the other hand, is an intra-aortic filtration device in combination with a special delivery piece that is intended to capture showers of debris and emboli during the surgery (Edwards Lifesciences, Irvine, CA, see **Table 3, Schematic of Device, EX Access Device / EX Intra-aortic Filter**). It is deployed into the aorta before cross-clamping of the aorta, removed,

and re-deployed while removing the cross-clamp. EX was tested for safety and efficacy in a larger, multicentered and randomized trial of 1,289 patients undergoing isolated CABG, aortic VS, or mitral VS. While it captured “particulate emboli” for 97% of the patients, just like CEPC, the device failed to meet important clinical end-points of stroke, death and major adverse events between the controlled group and EX group [9].

The conflicting data urged National Heart Lung and Blood Institute-sponsored Cardiothoracic Surgical Trials Network to conduct a clinical trial: a randomized trial with 383 patients undergoing aortic VS with or without CABG, using EX, CEPC or control cannula in a 1:1:1 ratio [9]. Both of the devices successfully captured debris and reduced the incidence rate of postoperative delirium. However, neither of the devices prevented the incidence of clinically or radiologically diagnosed central nervous system (CNS) infarction, stroke, or cognitive decline at 90 days, the primary end-points of the trial [9].

While the capture efficiency of the devices were satisfying, there are few theories for why serious events were not prevented. It is hypothesized that the lesions and stroke can arise from fine embolic showers, and while intra-aortic filters such as EX are good at capturing them, upon removal, either small ruptures occur or the flow dynamics within the aorta cause debris to dislodge from the filter and join the circulation. This could be attributed to three of EX’s features: a potentially unsafe delivery cannula, a non-canonical shape, and no added measure to prevent debris from dislodging during removal. Some of the “device problems” of EX as classified by and filed to the FDA were: **i)** Fluid Leak, **ii)** Leak/Splash, **iii)** Detachment of Device Component [19]. On the other hand, the velocity profile of the blood flow affects the embolic capture efficiency of CEPC, and a shower of emboli flowing with high velocity may not be completely captured. An important metric here is that neither of the devices is able to prove how much of

the debris it had caught, but only whether it caught any debris or not. The ratio of debris caught must be an important driving point for future designs.

G. Stakeholder Analysis

The ultimate receiver of an embolic protection device and its benefits may be the patient, but from ideation to market release, a medical device goes through important considerations by multiple decision-maker entities, namely stakeholders.

For the stakeholder analysis, it is important to clearly identify and understand the cycle of care and how a patient interacts with the medical system in place. Perioperative neurovascular diseases have their own unique cycle of care for which both cardiac and neural comorbidities occur, and they require a unique set of care providers for which specialists of both cardiac and neural fields are needed.

Figure 2 outlines the important stages in the cycle of care of PS from the start of the cardiac disease symptoms to the discharge of the patient from the hospital. From this cycle, it can be deduced that there are currently three important stakeholders: patients, cardiothoracic surgeons, and neurologists. While cardiothoracic surgeons are involved in eliminating life-threatening complications, neurologists also aim to prevent mortality and also prevent a decrease in the quality of life of the patient. Nevertheless a device that aims to prevent PS during the surgery, eliminates the neurologist as a stakeholder, and leaves the receiver of care (patient) and the provider of care (surgeon) as the main stakeholders most intimately involved with this cycle.

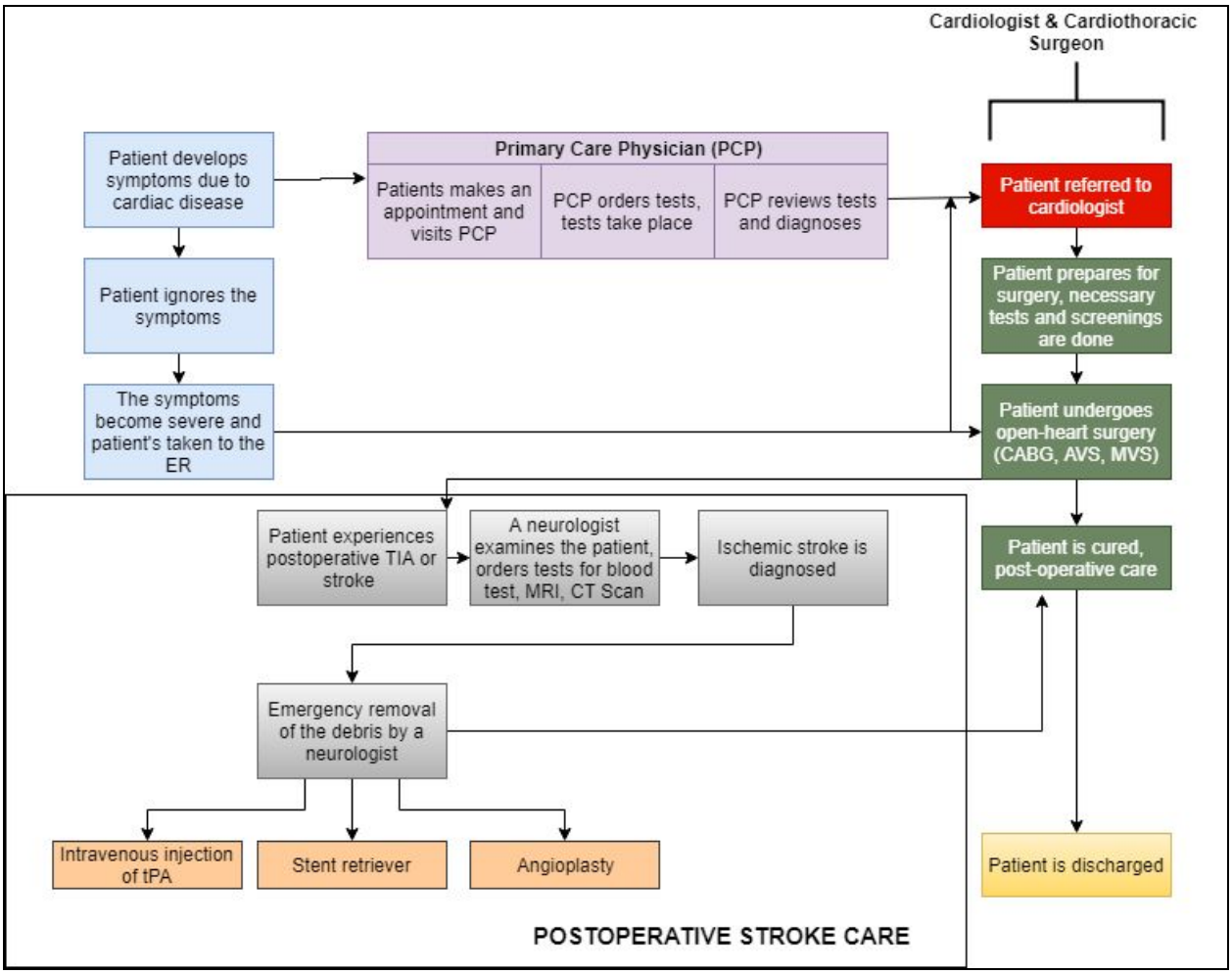


Figure 2 The cycle of care for PS: The cycle of care for PS, a complex network involving multiple provider facilities and healthcare specialists, produced after a thorough stakeholder analysis

At the higher level, an analysis of the money flow would identify stakeholders that directly or indirectly finance the cycle of care in **Figure 2**. The financial system in the US can be divided into four broad areas:

1) Funders:
    a) Taxes
    b) Employers and employees
    c) Individuals
2) Payers:

    a) Medicare & Medicaid
    b) Private Insurers

3) Providers:
    a) Physicians & surgeons
    b) Outpatient facilities
    c) Pharmacies
4) Patients

Employers, employees and individuals fund Medicare & Medicaid (M&M) through taxes, or Private Insurers. M&M, in return, pays either directly the providers or private insurers. While patients with no insurance directly pay the providers, other patients receive insurance privately or through employment. Outside of this flow of money analysis, there are associations and foundations, which can be considered as stakeholders, that are working with governments, insurance companies and providers so that the patients receive a fair treatment with a fair price.

In conclusion, stakeholders can be identified as such for PS and CD care and prevention with an EPD:

1) American Heart Association (AHA) / American Stroke Association (ASA)
2) Cardiothoracic surgeons
3) Hospital representatives or advocates
4) Private and public insurance companies
5) Patients

Stakeholder Analysis for PS and CD Care and Prevention with an EPD				
Stakeholder	**Role**	**Benefits**	**Primary costs**	**Assessment of net impact**
Payers Private and public insurance companies	Decision maker	Bringing life-saving and quality of life improving technology to patients	Decreased costs	**Positive** While the total cost of delivering cardiothoracic surgery will increase slightly, total cost of care including PS patients would decrease
Providers Cardiothoracic surgeon	Influencer	Shorten the average amount of time spent per patient, safer procedures	Learn to use a new device	**Positive** Hospital stay of patients would decrease on average, unburdening the surgeons postoperatively
Providers Hospitals	Influencer	Decreased cost of care per patient on average	New device purchase and regulation	**Positive** Total cost of care would decrease of a hospital over time, same way it did for **Payers**
Patients	Influencer	Decreased risk of PS and mortality	Slight increase in surgery cost	**Positive** Life-saving and quality of life improving technology for a small increase in price
Foundations AHA / ASA	Influence	Bringing life-saving and quality of life improving technology to patients at a fair cost	Vouching for a biomedical technology	**Neutral** While the price of the device would be fair, foundations play a risky game of vouching for the technology at hand while trying to keep payers, providers and patients financially satisfied.

Table 4: Stakeholder analysis for PS care, assessing the net impact for the stakeholders for the medical device proposed

As summarized and explained in Table 4 the overall impact of an EPD would affect the healthcare system positively. In addition to being financially beneficial, removing the **POSTOPERATIVE STROKE CARE** (summarized in **Figure 2**) would also decrease the duration of the cycle of care.

II. DESIGN DELIVERABLES

A. Proposed Solution

In order to reduce the incidence rate of PS and CD, save the patients and families from the financial and mental burden of postoperative care and lengthy ICU stays, and lift the economic burden the healthcare system is under, a biomedical intervention is greatly needed. The proposed solution is an EPD with a double-layered, pocketed and conical micromesh, supported by a collapsible conical frame with shape-memory characteristics. The EPD would be deployed before the cross clamping, stay at the site until after the patient is taken off of the HLM and cross-clamping is removed. The precedent devices have failed at meeting the significant safety and efficacy endpoints, which can be attributed to two general reasons: i) the devices targeted the inaccurate source of the disease, meaning there are other sources of PS and CD than the emboli captured during surgeries, or ii) the devices targeted the correct source, but failed to actually catch the source of the complications.

The design strategy of the proposed EPD assumes the latter reason to be the real case. To be more specific, Ignacio *et al*. [21] have hypothesized that the predicate devices were able to capture some of the debris, but not all. While the finer debris gets through, the larger debris gets loose during the removal of the device, against the strong current and pressure of blood. For that reason, the proposed EPD creates a one way trap for the debris, with a small pore size mesh for the outer layer, and a large pore size mesh for the inner layer. The larger debris (>350 μm) is caught at the inner layer and the finer debris (<350 μm) passes through the inner layer but gets trapped between the outer layer and inner layer. Furthermore, the mesh would be pocketed, which would i) enhance the one-way trap for the debris, ii) ensure that in the unlikely

scenario of a rupture, only the debris in the specific pocket would be at risk for being released into blood flow, not everything that's caught.

