Published in final edited form as:

J Vasc Surg Venous Lymphat Disord. 2016 October ; 4(4): 472–478. doi:10.1016/j.jvsv.2016.05.006.

In-vitro Evaluation of Clot Capture Efficiency of an Absorbable Vena Cava Filter

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Abstract

Purpose—Determine the in-vitro clot capture efficiency (CCE) of an investigational absorbable inferior vena cava filter (IVCF) versus the Greenfield IVCF.

Materials and Methods—Investigational absorbable and Greenfield filters were challenged with polyacrylamide (PAM) clot surrogates ranging from 3×5 to 10×24 mm (dia. × length) in a flow loop simulating the venous system. Filters were challenged with clots until CCE standard error of 5% or less was achieved under binomial statistics. Pressure gradients across the filters were measured for the largest size clot, enabling calculation of forces on the filter.

Results—The absorbable IVCF in-vitro CCE was statistically similar to the Greenfield filter for all clot sizes apart from the 3×10 mm clot, where there was statistically significant difference between filter CCE's (absorbable filter: 59%, Greenfield: 31%, $p=0.0001$). CCE ranged from an average 32% for the 3×5 clot to 100% for 7×10 mm and larger clots for the absorbable IVCF. Pressure gradient across the absorbable filter with 10×24 mm clot averaged 0.14 mmHg, corresponding to a net force on the filter of 2.1×10^{-3} N, compared to 0.39 mmHg or 5.8×10^{-3} N ($p<0.001$) for the Greenfield filter.

Conclusions—CCE of the absorbable filter was statistically similar to, or an improvement upon, the Greenfield stainless steel filter for all clot sizes tested. CCE of the Greenfield filter in this study aligned with data from previous studies. Given the efficacy of the Greenfield filter in attenuating the risk of pulmonary embolism, the current study suggests the absorbable filter may be a viable candidate for subsequent human testing.

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No material from this article or study has been submitted for any other publication nor presented in any conference.

Potential Conflict of Interest:

S.J.D. and M.D.E. receive salaries from Adient Medical, which developed the investigational device evaluated in the study. S.J.D. owns stock options in Adient Medical. M.D.E. owns shares in Adient Medical.

Introduction

Venous thromboembolism (VTE), which includes both deep vein thrombosis (DVT) and pulmonary embolism (PE), annually affects 350,000 to 600,000 people^{1–3} and causes over 100,000 deaths in the United States.³ VTE cases are likely higher due to lack of identification of VTE without autopsy.² One model for Europe estimated 370,000 VTE-related deaths, with an estimated 760,000 non-fatal VTE events.⁴

While anticoagulants are the preferred method for preventing VTE, anticoagulants sometimes fail to prevent VTE or are contraindicated, in which case inferior vena cava filters (IVCFs) are recommended.^{5–7} Even if VTE is not present but there is a high risk for bleeding where anticoagulants are contraindicated, such as in major trauma and surgery, the Society of Interventional Radiology, which represents the specialty that places most IVCFs, recommends the use of IVCFs.⁵ IVCF usage is rapidly increasing in the United States, with an estimated 92,000 IVCFs placed in 2006 – a threefold increase over 5 years earlier⁸ – and an estimated 250,000 placed in 2012.⁹

However, significant complications can result from use of existing IVCFs. These include migration, fracture, and IVC perforation.^{10–14} The rates of such complications increase when retrievable IVCFs are not retrieved within the manufacturer-recommended time. The FDA recommends physicians remove filters as soon as risk of PE subsides,¹⁵ citing a quantitative risk/benefit decision analysis utilizing data from 19 IVCF studies which suggested risks outweigh benefits for keeping an IVCF in situ after 29 to 54 days postimplantation for patients at transient PE risk.¹⁶ A systematic review of literature found mean retrieval rates of retrievable filters at only 34%,¹⁰ and even with significant effort to improve this rate, retrieval rates only improve to 52–60%.^{17,18}

Conceptually, a filter which simply vanishes following transient PE risk would avoid the complications from chronic use. An investigational IVCF braided from absorbable polydioxanone commonly used in absorbable suture demonstrated both feasibility and sufficient strength retention for a clot-capture period of 5 weeks in a porcine model.¹⁹ Ideally, any new absorbable filter should demonstrate that it is just as effective as existing metal filters at capturing blood clots and thus preventing PE. The purpose of this study was to assess the in-vitro clot capture efficiency of the previously studied absorbable filter versus the Greenfield stainless steel filter.

