



# Influence of Exercise on Inferior Vena Cava Wall Interaction with Inferior Vena Cava Filters: Results of a Pilot In Vivo Porcine Study

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## Abstract

**Objectives** The aim of this study was to assess the effect of mild exercise on inferior vena cava (IVC) filter interaction with imaging and pathological features with the neighboring vessel wall utilizing a porcine model.

**Materials and Methods** After Institutional Animal Care and Use Committee (IACUC) approval, retrievable Option Elite IVC filters were implanted in six Yorkshire pigs utilizing the right common femoral vein approach under general anesthesia. Group A ( $n = 4$ ) pigs remained sedentary for 4 weeks. Group B ( $n = 2$ ) pigs were exercised using a harness and treadmill for 10 minutes/day for 4 days/week. At approximately 4 weeks, IVC venograms were performed and the pigs were sacrificed. After laparotomy, the IVC was ligated above and below the filter, excised and fixed in formalin. Gross and histological examination of the IVC was performed. Gross images of each sample were captured before removal of the filters. One longitudinal, one tangential, and five transverse representative sections were processed for paraffin sectioning and hematoxylin and eosin slides were prepared. A pathologist examined all tissues to assess differences between normal vein, group A and group B pigs. The pathologist provided an overall assessment and representative images.

**Results** All IVC filter implantations were technically successful without adverse effects. There was no incidence of caval thrombosis, filter strut fracture, or filter migration in either group. On gross pathological examination, IVC of the pigs in group B demonstrated more perivascular and mural fibrosis than those pigs in group A. Histopathological findings correlated with gross findings.

**Conclusions** In this pilot study, there were no incidence of IVC filter strut fracture, penetration or IVC occlusion in sedentary or exercised pigs. However, there tended to be more perivascular and mural fibrosis on pathological examination of inferior vena cava from exercised pigs. Further larger scale studies may employ the porcine model to further understand the role exercise may play on IVC filter and caval wall interaction.

## Keywords

- ▶ inferior vena cava
- ▶ inferior vena cava filter
- ▶ thrombosis

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## Introduction

Inferior vena cava (IVC) filters have been the gold standard for prophylaxis against pulmonary embolism in patients with chronic deep vein thrombosis.<sup>1</sup> Since the U.S. Food and Drug Administration issued a service warning regarding IVC filters in 2010, there has been a larger focus on the retrieval of these IVC filters once no longer indicated.

Despite the push for timely filter removal, retrieval rates have consistently been low—ranging between 20 and 58%, largely due to complicated retrieval conditions after the filter has been in place for longer than necessary.<sup>1–4</sup> Multiple factors have been noted to lower success of filter removal such as advanced age, presence of IVC thrombus, and increased interaction between the IVC filter and caval wall.<sup>5</sup> The mechanism of interaction between the filter and caval wall is not very well understood—prior studies have shown correlations between the presence of free struts, increased filter tilt, and stiffness of the filter but no definitive evidence has been found that completely describes filter–caval wall interaction.<sup>6</sup>

One possible additional factor for filter–vessel interaction that has not yet been extensively studied is exercise. Computational models based on the flow dynamics of the average human IVC vessel have shown significant changes in vessel and flow dynamics in exercise conditions.<sup>7</sup> Due to respiratory physiology during exercise, the cross-sectional area of an individual's IVC was noted to decrease significantly, theoretically leading to increase filter–wall interaction and an increased chance of filter penetration. Another study found that exercise increased stagnant and regurgitant flow in the IVC, especially around the filter. In addition, exercise significantly increased shear stress forces on the vessel wall from the IVC filter.<sup>7,8</sup> A third model also found significant higher central and peripheral flow velocities during exercise. These findings suggested that the asymmetric flow around the IVC during exercise conditions may potentially facilitate thrombus formation or IVC filter movement.<sup>8,9</sup> However, no further studies were done to evaluate these effects *in vivo*. Therefore, this pilot study aimed to examine the effects of mild exercise on IVC filter interaction with imaging and pathological features with the neighboring vessel wall utilizing a porcine model.

## Methods

This study was approved by the International Animal Care and Use Committee and made possible by an internal grant provided by the Department of Radiology at our institution. Between June 2018 and June 2019, six Yorkshire pigs underwent placement of Option Elite filters (Argon medical, Frisco, Texas, United States).

Pigs were placed under general anesthesia. The right common femoral vein was accessed under ultrasound guidance and a 6F sheath was placed. A IVC venogram was performed and the inflow of the renal veins was identified. The filters were then deployed in an infrarenal position. A completion venogram was performed. Group A ( $n = 4$ ) was

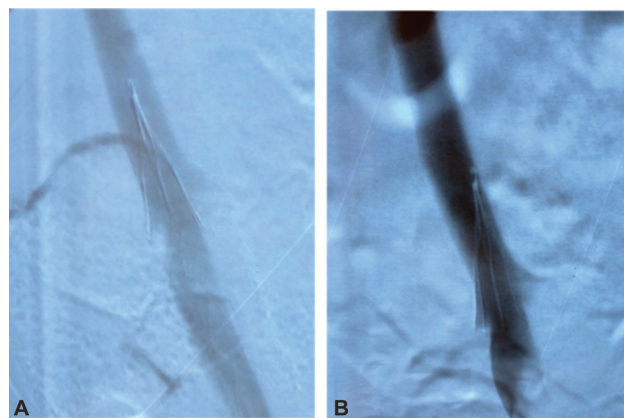
defined as the control group and these pigs remained sedentary, unchanged from their regular lifestyle. Group B ( $n = 2$ ) was defined as the experimental group and these pigs were exercised daily on a treadmill for at least 10 minutes/day for 4 days/week. For both groups, filters were kept in place for approximately 25 days (25–28 days). The weight of each pig was also measured every week.