B. Ranked Design Objectives

The design of the EPD must meet the following objectives for safety, efficacy and ease of use:

1) The device must not harm the patient
2) The device must maintain its physical integrity under surgical conditions
3) The device must not damage blood cells
4) The device must allow for the passage of cellular blood contents (red blood cells (RBCs), white blood cells (WBCs), platelets, etc.)
5) The device should allow for adequate blood flow and perfusion, within 10% of the minimum required flow rate (~4.2 L/min)
6) The device should capture blood clot, cholesterol, fatty tissue, calcium deposits, that are larger than 100 μm [20]
7) The device should comply with current cardiothoracic surgical procedures

C. Design Requirements and Specifications & Rationale

The requirements and specifications as agreed with Ignacio *et al*. [21] are ranked in importance and their rationales are explained as follows:

I. The device must be biocompatible

A. Under the strict guidelines of FDA, as explained and detailed in ISO - 10993, the device should not cause an adverse effect on the body due to used material

II. The device must maintain its physical integrity under the surgical conditions in the operating room (OR): temperature range from 28°C to 37°C, blood pressure (BP) range from 90/60 mmHg to 40/20 mmHg, blood flow rate of 4.2 - 4.9 L/min [38].

A. OR environment and surgery conditions may depend on the patient, for instance certain patients may need a lower body temperature to be operated on (28°C)

III. The EPD must be sterilized prior to packaging, to a sterility assurance level (SAL) of 1 x 10^{-6}, using the validated Quality System Regulation sterilization cycle.

A. The device must not cause any infections and be safe for use in the body.

IV. The device must meet the primary safety endpoints.

A. It must not increase the risk of any major health complication: such as renal insufficiency, stroke, gastrointestinal complications, peripheral vascular injury. The incidence rate of any of the complications must be equal or less than the standard treatment.

V. The device should be inserted at the same incision point for the cannula.

A. For ease of use and rapid adoption by surgeons, given the often time-sensitive nature of cardiac surgeries, the device should be easily deployed and retrieved without much effort and new skill.

B. Additional incisions exacerbate the risk of embolic showers

VI. The device should maximize capture of any particle larger than 100 μm in diameter.

A. To protect the patients from cerebral injury [20]

VII. The device, specifically the frame, should not exacerbate the risk of embolic showers

A. Outward pressure and friction against the aorta must be low in order to minimize the risk of more debris, specifically 15 kPa for outward pressure, which is the average peak pressure during healthy cardiac cycle

VIII. The device should enter from an incision point with the size of 1.5 cm in diameter. [38]

IX. The device should not hinder blood flow below 10% of the minimum required flow rate (~4.2 L/min) [38]

A. The device should not cause hypoxia due to slowed down blood flow in the brain, organs and peripheral tissue.

X. The design should be effective across the whole diameter.

A. To allow for total coverage of the aorta of any size, 3.0 cm in diameter being the largest.

D. Design Strategy & Rationale

In order to meet the design objectives, within requirements and specifications, the design of the EPD adhered to the following strategy:

I. The inner layer of the double-layer should have pores that are 200-400 μm in diameter.

A. It should allow for natural blood contents to pass. It should also allow for finer debris to pass so that they could be captured between the outer layer and inner layer.

II. The outer of the double-layer should have pores that are 100-150 μm in diameter.

A. It should allow for natural blood contents to pass but not any other debris that is larger than 100 μm.

III. The mesh should be in conical shape

A. Cover all main three main branches in the aorta, and protect against the sandblasting effect by reducing high-velocity blood's impact on the aortic walls

IV. The meshes should be pocketed

A. Pockets would capture and make a one-way trap for the debris for safe removal of the device and debris together

V. The frame should be made of the bi-metal alloy Nitinol.

A. The shape memory characteristics, biocompatibility, and durability of Nitinol allows for perfect fit in the aorta.

VI. The device should be 8-10 cm.

A. In order to ensure total coverage of the aorta.

E. Design Variables & Rationale

The independent variables of the design are:

1) Inner & outer pore size for the mesh
    a) To create a one way trap for the embolic debris, inner and outer layer pore sizes should be optimized
2) Pocket size on the mesh
    a) Presence of pockets and whether they work as intended during retrieval of the device
3) Mesh shape
    a) The proposed conical shape should be tested for capture efficiency and safety
4) Choice of material for the frame
    a) Should be biocompatible, flexible, conform to variety of aortic shapes and sizes, and maintain physical integrity during surgical conditions

5) Choice of material for the mesh
    a) Should be biocompatible, conform to variety of aortic shapes and sizes and maintain physical integrity during surgical conditions

What sets the proposed EPD apart from other predicate devices is the shape and its pocketed, double-layered mesh. For that reason, this report focuses on the impact of **variable 2** and **variable 3** on capture efficiency and safety. Variables 1, 4, and 5 were decided according to previous studies and testings done by Ignacio *et al*. [21], as will be detailed in the *Materials and Methods* section.

F. Materials and Methods

Mesh

Due to the nature of medical grade meshes, and the proposed EPD's double-layered, woven, and pocketed features, the cost of material quickly becomes a deciding factor. An ideal medical grade mesh would be weaved from biocompatible [22] nylon 12 (PA12) fabric. PA12 demonstrates low water absorbing (1.08% on average) and high tensile strength (~125 MPa at 30°C) [23]. Low water absorbing quality is crucial for keeping the pore sizes fixed and pores unclogged by material volumetric expansion. Furthermore woven fabrics characteristically show flexibility and low elongation [24], factors that would contribute to decreasing the risk of rupture by maintaining physical integrity while being mechanically strong. Such detailed and specific requests for medical textiles have exceeded the budget of this report as the interviews with medical textiles companies have revealed a cost of $15,000-20,000 for prototyping in the scale that is required. For that reason a close approximation in terms of material for the mesh was used. As the outer layer, a nylon mesh with a pore size of 100 μm and thickness of 78 μm was

chosen (acquired from Spectra®, 22 cents/cm^2). As the inner layer, a polypropylene mesh with a pore size of 350 μm and thickness of 525 μm was chosen (acquired from Spectra®, 36 cents/cm^2). The pore sizes were decided according to previous tests done by Ignacio *et al.* [21] but the tests did not account for the presence or the size of the pockets on capture efficiency, main driver behind the capture efficiency experiments of this report.

To decide the pore sizes, Ignacio *et al.* ran an orthogonal design of experiments, testing the optimal combination of inner and outer pore size. Testing 500 and 1000 μm pore sizes for the inner layer, and 105 and 160 μm pore sizes for the outer layer, the optimal combination of 105 μm and 500 μm were found. Nonetheless, the capture efficiency of the combination was 88.8% [21] and for that reason it was concluded that the pore size in the range of 300-400 μm has the potential to increase the capture efficiency, which is the main reason behind the choice of an inner layer with a pore size of 350 μm.

Frame

Shape memory alloys are metal alloys capable of returning to their original shape after physical perturbations. Often, alloys have a range of transformation temperatures, that allow them to be flexible and be biocompatible [25]. Nitinol, for instance, has a transformation temperature range of -220-100 °C, a Young's modulus of ~83 GPa [26] and hence, demonstrates biocompatibility. For these reasons, Nitinol was the ideal candidate for the design. The purchased Nitinol wires (acquired from Small Parts®) were 0.2794 mm in diameter. Three wires of 80 mm length were used. Designs leading upto the final frame (**Figure 3C**) were tested with respect to number of wires that would be able to both carry the mesh structures and collapse into a tube. Therefore, the least amount of wires for the frame was ideal to ensure the least amount of outward radial pressure, and friction against the inner aortic wall during deployment and retrieval, two factors that can exacerbate debris circulation. Therefore, as the

final product, a conical shape with three wires were chosen to be built. To create the conical shape, wires were slightly bent and a point 20 mm from an end was exposed to an open flames, which created a permanent bend of about 120° (**Figure 3A, B**). Soldering the three wires from either ends, the required Nitinol frame was built .

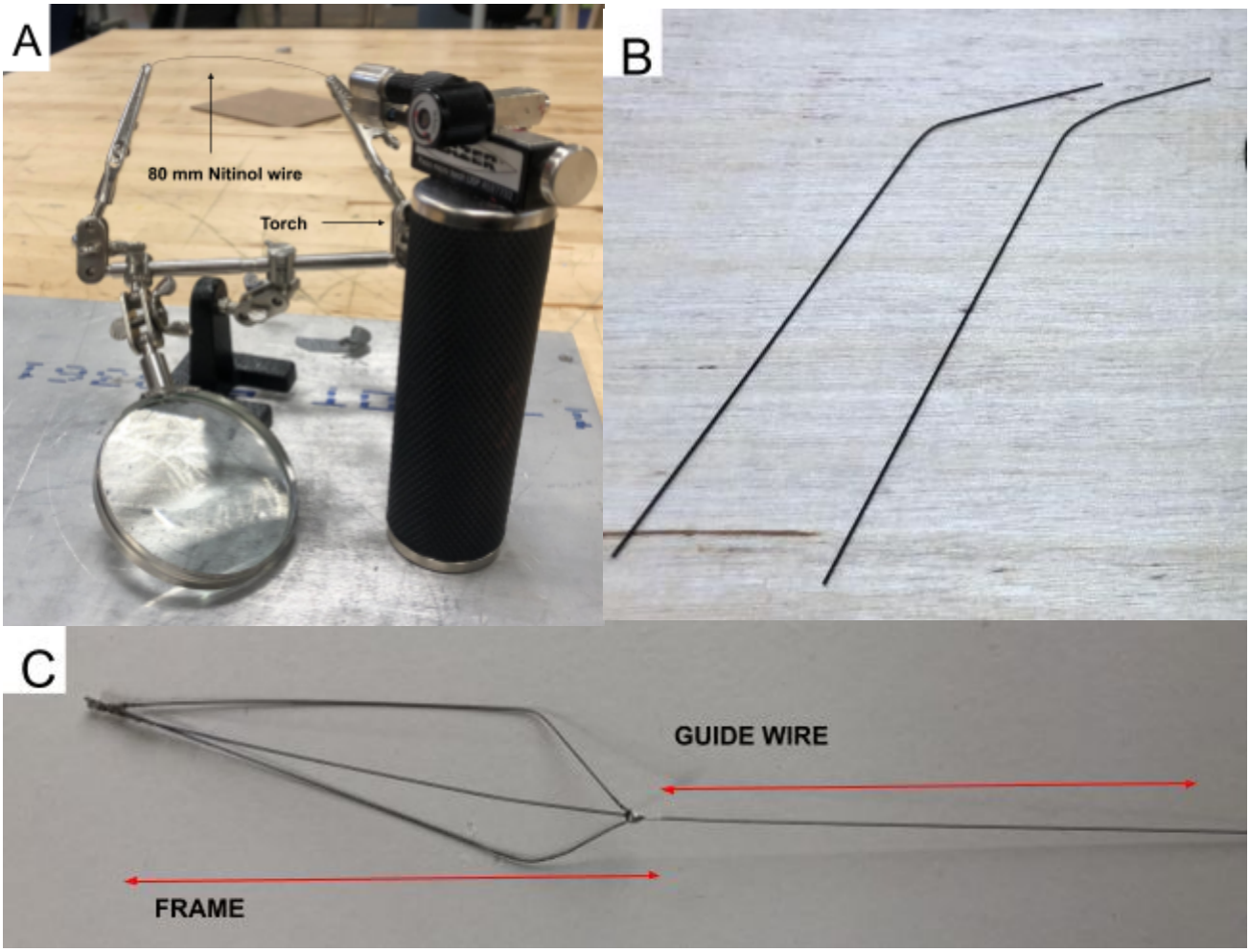


Figure 3: Methods and Means for Building the Frame A. The setup to permanently bend the 80 mm Nitinol wires. A torch has been used to provide open flame. **B.** Permanently bent Nitinol wires **C.** The Nitinol frame soldered, with a Nitinol guide wire.

Building Planar Mesh Structures (PMSs)

Planar meshes were fabricated for the first capture efficiency testing. Single layer meshes were formed by cutting 3 cm x 3 cm sheets of nylon from bulk material. 3 single layered (SL) meshes with 100 μm pore size, 3 double layered (DL) meshes (outer 100 μm pore size, inner 350 μm pore size), 3 double layered meshes with large pockets (LP DL) (pockets that are 20 x 20 mm squares), and 3 double layered meshes with small pockets (SP DL) (pockets that are 10 x 10 mm squares) were tested for their capture efficiency (**Figure 5A)**. To form double layered meshes, layers were glued at the edges with silicon hot glue and hot glue gun (both acquired from CCBetter®). Pockets were made by hand sewing with nylon thread (~0.2 mm in diameter).