Materials and Methods

Filter Design

The investigational filter is an absorbable IVCF designed to retain structural integrity well beyond the PE prophylaxis period of 5 weeks before completely resorbing.²⁰ The absorbable filter is woven from polydioxanone (PDS) monofilament, similar to PDSII suture (Ethicon, NJ), with two sections, both woven from PDS monofilament: a circumferential stent section that stabilizes the filter in the IVC and a basket section that catches clots (refer Figure 1b). The basket portion, with a relaxed diameter of 33mm and length of 31mm, was designed to

have a similar aspect ratio and filament spacing to many of the currently marketed conical metal IVCs, including the Greenfield filter, shown in Figure 1a. The primary endpoint of this study was comparison of the investigational absorbable filter (Adient Medical, Pearland, TX) to the stainless steel Greenfield filter (Boston Scientific, Marlborough, MA) with regard to CCE. The Greenfield stainless steel filter was chosen due to its history of relatively safe performance with one million deployed over 30 years.

Venous Simulator

A closed-loop venous flow simulator was constructed using PVC, stainless steel pipe, and silicone tubing, as diagrammed in Figure 2, with the filter oriented horizontally in a 25.4 mm (ID) silicone tube. In order to simulate human physiology and mimic flow patterns as seen on contrast fluoroscopy, a continuous flow centrifugal pump (Cole-Parmer 75211-62, Barrington, IL) was used in series with a peristaltic pump (Cole-Parmer 77600-62, Barrington, IL). Thin-walled (3/16 in) tubing was used in the peristaltic pump to reduce extreme recoil observed between flow pulses. Flow was maintained at 3.5 L/min with 96 pulses/min, consistent with human physiology. Flow was monitored (Georg Fischer Signet 8150, El Monte, CA). Average pressure was continuously recorded (GE Druck DPI-104, Leicester, UK) upstream and downstream of the filter, and was maintained between 5 and 15 mmHg. Glycerin solution (52% by weight in water, 1.12 g/ml) was used to simulate the viscosity and density of blood.²¹ A heating coil wrapped around stainless steel pipe with a thermostat controller (Love Controls, Michigan City, IN) maintained the temperature at 37°C $\pm$ 2°C.

Clot Fabrication and Characterization

Polyacrylamide (PAM) surrogate clots were prepared from 3.6 ml of 40% acrylamide stock solution, 2.04 ml of bisacrylamide fixer solution, 42 ml distilled water, 240 μ l ammonium persulfate, and 35 μ l tetramethylethylenediamine for a total volume of 48 ml (all from Bio-Rad, Hercules, CA), as described by Robinson et al. at the FDA.²¹ The PAM was cast in tubing with inner diameters of 2.4, 4.8, 5.7, 9.5, and 25.4 mm for 3 hours. These were cut to lengths of approximately 3.6mm (2.4 mm ID), 7.1 mm (2.4, 4.8, and 5.7 mm IDs), 14.3 mm (2.4, 4.8, and 5.7 mm ID's), 17.1 mm (9.5 mm ID), and 10 mm (25.4 mm ID). PAM casting and cutting lengths were undersized to accommodate later swelling to nominal sizes of (dia. $\times$ length) 3 $\times$ 5, 3 $\times$ 10, 3 $\times$ 20 5 $\times$ 10, 5 $\times$ 20, 7 $\times$ 10, 7 $\times$ 20, and 10 $\times$ 24mm, along with the 25.4 $\times$ 10mm section for mechanical testing. These PAM clots were washed with distilled water and allowed to soak in bovine serum albumin for 24 hours. Subsequently they were washed with distilled water and stained with Coomassie blue dye solution for 24 hours. After dyeing, the PAM clots were washed and allowed to soak in 1.12 g/ml glycerin-water solution for 5 days, with multiple exchanges of solution to compensate for dilution due to water retained in the PAM clots. Prior to each trial, the dimensions of the clot were measured. The final clot sizes are shown in Table I.