Building Conical Mesh Structures (CMSs)

As precursors to CMS, twelve triangular meshes were formed by cutting sheets of nylon from bulk material, with the same features and quantities as planar meshes, with an average length of 70.4 mm and average height of 69.9 mm (**Figure 4A, B).** Then triangular mesh structures were rotated around a vertical axis to form cones, and the edges were hand sewn together, while any visible holes between the edges were sealed with hot glue to form CMSs. The average diameter of the circular bases of the cones were measured to be 20.7 mm and the average area of opening at the circular base was calculated to be 3.358 cm^2 (**Figure 4C).**

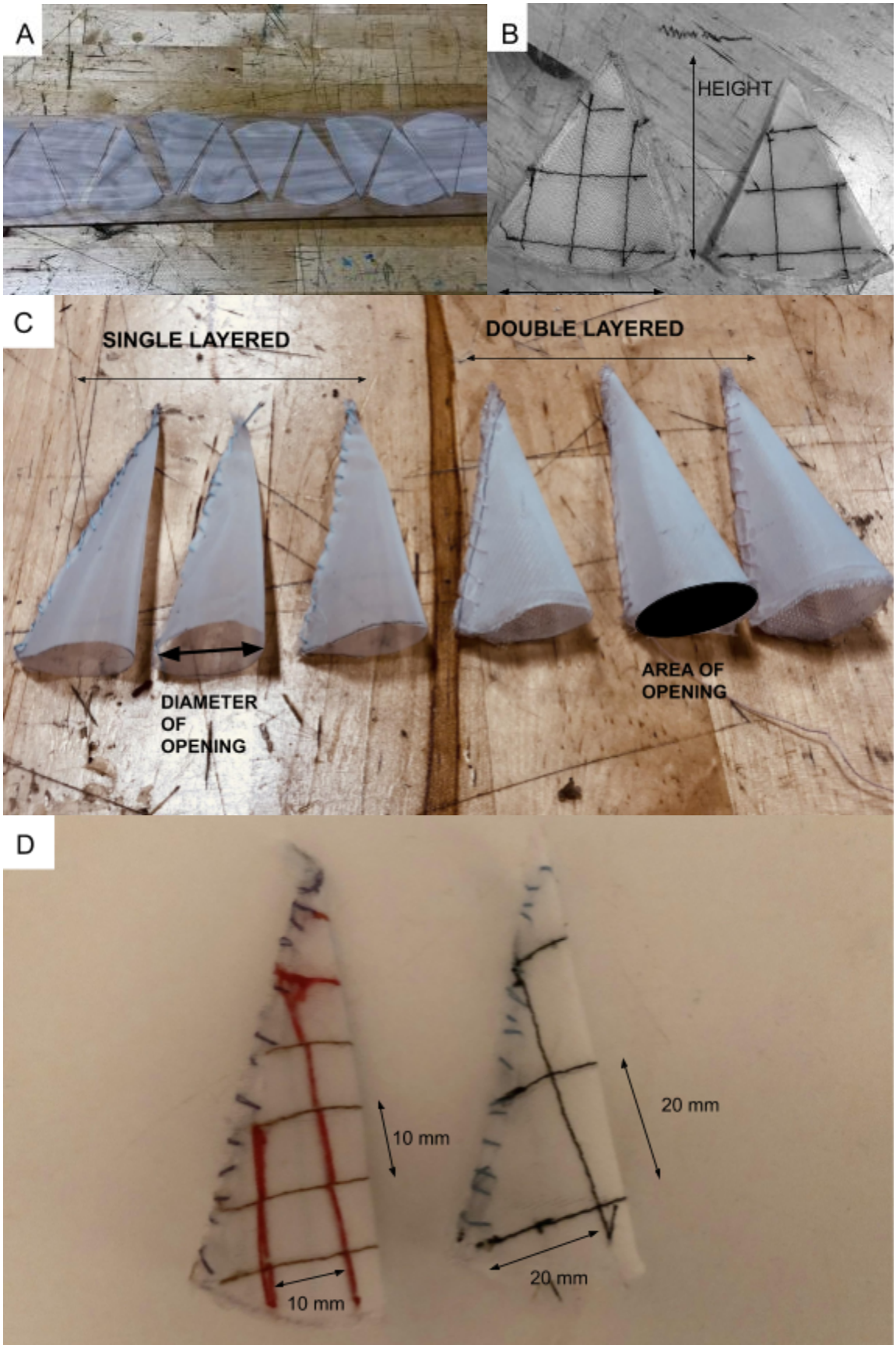

A
B
HEIGHT
C
SINGLE LAYERED
DOUBLE LAYERED
DIAMETER
OF
OPENING
AREA OF
OPENING
D
10 mm
10 mm
20 mm
20 mm

Figure 4: Built CMSs from Triangular Mesh Structures A. Triangular single layered meshes **B.** Double layered and large pocketed triangular mesh structures **C.** CMSs, single layered on the left, double layered on the right **D.** CMSs, small pocketed on the left, large pocketed in the right.

Debris

The design aims to mitigate debris >100 μm in diameter. To imitate debris in pilot experiments, 20# pool filter sand was used (Lighthouse Pool Filter Sand™). Analogous to embolic debris, sand has heterogeneous size and shape. The literature suggests that the grain size of 20# pool filter sand is, on average, between 450 and 550 μm in diameter [27, 28]. However, a simple visual test of placing the sand on the polypropylene mesh revealed that there are indeed particles with size less than 350 μm in diameter, as there were particles on the plane placed below the mesh. Therefore, taking the online sources and the test into consideration, it was deduced that the grain size were comparable to fine and large debris size.

Capture Efficiency Testing with Planar Mesh

Planar meshes were placed at the end of a vinyl tubing with 20 mm inner diameter, as an aortic model (**Figure 5B)**. Each planar mesh was weighed (with the digital scale Weigh Gram, TPO-100), dry and wet, then were hot glued to the end of the aortic model. Then the aortic model was attached to a water supply with a flow rate of 4.2-4.9 L/min, to imitate the conditions of the surgical environment . Finally, 0.2 g sand was introduced into the flow to imitate flow with debris, after 10 seconds, the flow was cut off, the mesh was removed, weighed wet and then weighed dry, to find the percentage of debris caught by the meshes. Measuring the weight of the structures when they were wet revealed values that could be cross-checked for after the experiments were run, that the mesh structures were completely dried.

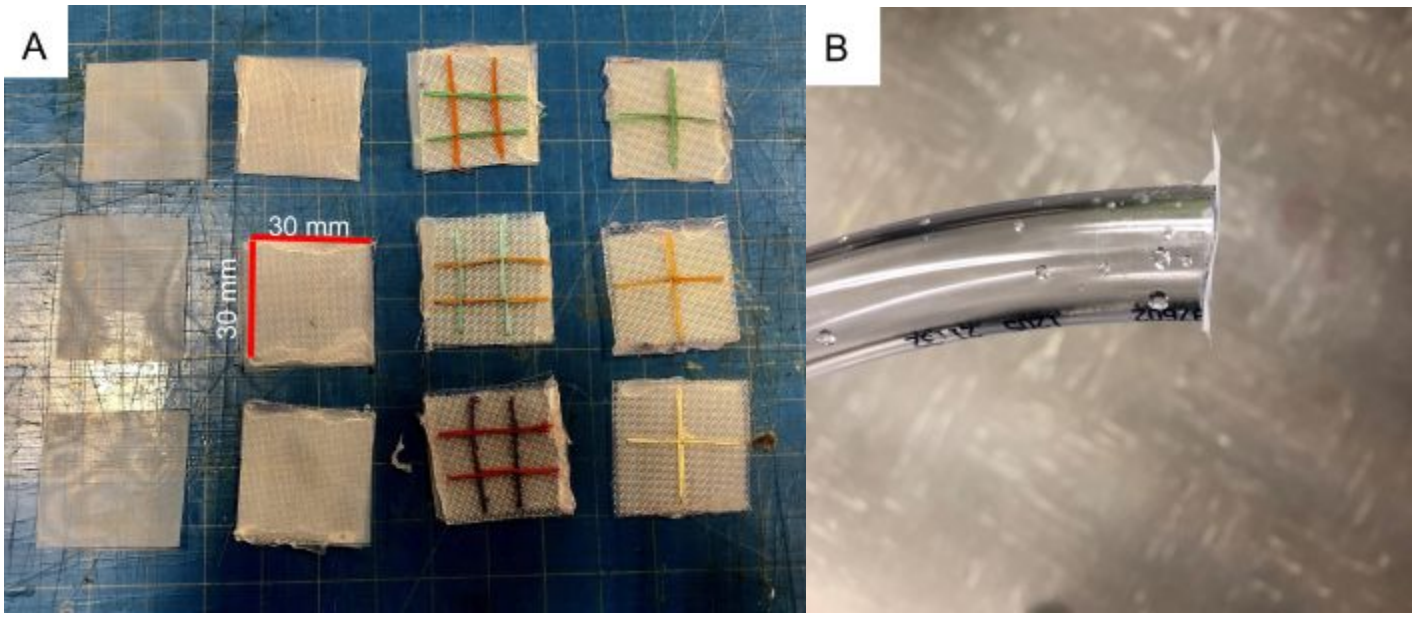


Figure 5: Planar Mesh Structures and the Capture Efficiency Testing Setup A. Planar meshes, single layered (leftmost), double layered (2nd from the left), double layered large pocket (rightmost), double layered small pocket (2nd from the right). **B.** Planar mesh at the end of the aortic model.

Sandblasting Effect Reduction Through Velocity Drop

The flow rate change through the conical mesh was measured as water flowed through. A 20 Fr cannula by Medtronic®, connected to the water source, was fixed in location with a ring stand and a clamp, as the tip faced downward to the sink. CMSs were placed directly under, their area of opening facing the tip of the cannula, similarly fixed in location with a ring stand and a clamp. The inlet and outlet flow rate was measured, by measuring the amount of time (with an iPhone© stopwatch) the water took to fill a 500 mL beaker placed 15 cm below the cannula for the inlet, and 5 cm below the CMSs for outlet flow rates (**Figure 6**). The inlet velocity was calculated by dividing the measured inlet flow rate by the area of the cannula tip. The exit velocity was calculated by dividing the measured exiting flow rate by the total open surface area of the CMSs. For the double layered CMSs, the distance between two layers was assumed to be negligible, and only the total open area of the outer layer was used for calculation.

It is possible to provide a more exhaustive understanding on the flow profile and the effect of the conical shape on the flow with computational modeling, such as COMSOL, or an in depth flow profile analysis of how water behaves exiting a small diameter with high velocity, into a conical mesh structure. Nevertheless, this experiment aims to discover and produce preliminary ideas about flow and velocity, that will be the driver and motivator of the next set of experiments. At this stage, a comprehensive flow analysis requires more sophisticated material, for instance a Doppler ultrasound, but such work is not within the scope of this study. Therefore, the assumptions described above are deem satisfactory and necessary to demonstrate the effect of conical shape on the velocity of fluid after it exits the cannula.

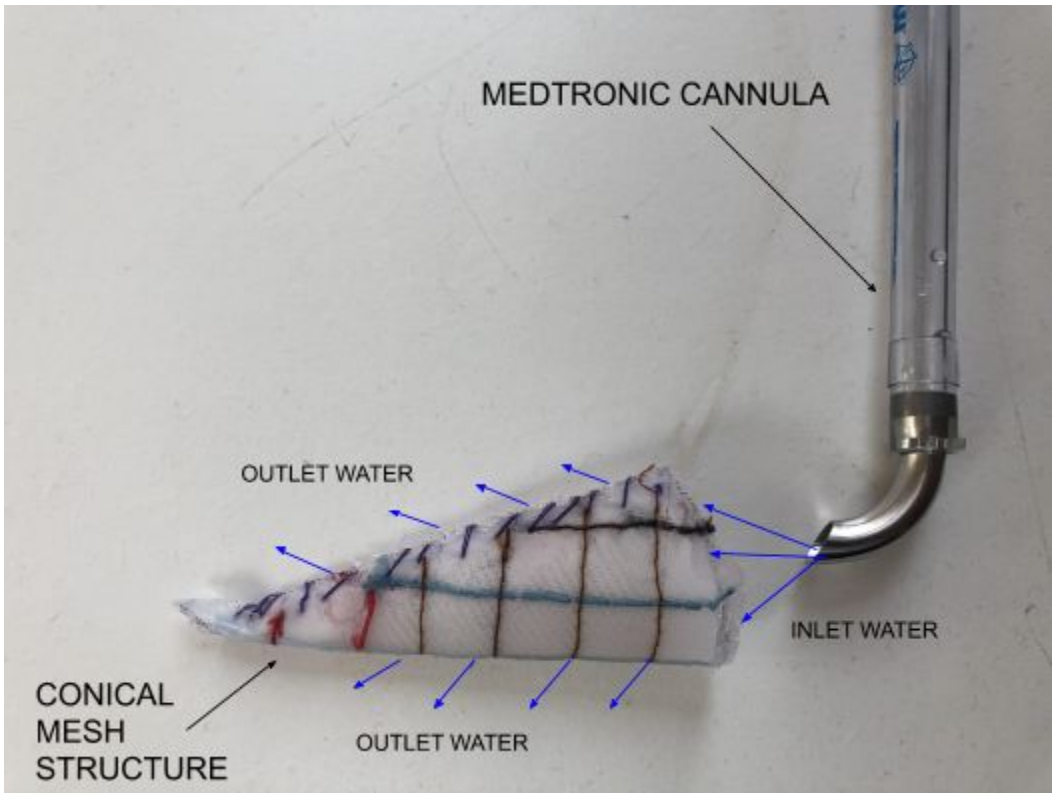


Figure 6: Drawn Representative Setup of Velocity Drop Experiment. Cannula and CMS. The cannula was connected to a water source. CMSs and the cannula were fixed to a stable position with two ring stands and two clamps, arranged so that the water coming out of the cannula flowed directly into the CMSs.

Capture Efficiency Testing with Conical Mesh and Retrieval

CMSs were weighed dry and wet, and then placed in the aortic model with the Nitinol frame attached inside. While the capture efficiency were calculated through the ratio of pre- and post-experiment dry CMSs, the wet weight values were used as means to cross-check to make sure if the CMSs completely dried off. The cannula, connected to the water source, was fixed in location with a ring stand and a clamp, the tip of the cannula facing downwards to the sink. Similarly, with a ring stand and a clamp, the aortic model with the CMS was placed vertically below the tip of the cannula. Through the conical structures, water flowed from the cannula with an average rate of 4.58 L/min. 0.2 g of sand was weighed and introduced into the flow. The time was measured (with an iPhone© stopwatch) from the moment the 500 mL beaker was placed 15 cm below the tip of the cannula or 5 cm below the aortic model, to the moment that the 500 mL beaker was visually confirmed to be filled with water, to calculate the inlet and outlet flow rates.

10 seconds after the debris was introduced, the mesh was pulled out of the tube by pulling the guide wire in the direction of the cannula, while the flow continued, to imitate the retrieval phase of the procedure (**Figure 7)**. The CMSs were then weighed when wet, let dry, and weighed when dry, to calculate the percentage of debris caught.

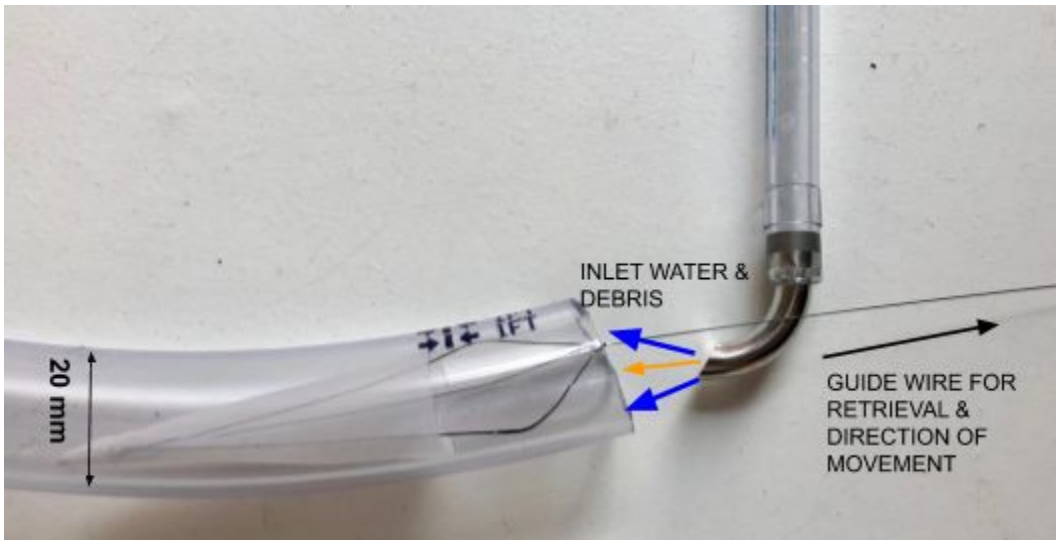


Figure 7 Drawn Representative Setup of Debris Capture During Retrieval Experiment : CMS with the frame attached inside and representative setup of debris capture during retrieval experiment

Flow Analysis and the Use of Water

In this study, blood is modeled as a Newtonian fluid and its viscoelasticity is ignored. This is for two reasons: i) the shear thinning properties of blood is considered to influence flow insignificantly through large arteries, and in this case, large tubes [37], ii) the experiments were conducted to test the different designs of the CMSs for their mechanical ability to capture and safely remove debris and their ability to reduce sandblasting effect by reducing the velocity, and not to ensure that the blood cells passed unharmed, at this stage. Therefore, the need of a fluid that would carry the debris to the PMSs and CMSs was satisfied by using water.

To understand and describe the flow model in the sandblasting effect experiment and retrieval replicating experiment, the Reynolds number (Re) of the flow was calculated (by multiplying the diameter of the tip of the cannula with the average inlet velocity, and dividing the that number by kinematic viscosity of water). Reynolds number, the ratio of inertial forces to viscous forces, is a dimensionless value that provides a threshold (2300 [36]) for the fluid

passing from laminar to turbulent flow, lower than 2300 being laminar. It was assumed that the flow was fully developed and the velocity profile was parabolic as it exited the cannula.

III. RESULTS

In order to reduce the incidence rate of PS and CD that stems for cerebral hypoxia and ischemia due to emboli forming during cardiac surgeries, this report presents an EPD design with a conical, double-layered, pocketed mesh supported by a collapsible Nitinol frame. The mesh was tested for its safety and efficacy, with the metrics of capture efficiency, velocity and flow rate. This report describes a proof of concept prototype. Although there were deviations from the intended final design (e.g. use of hand sewn nylon or polypropylene mesh instead of customized and professionally manufactured medical textiles, etc.), the results of the experiments described herein portray an approximation of key features of the proposed design.

A. Safety: Reducing Potential Risks Associated with Sandblasting Effect and Reduced Blood Flow Rate

Safety tests were designed to ensure that the design of the proposed EPD does not exacerbate cerebral hypoxia and ischemia by hindering blood flow, while also eliminating the sources of complications. The following results present the velocity profiles and ranges of flow rate of water as it passes through the CMSs, in an attempt to illustrate that it would reduce the sandblasting effect and would not hinder blood flow significantly.

Velocity Drops Significantly Through the Conical Mesh

Sandblasting effect had been identified as a source of emboli during cardiac surgeries. The complication originates from the impact the blood has on the aortic walls, exiting the aortic cannula with high velocity. The conical mesh of the proposed EPD had been tested for its ability

to reduce the sandblasting effect by simply enlarging the surface area that the blood flows through, while not hindering the flow rate more than 10% in order not to cause oxygen desaturation during cardiac surgeries.

For each of the tested CMSs, the velocity of water had dropped 36-fold on average. Water exiting the cannula had an average velocity of 225.08 ∓ 1.40 cm/s (mean ∓ SEM) (SD = 4.80) and water exiting the CMSs had an average velocity of 6.23 ∓ 0.15 cm/s (SD = 0.50) (**Figure 8).**

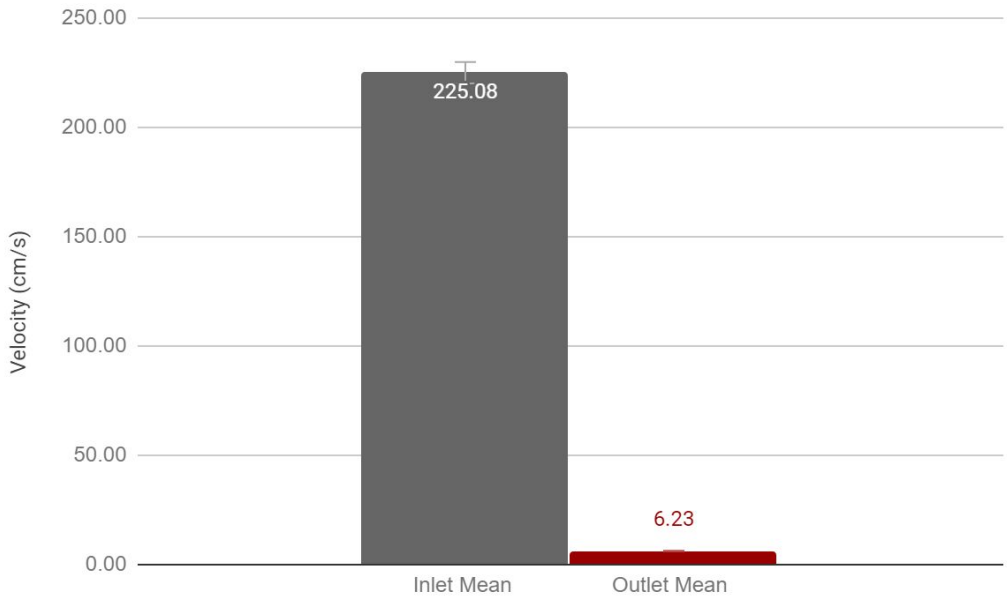


Figure 8 Mean Inlet and Outlet Velocity of Water Flowing Through CMSs: Bar chart representing the average velocity of water exiting the cannula shown in gray (standard deviation (SD)= 4.86), and the average velocity exiting the CMSs shown in red (SD = 0.50). *P<0.00005 inlet vs. outlet.*

Furthermore, the SL, DL, SP DL and LP DL did not show any statistically significant difference in terms of their effect on exit velocity. Each CMS caused a larger than 30-fold drop in the velocity (**Figure 9**).

The kinematic viscosity of water was taken to be 1.002 x 10^{-6} m^2/s [30], so the inlet Re was calculated to be 1347, which means water entering the CMSs had a laminar flow profile

(1347<2300). Assuming the full development of the flow, the shape of the velocity profile was parabolic, meaning the velocity was highest at the middle of the cannula (r = 0 cm) and zero at the walls of the cannula (r = 0.667 cm). The Re and the fully developed flow assumption suggests that the conical tip of the CMS experienced a higher velocity and thus a higher impact of water, towards circular base the velocity have decreased.