Prior to clot capture experiments, the modulus of elasticity was measured for the 25.4 $\times$ 10 mm section of PAM using an eXpert 7601 mechanical testing machine with MTEST Quattro software (ADMET, Norwood, MA). Moreover, qualitative assessment of how easily clots could fold was also conducted by placing clots in a weigh boat and attempting to fold the

clot over on itself. For comparison, porcine blood clots were formed by extracting porcine blood in 20ml and 60ml syringes and refrigerating the syringes overnight. Elastic modulus and foldability of porcine clots were assessed for comparison to PAM surrogate clots. The modulus of elasticity for the PAM surrogate clots was 1.19 (SE=0.06) kPa, compared to 1.35 (SE=0.26) kPa for porcine blood clots. The slightly lower elastic modulus of the synthetic clots was by design, as it represents a balance between matching elasticity and foldability – both important parameters in simulating thrombus flow. Similar to Robinson et al.²¹, the PAM clots in this study were slightly less foldable than blood clots even with the lower elastic modulus.

Clot Capture Statistics

CCE is defined as the proportion of clots captured by the filter as the filter is challenged by a number of clots. The filters were challenged by only one PAM clot at a time to limit confounding. If the clot was retained by the filter for 15 seconds, the clot was considered captured. After each trial, the flow was reversed until the clot returned to the start position adjacent to the pump. After every 10 trials the binomial sample standard error was calculated. Tests were repeated until the standard error was less than 5%; at least 20 trials were conducted for each clot size. Statistical significance in difference between capture efficiency for the absorbable and Greenfield filters for each clot size was determined using two-tailed binomial hypothesis testing. Significance level with Bonferroni correction for 8 tests was $\alpha=0.05/8=0.00625$.

Pressure and Flow Rate Measurement

The peristaltic pump used to create the mild pulsatile action in the IVC caused significant variation in pressure, obscuring pressure changes caused by clot capture. To measure pressure change resulting from clot capture, the peristaltic pump was turned off and the centrifugal pump was adjusted to maintain 3.5 ± 0.1 L/min flow and pressure was maintained at 10 ± 3 mmHg. Pressures were measured for two minutes during each of 5 trials per filter: without any filter and following each of four different clot captures to account for various clot capture positions in the filter. Statistical significance was determined using two-tailed Student's t-test with $\alpha=0.05$. Flow rate was measured during the course of clot capture.

Results

Clot Capture

As demonstrated in Figure 3, the performance of the investigational absorbable filter was statistically similar to the Greenfield filter for all clot sizes with the exception of the approximately 3×10 mm clot where the filters showed statistically significant differences in capture efficiency (absorbable filter: 59%, Greenfield: 31%, $p=0.0001$). Most importantly, the larger clots that could cause noticeable disruption to blood flow and more likely cause fatal PE, with diameter near or greater than 7mm, had 100% capture efficiency for the absorbable filter.

Table II details the statistics of the clot capture studies. Note the larger number of trials for smaller clots. As clot size decreases, there is a greater opportunity to escape from the filter and hence CCE decreases, which in turn increases standard error (defined as $((p(1-p)/n)^{1/2}$ where p is the probability of capture). Hence, if standard error is fixed at 5%, the number of trials increases as the probability of capture decreases from 100% to 50%.