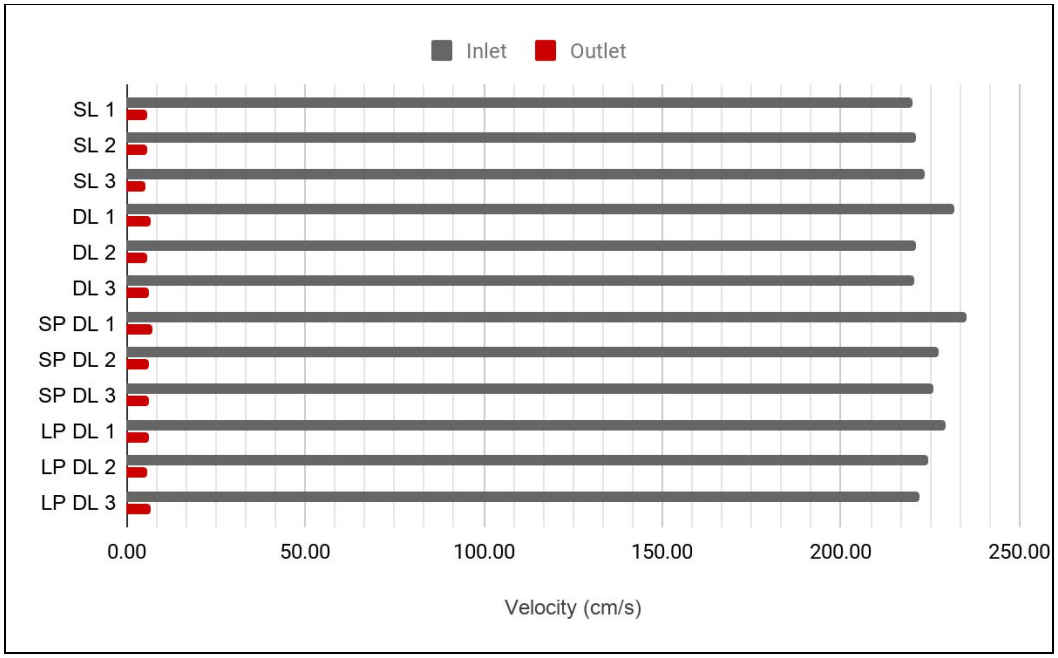


Figure 9 Individual Inlet and Outlet Velocity of Each CMS: Velocity drop of water from the cannula (IN vel, black), through the CMSs (OUT vel, red).

Flow Rate Drop in the Aortic Model Stays Within the Range of Surgical Conditions (4.2 - 4.9 L/min)

Taking the flow analysis a step further, the CMSs were tested in the previously described aortic model (20 mm diameter). The inlet flow rate as the water exited from the cannula, and the outlet flow rate as it flowed through the CMSs were measured. The average inlet flow rate was 4.58 ∓ 0.03 L/min (SD = 0.06) and the average outlet flow rate was 4.31∓ 0.02 cm/s (SD = 0.12). The drop in the flow rate was 1.06-fold on average and was statistically

significant (P<0.0005); nevertheless, the range of outlet flow rates was within the previously described surgical conditions (**Figure 10**). Additionally, the SL, DL, SP DL and LP DL did not show any statistically significant difference in terms of their effect on outlet flow rate.

Similarly for this experiment, the kinematic viscosity of water was taken to be 1.002 x 10^{-6} m^2/s [30]. For this experiment, the inlet Re was calculated to be 1347, meaning the flow was laminar as water exited the cannula.

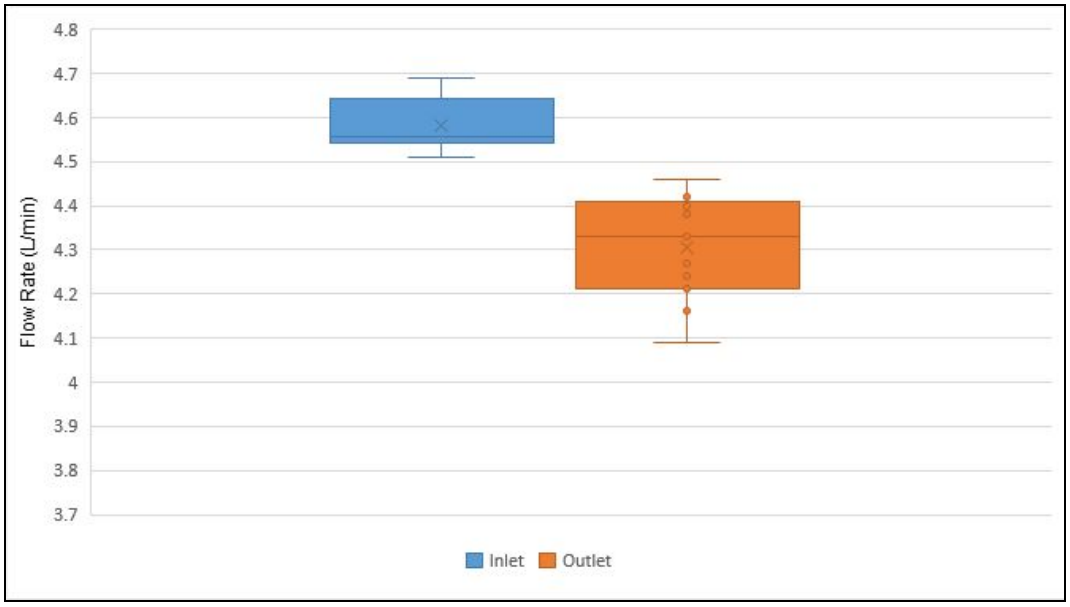


Figure 10 Box Chart of the Range of Flow Rates ar Water Flowed Through CMSs: While the flow rate dropped through the CMSs, the spread shows that it is within the desired range for the cardiac surgeries. *P<0.0005 inlet vs. outlet*.

B. Efficacy: Effect of Shape and Pockets on Debris Capture

The efficacy of the proposed design was tested with respect to its capture ability with different mesh shapes and features. The proposed EPD design must thoroughly catch the debris and allow the safe removal of the caught particles against the strong current of blood exiting the cannula with a high velocity. The following results present the debris capture efficiency as water flowed through the built PMSs and CMSs.

No Significant Difference for Amount of Debris Caught Between PMSs

The PMSs were placed at the end of the aortic model as water with 0.2 g introduced debris flowed through them (average flow rate of 6.55∓ 0.03 L/min). Three SL, three DL, three SP DL, and three LP DL PMSs were individually tested in order to analyze the effects of layering, pocketing and pocket size on debris capture (**Figure 11**). On average, the PMSs caught 92.47 ∓2.02% (SD = 6.99%) of the debris introduced. In descending order, average capture efficiency of DL PMSs was 98.25∓ 4.64%; 95.08∓ 2.89% for SP DL PMSs; 88.57∓ 3.22% for LP DL PMSs, and 87.98∓ 3.38% for SL PMSs (**Figure 12**). However, none of the double layered PMSs showed any statistically significant difference from single layered PMSs in terms of their capture efficiency (**Figure 13**).

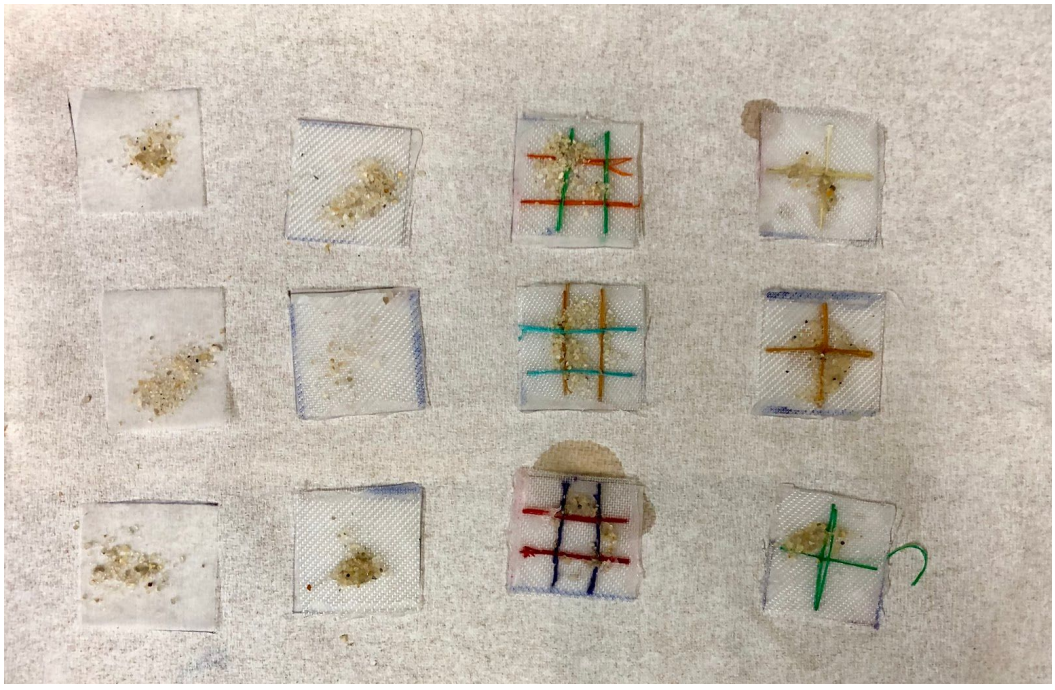


Figure 11 Post-Experiment PMSs with Debris: PMSs with the yellow-brown debris they caught. From left column to right: SL, DL, SP DL, LP DL**.**

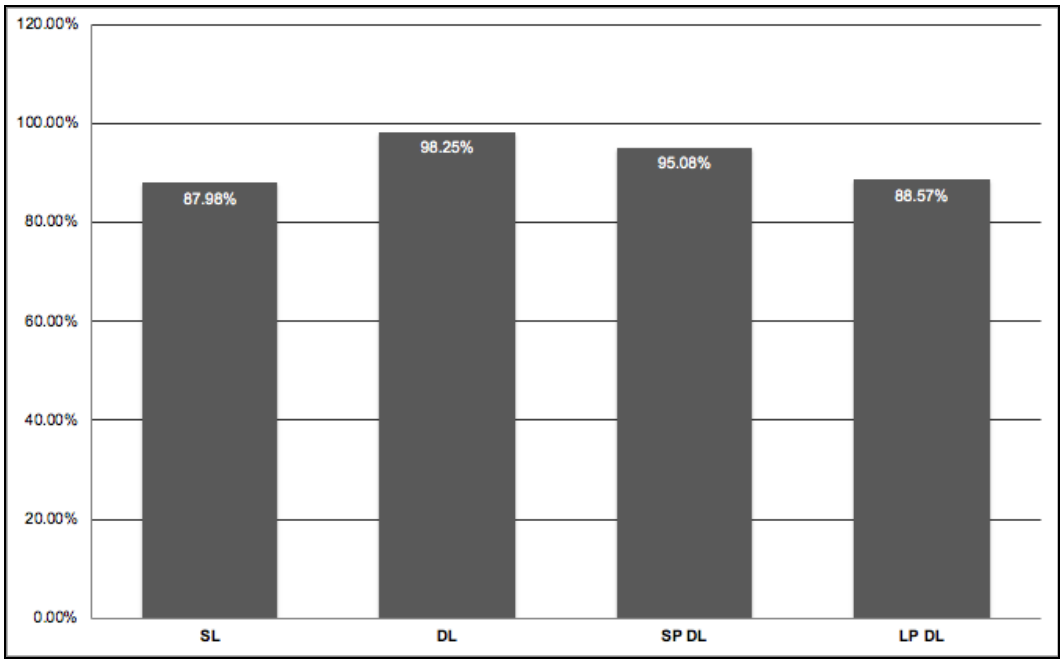


Figure 12 Average percentage of debris caught by PMSs: DL and SP DL PMSs caught more debris on average. No significant difference is observed between the tested designs *(P>0.05)*.

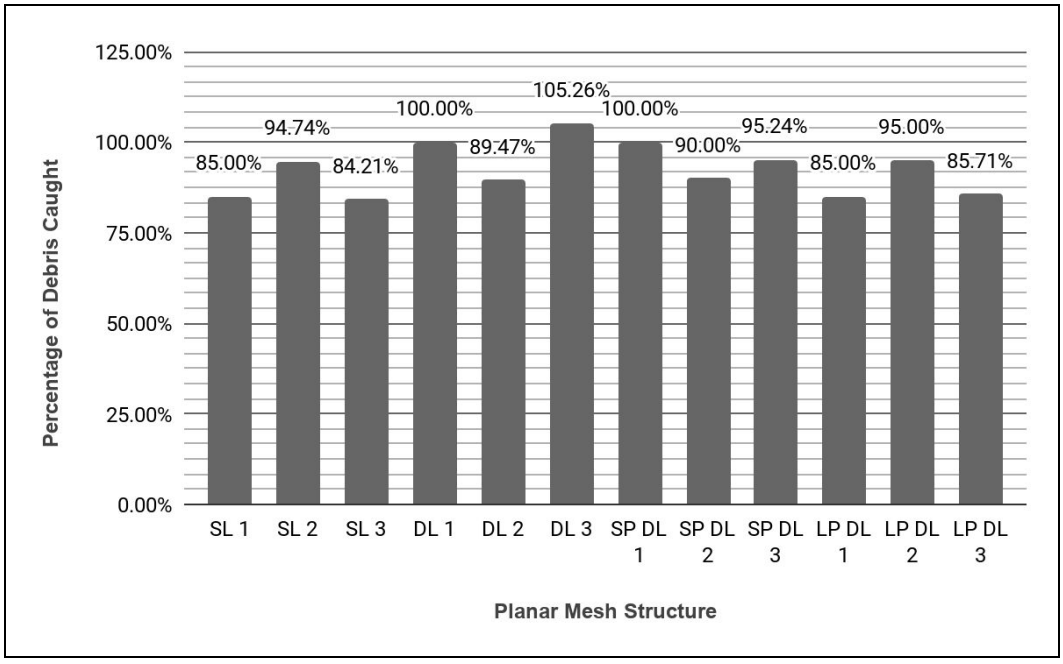


Figure 13 Percentage of debris caught by each PMS tested

SP DL CMS Performs Well in the Aortic Model and Retrieval

The CMSs were tested for their capture ability in the aortic model. 10 seconds after the debris was introduced, the CMSs were retrieved along the axis of the guide wire, to imitate the retrieval of the device, during which the debris has the potential to get loose and join the circulation. Visual inspection revealed that the debris introduced accumulated at the tip of the cone in each CMS tested (**Figure 14**).

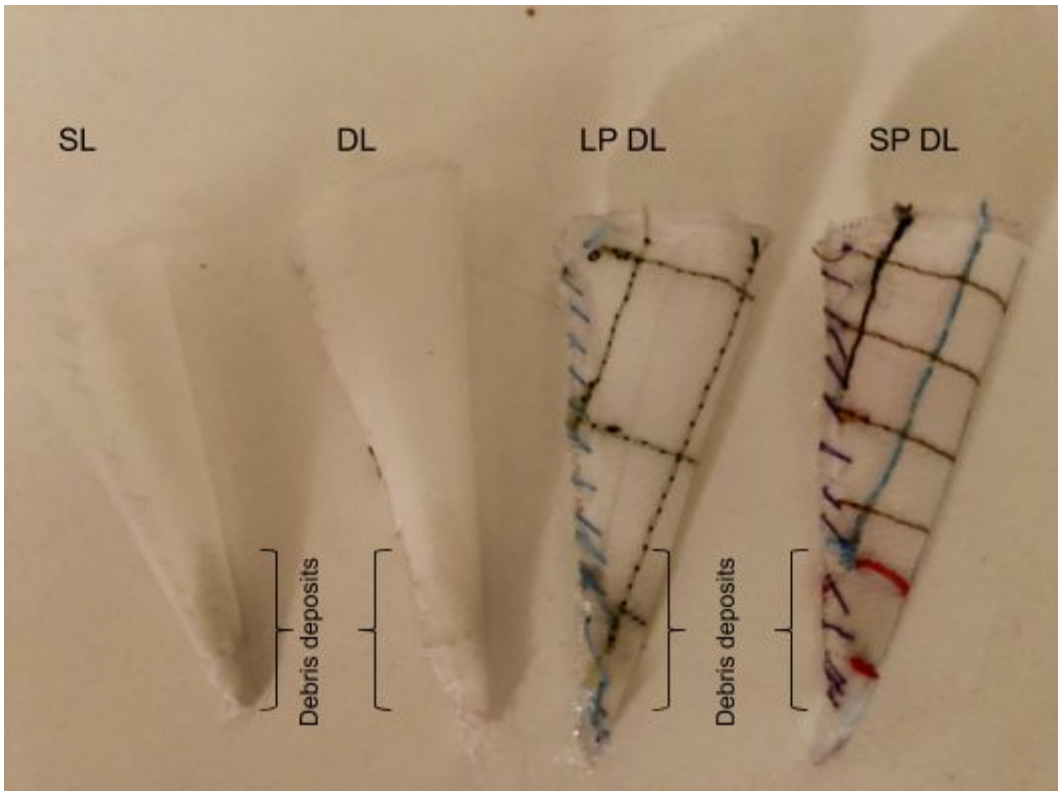


Figure 14 Post-Experiment CMSs with Debris: CMSs with the debris they caught, seen as yellow-brown shaded deposits at the tip of the cones.

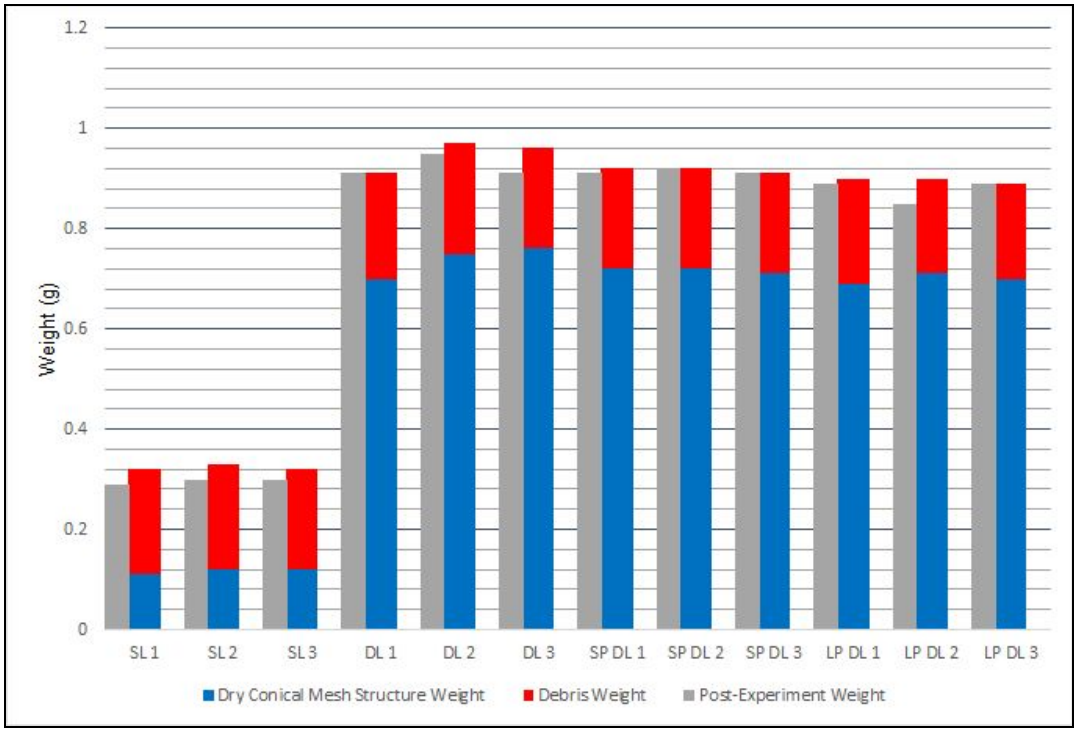


Figure 15 Weight Comparison of Post-Experiment CMSs with Pre-Experiment CMSs Combined with Debris: CMSs were weighed before and after the experiment to measure the amount of debris they caught during the retrieval phase. Shown here in multi-color columns is the total weight of debris added to the flow (red) and the dry CMSs before the test (blue). Column next to them represents the weight of CMSs with the debris they caught (gray). Only SP DL CMSs had caught significantly more debris than the CL CMSs.

Figure 15 visually compares the weight of post-experiment CMSs and the weight of pre-experiment dry CMSs combined with the weight of the debris. The percentage of debris caught was calculated by subtracting the dry weight of the pre-experiment CMSs from the weight of the dried off post-experiment CMSs and dividing the results by the weight of the debris introduced. The mean percentage caught for all the CMSs was 90.52∓2.62%; however, it is

important to note that only SP DL CMSs caught more than 90% of the debris on average (**Figure 16**), with a significant improvement over the the SL CMSs (*P<0.05)*. It is important to note that after each experiment, visual inspection revealed that the physical integrity of the CMSs stayed intact. The frame attachment and detachment caused no physical alterations to the CMSs.

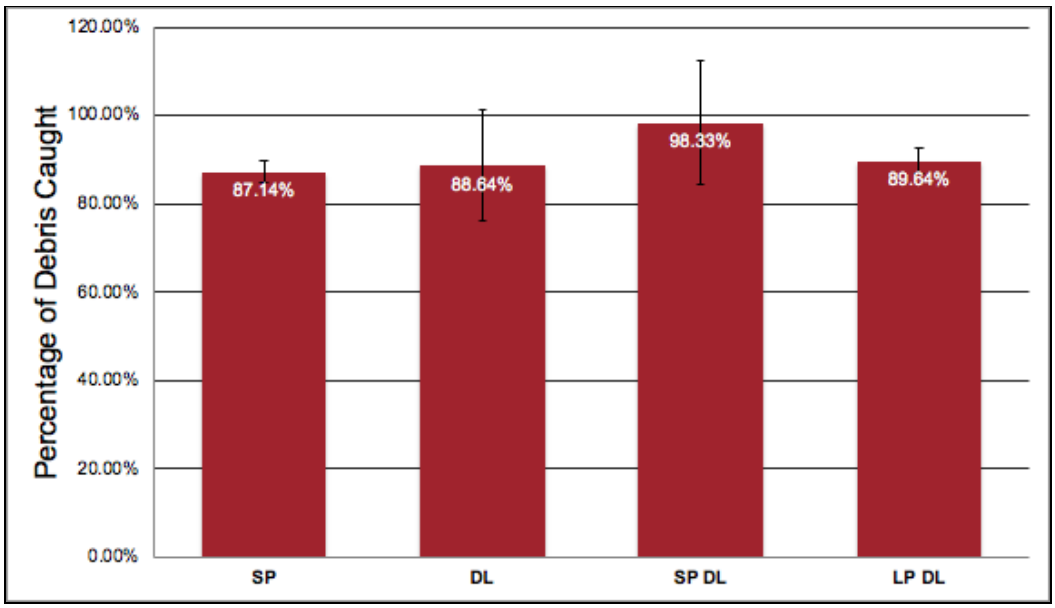


Figure 16 The mean percentage of debris caught by the CMSs: From left to right, mean percentage of debris caught: 87.14∓1.43%, 88.64∓7.30%, 98.33∓8.09% and 89.64∓1.67% SP DL CMSs caught significantly more debris versus other designs. *P<0.05.*

IV. DISCUSSION

A. Overview

PS and CD are major and devastating complications related to open heart surgery. In the US alone, open heart procedures averages more than 290,000 every year [1] and puts thousands of people under the risk of PS and CD. As the population over the age of 65 in the US is expected to double in the next 40 years [3], and considering that 50% of all patients

diagnosed with heart failure are over the age of 70, the number of procedures is expected to continue to rise significantly in the next few decades. Moreover, PS is not only a documented health risk, but also doubles the cost of care to $30,000 per patient [6] and increases cost of healthcare in the US to $1bil [12].