Pressure and Flow Rate

The pressure gradient across the absorbable filter with a 10×24 mm clot averaged 0.14 (SE=0.02) mmHg, versus 0.39 (SE=0.03) mmHg for the Greenfield filter with clot (pressure gradient for no filter in the cava was 0.00 mmHg). These equate to forces of approximately 2.1×10^{-3} N and 5.8×10^{-3} N, respectively, with statistical significance ($p = 1.5 \times 10^{-5}$). Average drop in flow for both the absorbable (.08 L/min) and Greenfield (.05 L/min) were smaller than the flow rate measurement resolution (0.1 L/min), and were not significantly different ($p=0.54$).

Discussion

Due to the relatively low occurrence of PE even among high-risk patients, the large number of patients required for a true PE-prevention clinical study for each filter is challenging. However, given the proven efficacy of IVCs in a previous prospective randomized controlled study and the performance of IVCs in retrospective studies broadly,^{11,22,23} there is support that IVCs which demonstrate in-vitro efficacy in capturing clots will also be effective clinically in reducing PE. Thus, the aim of this study was to establish the in-vitro CCE of the investigational absorbable filter relative to the established effective Greenfield filter, to provide efficacy insight.

The absorbable filter caught 100% of large-diameter (7 mm) clots, and lower rates of smaller-diameter and smaller-length clots. As noted by Robinson et al.²¹, the position and orientation of small and medium clots relative to the filter upon contact with the filter quickly emerged as the most critical factor on whether a particular trial resulted in clot capture or escape. Clots oriented with long axis parallel to the cava wall were much less likely to be caught if they were traveling in close proximity to the caval wall as opposed to traveling along the center of the cava. For the smallest clots (3×5 mm) orientation was less important than position, since the diameter and length were similar dimensions. Clots striking the filter with larger cross-sectional areas were much more likely to be captured.

An interesting phenomenon occurred with the 3×10 and 5×20 mm clots. These clots had diameter to length ratio such that they did not fold or wrap around the filter filaments very well; thus, when they were captured on one end, the opposite end would sometimes leverage the clot out of the filter. However, the 3×10 mm clots and to a lesser extent the 5×20mm clots were long enough to be pinched between and partially wrap around two filaments where the filaments intersected; this same phenomenon occurred with the Greenfield filter where the struts narrowed. The difference in numbers of strut or filament intersections between the filters (10 relevant intersections for the absorbable filter versus 6 for the Greenfield) may have contributed to the different capture efficiency of the 3×10 mm clot size for the two filters. In contrast, Robinson et al.²¹ demonstrate that natural blood clots

wrap around the filter filaments more readily than even the soft PAM clots, thus if these two clot sizes had been blood clots, they may have resulted in even higher clot capture rates. However, the relative efficiency of the absorbable and Greenfield filters with natural blood clots should be similar to that of the soft PAM that was used in this experiment.

The absorbable filter did not show any change in shape over the several days experiments were run. This, along with observations from previous degradation studies showing no change in shape until structural failure of the capture basket at 12 to 15 weeks suggest CCE should remain constant throughout the 5-week PE prophylaxis period.

It is challenging to compare in-vitro IVCF clot capture studies in general since venous simulator loops differ between studies and there exists significant variation in clot size and composition. The authors could only identify six studies testing Greenfield filters with at least one clot size the same as used in this study, displayed in Table III.^{24–29} All of these differed in the venous simulator loop, clot composition, and parameters under which filters were tested. CCE for each clot size in this study fell within the range of capture efficiencies found in the identified studies, with the exception of the 7×10 mm clot size, for which no study could be found to compare, and for the 10×24 mm clot size, for which the 100% CCE was extremely close to the 98% identified by Mahnken et al.²⁴

Another discrepancy in comparing to other studies is that most previous in-vitro clot capture studies have relied on small numbers of trials. Some relied on only 10 trials for a single clot size; others combined trials from different setup parameters for each clot size, introducing variability not captured in the output statistic; others vary the number of trials without clearly defined justification.^{21,24–27,30,31} Using such small numbers of trials especially with the smaller clot sizes creates large standard error for binomial distributions. Assigning the number of trials to achieve a standard error of 5% as performed in this study ensured adequate number of trials to yield high confidence in the statistical parameters.