There is a plethora of conflicting evidence for the incidence rate and risk factors for both PS and CD. Nevertheless, a review of the articles published in the last two to three decades helped synthesize the incidence rate data into an accurate approximation. The average incidence rate of PS was calculated to be 4.00%. The research on CD, however, was sparse and the sample sizes and characteristics varied from study to study. Therefore it would only be accurate to make the conclusion that the incidence rate of CD is at least 10%, although the studies show that it can increase to significantly higher levels.

The abundance of conflicting and expansive data on risk factors of PS and CD, illustrates that the neurovascular complications related to cardiac surgeries has been a topic of research in terms of quantification and prediction, for a long time. However, it also reveals that risk factors, too, are in abundance. Age, peripheral vascular disease, previous cardiac conditions, or the type of surgery the patient is undergoing are a few examples identified by researchers. It is important to notice that aforementioned risk factors are all non-modifiable. In any case, it wasn't a difficult task to find the common culprit among intraoperative risk factors, as it is mentioned and studied in almost every study on the topic: cerebral hypoxia or ischemia.

Cerebral desaturation of oxygen stems from reduced blood flow to the brain. The reason of this reduction is often attributed to emboli. During the cardiopulmonary bypass procedure, techniques that are used to insert the cannula, clamp and unclamp the aorta, and the impact of blood on the aortic walls as it exits the cannula with high velocity, are identified to be the sources of embolic showers. The emboli, then, have the potential to flow from the aortic arch

into carotid arteries and clog capillaries in the brain, causing regional cerebral hypoxia, or ischemia. While the larger debris cause PS, it is also hypothesized that the finer debris causes undetectable CNS infarctions and regional cerebral hypoxia, that results in CD [29] .

Previously, benchmark and emerging medical device companies attempted to resolve the complications with EPDs. Two predicate devices that were significant in terms of technology and market power were identified during the prior-art research: CEPC and EX. Both of the devices received FDA approval and were put in the market, but recent findings from large and expansive trials revealed that neither device managed to meet the important clinical endpoints; there were no significant reduction in PS and CD [9].

Although the capture capability of the devices is documented, this report hypothesize that the reasons for failure to meet clinical endpoints originates from that the devices did not capture all the debris, both fine and large, and a percentage of those that were captured, got dislodged and joined the circulation during the removal of the device. EX devices have no preventative measure to safely remove the debris against the blood exiting the cannula with a high velocity, as the device is being retrieved. Furthermore, neither of the devices have protection against an important source of emboli: sandblasting effect.

In conclusion there is an unmet clinical need to prevent cerebral hypoxia and ischemia by effective mitigation of debris in order to reduce the incidence rate of PS and CD related to open heart surgeries, and relieve the economic burden of care for patients, their families and the healthcare system.

B. Proposed EPD and Qualitative Comparisons with Predicate Devices

The proposed EPD aims to eliminate the sources of debris while ensuring its capture and safe removal. The EPD will be composed of two main parts: i) mesh, ii) frame. In

comparison to predicate devices, the proposed EPD will have a double-layered and pocketed mesh in an attempt to create a one-way trap for any debris caught, eliminating the possibility of debris dislodging and joining the circulation. It is important to note that the layers of the mesh must be composed of pores that are large enough for blood cells to pass with no harm to the cells, while also ensuring the capture of debris that is larger than 100 μm to protect the brain from cerebral injury [20]. The inner layer mesh will have large pore size (300-500 μm) and the outer layer will have small pore size (80-100 μm). While any debris larger than 300-500 μm will be caught in the inner layer, the finer debris will pass the first layer but be caught in the outer layer, and trapped in between two layers. Furthermore, the mesh will be pocketed, to enhance the entrapment of debris between the layers, and as an added measure to possible rupture. The conical shape of the mesh will ensure total coverage of the carotid arteries and will be in contact with the aorta only at its circular base, reducing the possibility of fall of debris from the aortic walls due to friction. Finally, the mesh will be manufactured from medical woven textiles that are biocompatible.

Choice of material for the frame is the bi-metal alloy Nitinol for its elastic, shape-memory and biocompatible characteristics [25]. The base of the frame will be 3.0 cm in diameter, and the frame will be collapsible into a guide tube, and due to its shape-memory properties, will expand in the aorta, conforming to its size and shape. This frame design eliminates the necessity for manufacturing a range of frames with different and constant diameters.

The EX Intra-Aortic Filter must remain in the aorta for less than an hour and through the EX Access Device (see **Table 3, Use Duration, EX Intra-Aortic Filter)**, it is placed proximal to the heart, facing the aortic valve. It mainly targets the embolic debris produced at the clamping and unclamping of the aorta and for that reason it is deployed right before the clamping, removed and deployed again before the unclamping. This method provides no protection from

the sandblasting effect. CEPC, too, has no protection against the sandblasting effect. Moreover, CEPC relies on hemodynamics and aims to catch large debris particles which bears the potential of missing the finer debris that is closer to blood cells in size.

The proposed EPD, in comparison, will be deployed before the clamping of the aorta, stay in the aorta for the duration and will be retrieved after the clamping is removed. Furthermore, it will be placed distal to the heart, directly protecting the three main branches in the aortic arch and its base will face the cannula directly, which will reduce the sandblasting effect.

This study presents its findings with regards to the effect of presence and size of pockets on the capture and safe removal of debris. Moreover, preliminarily, in an attempt to set a precedent for the next set of safety experiments concerning the effect of the EPD on the flow rates and the velocity profile of the blood, this study reports the volumetric flow rate and velocity changes influenced by the presence of CMSs. The most important finding that this study presents is that retrieval phase replicating experiment have shown that SP DL CMSs are able to capture and safely remove debris, better than any other mesh designs tested. This result suggest that the mechanical properties of the design, double layered and small pocketed, have a considerable effect on the capture efficiency. The results, also provided a general conceptual framework that can be built on, by reporting that the flow rates remained in the required surgical conditions in the presence of the CMSs, and the velocity had dropped significantly through the CMSs, as an added measure for sandblasting effect.

The capture efficiency results are promising, and agrees with the hypothesis that double layer pocketed meshes capture and entrap debris better than other designs tested. Nevertheless, before concluding that CMSs were safe, the conceptual framework mentioned above must be enlarged and built on with computational fluid modeling and experiments

completely dedicated to understand the flow and velocity profile of blood as it flows through the mesh. The assumption that the blood is Newtonian doesn't account for the particulate nature of the blood which causes shear thinning and viscoelasticity. The red blood cells are accounted for the non-Newtonian behavior of blood [31]. In light of this, the next step of experiments would include using the intended woven nylon 12 material for the CMS prototype, and the use of porcine blood, and a wide range of debris-mimicking microspheres (50-1000 μm), with a similar setup described in this report. Studying the capture efficiency and the flow profile at the same time, in the same experiment would allow for better prototyping for the next generation design. Ideally the next experiments would test a set of different pore size combinations, and find the optimal combination, backed by computational modeling, that can capture and safely remove debris, while decreasing the sandblasting effect and not hindering the blood flow significantly. The experiment, should collect the blood that ran through the meshes, and do an analysis of hemolysis, as well.

C. Reduced Sandblasting Effect and Safe Range of Flow Rate in the Aortic Model

Drastic Velocity Drop Through the CMSs

The flow rate of blood must be within the range of 4.2-4.9 L/min [39], for that reason the blood exiting an aortic cannula often have a very high velocity. For instance Muehrcke *et al.* reports that an 8.00 mm in diameter, cannula with a non-metal tip, can have a peak velocity of 288 ± 51 cm/s [32]. Additionally, Grooters *et al.* showed that a 7.3 mm in diameter cannula with a steel tip, can jet blood at a peak velocity of 318 ± 63 cm/s [33] The impact of blood on the aortic walls cause debris joining the circulation. The experiments illustrated that the CMSs, regardless of mesh structure and pockets, drastically decreased the velocity of the water. Not surprisingly, the velocity of water was calculated to have dropped significantly, 36-fold as it

passed through the CMSs, from 225.08 ∓ 1.40 cm/s to 6.23 ∓ 0.15 cm/s . Nevertheless, the SL, DL, SP DL and LP DL MSCs did not show any statistically significant difference from each other *(P>0.05)*, meaning double layered and pocketed features of the proposed EPD had no effect on reducing the sandblasting effect, but they did not exacerbate the complication either.

It is important, however, to note the limitations of the experiment in terms of calculations. While the velocity calculations were made by dividing the measured outlet flow rate by the surface area of the CMSs, there have been made two assumptions: i) the water exits the CMSs using the whole open surface area, ii) the inner layer causes an insignificant reduction of the total open area of the outer layer. It is also important to note, however, that even if the real values of total open surface area that the water flowed through was calculated, since the velocity drop is so drastic, minor changes in calculations are not expected to alter the reduction of sandblasting effect. On the other hand, the flow was found to be laminar (Re = 1347) and another assumption made was that it was fully developed as it exited the cannula, which means that the flow was parabolic and the velocity peaked in the middle of the cross-sectional area and was zero at the cannula walls. This assumption suggest that the water exiting the cannula in the middle of the cross sectional area corresponded to the tip and the around the tip of the CMSs (farthest point from the cannula) and the water exiting from closer to the cannula walls corresponded to the mesh closer to the circular base. This means that the high velocity water travels more than the lower velocity water before it hits the CMS. Grooters *et al.* showed that blood exiting a steel-tip cannula, much like the one used in this study, decreases in velocity around 20 cm/s for every centimeter it travels [32]. In light of this, in spite of the parabolic shape, it is possible that the velocity profile of water is more evenly distributed at the point of contact with the CMSs. This would support the assumption that the water exit the CMSs evenly through

the whole open surface area, rather than having a higher velocity and impact at the tip of the cannula.

To sum up, more detailed studies could be done to eliminate these assumptions. Firstly, a computational model with COMSOL would be conducted. Using the Free and Porous Flow Media Package (which uses Navier-Stokes and Brinkman equations to solve for flow profile in the free and porous media, respectively) of COMSOL, a 3D flow simulation in an aortic model, with a CAD model of the proposed EPD placed under the three aortic branches with full wall apposition, it is possible to obtain a velocity and pressure profile. Moreover, the aortic model would be obtained and averaged from MRI imagings of cardiac patients that underwent open-heart surgery. Similarly, as blood is not a built-in feature of COMSOL, to model an approximate fluid, the average kinematic viscosity and shear rate of blood samples of a set of cardiac patients undergoing open-heart surgery would be obtained. To describe the mesh pore sizes, porosity (ratio of open space to solid mesh) and permeability (the quantifiable quality of a material that allows it to let fluids flow through it) would be used. The source of fluid would be modeled as a short tube placed one or two centimeters away from the CAD model of the EPD to imitate the aortic cannula. Finally, setting the range of inlet flow rates, a more accurate velocity profile would be obtained.

Secondly, a physical experiment of observing the velocity profile of blood under Doppler ultrasound would be beneficial. In an experimental setup that places a set of CMSs with different inner and outer layer pore size combinations into a dissected pig aorta, recording and analyzing the blood flow with a Doppler ultrasound, would provide a better understanding of the velocity drop and the shear stress of blood as it flows through the CMSs. However, to say the least, preliminary testings presented in this report show that the conical shape has a high

potential of significantly reducing the velocity of blood and therefore the sandblasting effect, eliminating a significant source of debris.

Flow Rate Drop in the Aortic Model was in the Desired Range

The CMSs were further tested in an aortic model to ensure that the flow rate was not hindered below the minimum required value (4.2 L/min). The average inlet flow rate was 4.58 ∓ 0.03 L/min (SD = 0.06) and the average outlet flow rate was 4.31∓ 0.02 cm/s (SD = 0.12), larger than 4.2 L/min. Similar to the sandblasting experiments, the mesh structure and pocket size had no significant effect on the outlet flow rate ($P>0.05$).

The results demonstrate that the proposed conical, double-layered and pocketed EPD would not hinder the flow below the required levels. Nevertheless the average inlet flow rate was intended to be higher than 4.2 L/min. This means that if the inlet flow rate was lower, there is a risk that the outlet flow rate would be out of range as well. For that reason, if the proposed EPD is being used in a surgery, the perfusionists and surgeons must make sure that the flow rate of blood from the HLM must be higher than 4.2 L/min as to ensure safety. The problem that could arise with this is that the blood pressure of the patient during the surgery may fluctuate and hence the inlet flow rate would be altered. It would be a difficult task to manage the blood pressure during the surgery while the EPD is in place. Therefore further studies should be conducted that finds a range of constants depending on patient characteristics that describes the absolute relationship between the EPD and the drop in flow rate.

Another limitation with this experiment is that the flow rate while the debris is caught is not measured. This is because of two reasons: i) it is not possible to know the amount of debris that an EPD will catch in real life so any result would be arbitrary, ii) 0.2 g of debris was assumed to be insignificant in volume in relation to the total open surface area of the CMSs.

Nevertheless, despite limitations, the CMSs show significant potential for their safety by both significantly reducing the sandblasting effect, and not hindering the flow rate as to cause any harm.

D. Increased Capture Efficiency with Double Layered Small Pocketed CMSs During Retrieval

PMSs Catch Debris Regardless of Pocket Size

The capture efficiency is the only and most important metric that this study reports for efficacy of the proposed EPD. PMSs were built from woven nylon meshes with 100 μm pore size as the inner layer, and woven polypropylene meshes with 350 μm pore size as the outer layer (30 mm x 30 mm in size). In order to measure capture efficiency, 0.2 g of debris was introduced into the flow of water that pass through the PMSs and the mesh weight was calculated before and after the experiment.

The average capture efficiency of DL PMSs was 98.25∓ 4.64%; 95.08∓ 2.89% for SP DL PMSs; 88.57∓ 3.22% for LP DL PMSs, and 87.98∓ 3.38% for SL PMSs, however, surprisingly none of the double layered mesh structures (both pocketed and not) showed any significant difference from the single layered mesh structures.

A possible reason for the lower capture efficiency of pocketed PMSs could be that the hand sewn pockets may have introduced unintended holes to the structure. While there was no visible holes, there was no errors made during the pocketing process, the threads also may have gotten loose as the water flowed through them. Furthermore, the discrepancy between DL PMSs and SL PMSs was expected, since the second layer adds both mechanical integrity, and an added measure for capture. The fact that the PMSs were glued to the end of the aortic model presents a limitation for this study. Nevertheless, visual inspection have revealed the glue

adhered to the aortic model more strongly and never stayed on the PMSs. However, minute glue traces undetectable with visual inspection may have adhered to the PMSs, introducing a source of human error.

In any case, the average capture efficiency of the double layered PMSs (pocketed and not) was 93.97∓2.32%, which is a strong number. Nonetheless, further studies must be done with larger sample sizes for each PMS categories and industrial pocketing techniques in order to comprehend fully the capture capability of these PMSs.

SP DL PMSs Catches Significantly Higher Debris

One of the most important problems identified with the predicate devices was that the lack of preventative measure against the dislodgement of captured debris during the retrieval, due to the strong current of blood flowing through the EPDs. In an attempt to illustrate the efficacy of a double layered and pocketed design for not only the capture but also the safe removal of the debris, CMSs were built, with the same pore size, pocket size, and material features as PMSs.

These CMSs then were placed in an aortic model, and a real surgical cannula was used for the delivery of water, at a high speed. Ten seconds after the debris was introduced, the CMSs were pulled out of the model in the direction of cannula, in an attempt to replicate the retrieval phase of the device. The average capture efficiency of SL CMSs was 87.14∓1.43%, 88.64∓7.30% for DL CMSs, 98.33∓8.09% for SP DL CMSs and 89.64∓1.67% for LP DL CMSs. Among the four CMS designs, SP DL CMSs have captured significantly more debris than the rest of the designs ($P<0.05$). Moreover, although not significantly higher, LP DL CMSs captured more debris on average than DL and SL CMSs. These finding suggest two conclusions: i) pockets improve the safe removal of the debris, ii) pocket size and capture efficiency during

retrieval is inversely correlated, meaning the smaller pocket ensured the entrapment of the debris between two layers and in pockets.

The experiment, however, revealed some issues that must be addressed moving forward. During retrieval, it was observed the high velocity water caused water built up in the CMSs. This could be attributed to the high stiffness of the inner polypropylene layer, bouncing water back due to a lack of flexibility. While that won't be the case when nylon 12 is used, but the issue prompts an R&D effort dedicated to understand better the fluid dynamics and its possible impact on debris capture and safe removal. To further understand the flow and its relation to debris capture and safe removal, the average inlet Re of water in this experiment (Re = 1347) can be compared to the hypothetical Re number if blood was used instead (Re_b). Blood's density was taken to be 1025 kg/m^3 and its dynamic viscosity was taken to be 1.95 mPa.s [33]. Using the same inlet flow rate that the water had in this experiment (0.224 cm/s), the Re_b was calculated to be 781. This means if blood was used, the flow wouldn't have been turbulent either, which is important because the chaotic nature of turbulent flow has the potential to either rupture the mesh, or dislodge debris even when it's entrapped. Moreover, often the cannulas used during procedures are curved at the tip, which requires a more sophisticated analysis that included Dean's number (De), which describes the fluid motion in curved pipes. High De means that fluid behaves like vortices during the flow, which would disrupt the captured debris. For that reason, further flow analysis must be made to ensure that the inlet flow has a low De, so that the debris is safely removed.

Nonetheless, the SP DL CMSs captured significantly more than any other CMS design, confirming one of the hypotheses of this report, that the double layer and pocketed mesh would entrap the debris, helping in its safe removal. Further studies must be done with a larger sample

size of CMSs, and debris imitating material that are closer to cholesterol and fatty tissue than sand.

E. Limitations

The experiments have revealed promising results in terms of addressing the problems mainly identified from the lack of efficacy of the predicate devices. While the capture efficiency of a double layered pocketed mesh increased the capture efficiency during the retrieval replication experiment, also the conical shape added an effective preventative measure against sandblasting effect. Nevertheless, due to the timeline and budgetary reasons this report comes with few limitations.

Firstly the use of water instead of blood is a significant limitation. The viscosity of water is 0.91 cP at 25 °C, which is 5- to 7-fold less than the viscosity of blood [34]. Viscosity is directly related to shear stress, meaning that the flow rate profile presented will differ for blood. Furthermore, blood is particulate in nature, which may cause it to behave differently under the filtering circumstances than water. Aggregation, alignment and deformation of RBCs are thought to be the cause of the viscoelastic and shear-thinning nature of blood [31]. It is possible that pores may be closed or clogged due to aggregation of RBCs which would hinder the blood flow, and in turn create clots that can dislodge and join the circulation. While this study focused on capture efficiency of debris, and therefore used water as a medium to carry debris, further studies must be conducted dedicated to understanding the effect of pore size and openings on RBCs, and its relation to flow rates

Another inexpensive alternative was the use of sand instead of debris. Albeit an unconventional choice, the tests aimed to provide a functional proof-of-concept, therefore metrics such as size and shape of the debris were of more importance than its behavior in

laminar or turbulent flow or friction coefficient against the mesh, at this stage. Cholesterol and fatty tissue are expected to have a different friction coefficient against the CMSs due to their organic nature. Moreover, while sand absorbed water, the hydrophobic nature of fatty tissue, for instance, would allow it to stay close to its original shape and size during flow. In future experiments, there are a range of materials that can be used, such as microspheres with similar density to blood or blood-mimicking fluid that would be used. However this way, possible clotting around the debris can't be observed since microspheres would have a smooth surface. Another example could be using dried fatty tissue from an animal model, granulate it and analyze its size range before the experiment. This would be the closest approximation before actually moving on to preclinical animal model experiments, since both the behavior of debris and the behavior of blood around the debris would provide close approximations to real scenarios.

F. Future Directions

In order to overcome the limitations of this report and manufacture a surgically viable EPD, moving forward the mesh pore sizes should be optimized for safe flow rates and debris capture efficiency. These experiments must be done with blood or a blood-mimicking fluid with a wide range of debris size and shape. Not only the flow rates and capture efficiency, but for safety, also the effect of the filter on blood cells must be understood.

Once the flow rate safety and capture efficacy in ensured, alongside the proof of no harm to blood cells, prototyping with the intended materials should follow: nylon 12 and Nitinol. The synthesis of frame and the mesh is a critical piece of the prototyping puzzle and a significant amount of R&D is expected to allocated for that part. Once a satisfying prototype is manufactured, in cooperation with animal labs, it will be tested in dissected porcine aorta. Concurrently, another R&D project will be launched concerning the delivery and retrieval

mechanism of the EPD, which will be another important portion of the project. Once the delivery piece is designed and manufactured, and the prototype produced promising results in the dissected porcine aorta, the whole design will be tested in a pre-clinical animal study.

VI. CONCLUSION

The need to mitigate debris release during open-heart surgeries is a relevant and important goal that can save tens of thousands of patients from suffering from PS and CD. In an attempt to relieve this unmet clinical need, that not only affects the patients, but also seriously burdens the healthcare economy in the US, this study proposed an EPD that aims to capture and safely remove debris. Predicate devices that have received FDA approval and were placed in the market, but extensive clinical trials have revealed their ineffectiveness. Based on both the literature review of the risk factors of PS and CD and the identified problems with the predicate devices, the proposed EPD aims to collect and trap debris through the novel features of a double-layered, pocketed conical mesh structure delivered with a Nitinol conical frame.

Table 5 summarizes the design requirements outlined and whether they've been met in the scope of this study. The most important finding of this report had been that during retrieval, double-layer and pocket features ensured a more effective removal of the captured debris. Additionally, preliminary fluid analysis of the conical shape shows reduction of fluid velocity as it exits the aortic cannula, eliminating the risk of sandblasting effect, a significant source of emboli during surgeries.

Assessment of Design Requirements and Experimental Results	
Design Requirement	**Results**
Biocompatibility	The prototypes built (PMSs and CMSs) were made up of nylon and polypropylene meshes, which are not biocompatible by ISO standards. Moving forward, nylon 12, a biocompatible material, will be used. The frame prototype that was built was out of Nitinol, which is indeed biocompatible.
Debris Capture and Removal	Debris capture rates were satisfactory for DL and SP DL PMSs. SP DL CMSs also outperformed other designs significantly during retrieval replicating experiment.
Flow Rate within Surgical Conditions	Presence of the CMSs did not hinder blood flow into the systemic circulation below the critical level (~4.2 L/min)
Prevention Against Sandblasting Effect	Velocity dropped significantly through CMSs, significantly reducing the sandblasting effect.
Compliance with Current Surgical Procedures	Currently there is no method and design devised for the EPD's compliance with current surgical procedures. Experiments should test different delivery and retrieval methods for minimizing the necessary surgeon training before its use.
Minimum/ No Effect on Blood Cells	Results have not revealed any information pertinent to effect of pore size and flow rate on blood cells. In next experiments that will use blood, it's behavior should be studied in and after it passes through the CMSs, for whether the blood cells remain intact and unharmed.

Table 5: The design requirements of the EPD and whether they've been met in the scope of this study.

There needs to be, however, further experiments that should aim to ensure the compliance of the proposed EPD with the current surgical procedures. Finally, it is of utmost importance to computationally run flow models, and physically experiment with real blood to

understand the velocity profile as it flows through the CMSs and the impact of flow through porous media on blood cells.

The verification tests presented in this study were promising in terms of the debris capture of the proposed EPD. With the conceptual framework that this study has built, and with the identified limitations, future verification experiments will aim to ensure and underscore the safety of use of the proposed EPD, by testing the effect of the EPD on passing blood cells, and overall flow profile. Computational modeling with COMSOL and a Doppler ultrasounds imaging of blood flowing through the EPD in a dissected pig aorta will further verify the safety of the EPD. These preliminary results and the next set of verification experiments should lead to validation studies in animal models for an extensive preclinical trial. Eventually, the iterative design process and early adaptation to challenges ahead will result in a product that would protect open-heart surgery patients from cerebral-injury, all around the world.

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