Impending forces on IVCFs from clot capture is particularly important for absorbable IVCFs, where the filter is slowly weakening during absorption. For polydioxanone, it has been shown that the strength of the monofilament degrades in-vivo to 79% at 5 weeks, and then 14% at 10 weeks.¹⁹ For an initial tensile strength of PDSII size 0 suture of 78 N, this corresponds to 62 N at five weeks and 11 N at 10 weeks. The impending force on the absorbable filter with the largest clot (10×24 mm) was calculated to be 2.1×10^{-3} N based on the observed pressure gradient.

Hence the impending force on the filter from the largest clot studied is three orders of magnitude less than the force required to break a single filter filament at 10 weeks postimplantation.

This study has a number of limitations. First, synthetic clots were used instead of blood clots for the purposes of hygiene and ease of maintenance; synthetic clot dynamics differ from blood clot dynamics, especially in post-capture folding, as discussed earlier and in more detail by Robinson et al.²¹ This likely resulted in slightly lower CCE than would be observed with blood clots. Using glycol-water solution may also result in clot dynamics that differ from circulating blood, though to the authors' knowledge no studies have determined

the effects of using blood versus solutions which match blood's viscosity and density. Also, blood clots can be much longer than the 20mm or 24mm used. However, the longest and largest clots demonstrated high CCE for both the absorbable and Greenfield filters; in fact, the longest and largest clots showed not only the highest CCE for both filters, but also the lowest probability of real difference in CCE. Thus it is expected that clots with length greater than 20mm would also result in no statistical difference and in high CCE for both filters. The pulse rate of the venous simulator loop was constant – as opposed to the naturally variable rate in humans – and on the high end for a typical patient. While the flow through the simulated IVC appeared visually similar to flow observed in contrast fluoroscopy of IVCs, the pressure difference between systole and diastole in the simulated IVC was approximately 12 mmHg, in contrast to the 6 mmHg found in human IVCs.³² Despite this slightly elevated pressure difference, the simulated IVC changes shape less than can be found in human IVCs due to proximity to the aorta, which compresses the IVC with each systole. This limited IVC shape change is likely due to the stiffer nature of the silicone tubing as compared to venous tissue. Most often the IVC is compressed to an oval shape instead of the constant, circular simulated IVC. It is expected that these changes would result in slightly greater variation of CCE, as it would depend on the shape of the IVC at the moment when the clot challenges the filter. The compressed oval shape of natural IVCs alters flow characteristics and thus may change CCE in ways that are difficult to predict, as Hammer et al.³⁰ saw changes in clot capture profile that were clot size- and flow rate-dependent. The only experimental variables tested in the current study were clot size and filter type. Ideally, to represent the CCE profile for the full range of patients, the filters would be tested at various IVC sizes, IVC orientations, filter tilting, and flow rates, all of which have been found to affect CCE.³⁰ However, filter tilt such that the tip of the filter is against the simulated IVC wall is difficult for the absorbable filter due to the stabilizing and centering effects of the stent portion of the filter. Despite such limitations, it is likely that these variables affect the Greenfield and absorbable filters similarly and thus the relative performances of the two filters across other physiologic variables would be similar to their relative performance in this study.

Conclusions

Overall, the investigational absorbable filter captured synthetic clots at least as well as the benchmark Greenfield filter for all clot sizes. The results suggest the absorbable filter may well be comparable to the Greenfield filter in efficacy and exhibit decreased caval flow perturbation due to the lower pressure differential observed across the filter, though clinical efficacy cannot be concluded until a clinical trial is conducted. Together with the previously published large animal feasibility study, there is growing support that the absorbable filter will perform effectively through the indication period and then simply vanish, alleviating filter removal procedures. Future directions are aimed at human studies.

Acknowledgments

The research was funded in part by the NIH National Heart Lung and Blood Institute, SBIR R44HL 127734-01.

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Clinical Relevance

Conceptually, an absorbable IVC filter constructed from a flexible polymer is clinically appealing since it obviates filter retrieval and is unlikely to perforate the IVC and impale neighboring organs. A recent in-vivo study demonstrated the investigational absorbable filter retained sufficient mechanical strength to function for the indicated prophylactic period with no migration, caval penetration, or tilt >15 degrees. This study assessed clot capture efficiency for the absorbable filter versus the Greenfield stainless steel filter as an indication of the filter's efficacy at preventing pulmonary embolism before commencement of human studies.

Figure 1.

(a) Greenfield and (b) investigational absorbable filters, viewed from the perspective of an approaching clot. The filters are in a one-inch inner diameter silicone tube.

Figure 2.
Diagram of the venous simulator loop.

Capture Efficiency vs Clot Size

Figure 3.

Clot capture efficiencies for stainless steel (SS) Greenfield and investigational absorbable filters for various clot sizes. Error bars indicate standard error.

Table I

Nominal and measured dimensions for synthetic polyacrylamide clots.

Diameter (mm)		Length (mm)	
nominal	mean (min/max)	nominal	mean (min/max)
3	2.8 (2.7/3.0)	5	4.4 (4.2/4.7)
		10	10.4 (10.2/10.5)
		20	18.9 (18.3/19.2)
5	4.8 (4.7/5.1)	10	10.3 (10.2/10.3)
		20	19.7 (19.5/19.9)
7	7.1 (6.9/7.2)	10	11.0 (11.0/11.0)
		20	20.1 (20.0/20.2)
10	11.3 (11.1/11.4)	24	27.0 (26.9/27.0)

Table II

Clot capture efficiencies for Greenfield Stainless Steel and investigational absorbable filters for all clot sizes in this study.

Nominal Clot Size (mm)	Greenfield Filter Capture Efficiency (95% CI ^a)	Absorbable Filter Capture Efficiency (95% CI ^a)	p-Value
3×5	21% (14%, 31%) (n=80)	32% (23%, 42%) (n=90)	p=0.11
3×10	31% (22%, 41%) (n=90)	59% (49%, 68%) (n=100)	p=0.0001
3×20	64% (54%, 73%) (n=100)	70% (60%, 78%) (n=90)	p=0.38
5×10	79% (69%, 86%) (n=80)	88% (76%, 94%) (n=50)	p=0.18
5×20	86% (74%, 93%) (n=50)	90% (79%, 96%) (n=50)	p=0.54
7×10	100% (84%, 100%) (n=20)	100% (84%, 100%) (n=20)	p=1.00
7×20	95% (76%, 99%) (n=20)	100% (84%, 100%) (n=20)	p=0.31
10×24	100% (84%, 100%) (n=20)	100% (84%, 100%) (n=20)	p=1.00

^aWilson score confidence interval

Table III

Clot capture efficiencies from the literature for Greenfield filters with clot size matching at least one clot size used in this study. For studies that detailed results by IVC orientation and filter tilt, only horizontal IVC and centered filter data were used. All studies had differences in venous simulator loop and parameters under which the filters were tested.

Paper	Mahnken et al. (2007) ²⁴	Stoneham et al. (1995) ²⁵	Katsamouris et al. (1988) ²⁶	Palestrant & Faykus (1991) ²⁷	Pavcnik et al. (1999) ²⁸	Irie et al. (1995) ²⁹	Range	Current Study
<u>Clot Size</u>								
3×5	33%	0%	—	—	—	—	0–33%	21%
3×10	38%	—	5%	—	—	—	5–38%	31%
3×20	—	—	15%	74%	90%	—	15–90%	64%
5×10	63%	90%	—	—	—	—	63–90%	79%
5×20	75%	100%	—	82%	—	—	75–100%	86%
7×10	—	—	—	—	—	—	—	100%
7×20	85%	—	100%	—	—	100%	85–100%	95%
10×24	98%	—	—	—	—	—	98%	100%