At the end of the 4-week period, each pig underwent an IVC venogram under general anesthesia. Images were compared with the post filter deployment venograms to assess for filter tilt, fracture, or penetration. The pigs were then euthanized and underwent postmortem laparotomy in which they had their IVCs ligated at points superior and inferior to the IVC filter. The IVC was excised and fixed in formalin. These samples were sent to a pathology laboratory for gross and histological examination. Images of the gross specimen were taken with and without the corresponding IVC filter for comparison. For histological analysis, one longitudinal, one tangential and five transverse representative sections were processed for paraffin sectioning using the Tissue Tek VIP tissue processor. Tissues were embedded in paraffin blocks, cut to 4 microns using a Microm semiautomated microtome, hematoxylin and eosin stained and coverslipped using a Leica Autostainer XL stainer with CV5030 cover-slipper and mounted on glass slides. A single anatomic and cytopathologist at our institution examined all tissues to assess differences between group A and group B pigs.

## Results

On the day of implantation, the average weight of the pigs in group A was 45 kg and that of group B was 23 kg. All of the six IVC implantation procedures were technically successful without any adverse events during the time of procedure or during the postoperative period (–Fig. 1).

During the time between filter placement and sacrifice, no adverse events were noted in any of the pigs. The IVC filters were retrieved after 27.5 days of placement in the group A pigs and after 25 days of placement in the group B pigs (–Table 1). IVC venograms at the time of sacrifice showed no visual evidence of filter migration, filter fracture, caval



**Fig. 1** Representative venogram images during inferior vena cava filter placement and just prior to sacrifice. (A) Venograms immediately postplacement. (B) Venogram prior to sacrifice.

**Table 1** Groups A/B with time between filter placement and sacrifice

Group A	Weight	Days w/implant
Pig 1	50 kg	28
Pig 2	50 kg	28
Pig 3	40 kg	27
Pig 4	40 kg	27
Group B	Weight	Days w/implant
Pig 1	23 kg	25
Pig 2	23 kg	25

penetration, or any thrombus at the site of implantation in either group.

Upon gross pathological examination of the excised IVCs, the pigs in group B showed more of perivascular fibrosis at the sites of the filter, as compared with those in group A (→**Fig. 2**). Histological analysis revealed similar findings of increased perivascular fibrosis and inflammatory cells in the pigs who exercised rather than the ones who did not.

## Discussion

The normal physiologic effects of exercise on the IVC, such as increased turbulent flow and decreased caval diameter, have been described with both computational modeling and human studies.<sup>7-9</sup> Studies have been performed in both animal and human models to examine these effects in other vascular implants, such as coronary and aortic stents. However, these have only been done in arteries, where the effects of exercise are well studied.<sup>10,11</sup> Given the prior success of IVC filter deployment and retrieval in porcine models, our pilot study aimed to examine the effects of mild exercise on the IVC filter interaction with the neighboring vessel wall in a porcine model.

Our study showed increased evidence of fibrosis and damage of the vessel wall near the IVC filter in the pigs who exercised compared with the ones who were sedentary. Histological analysis showed similar results with indications of increased perivascular fibrosis and inflammatory cells in

the pigs who exercised rather than the ones who did not. As a whole these results indicate that even mild amounts of exercise may have the potential to increase filter-caval interactions in patients with IVC filters. In addition, this study showed the feasibility of examining the effects of exercise on IVC filters and the caval wall using a porcine model. Multiple histological analyses specifically performed on complex retrievals have shown the presence of fibrosis and fibrous caps on struts of the removed filter, mostly in those patients with longer indwelling times.<sup>5,12</sup> Increased dwell times have also been associated with intimal hyperplasia, IVC stenosis, and an overall increased chance of complications such as failed retrievals or recurrent deep vein thrombosis.<sup>1,4,13,14</sup> Our results may also lead to future studies that examine the difficulty of filter retrieval in sedentary versus active patients.

Future studies may include large-scale animal studies comparing effects of activity on IVC and IVC filter interactions. Potential clinical studies could include retrospective analyses of patients with indwelling filters stratified based on activity versus sedentary lifestyle (i.e., chronic immobility).

Our pilot study had several limitations. First, the sample size was small, and duration of the study was short. It is plausible that only 4 weeks of exercise in two pigs was not enough to produce results that could be reproduced. In addition, the exercise protocol is difficult to standardize. The pigs in the two groups also differed in their weights. Lastly, we did not stain the histological specimen for specific markers of fibrosis, such as transforming growth factor-beta, to quantify the amount of fibrosis. Our study relied on visual inspection and impressions by a pathologist. Future studies may choose to use specific markers to better quantify fibrosis.

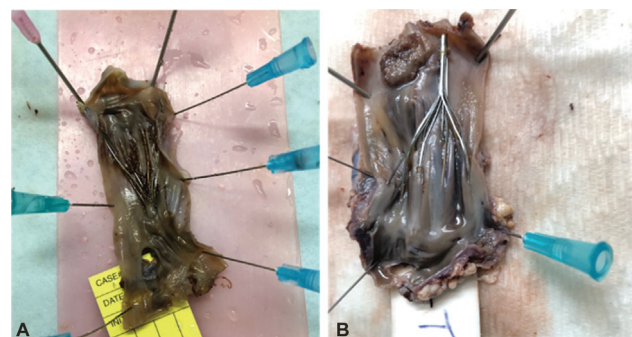
Despite these limitations, this report describes a feasible method of evaluating the effects of exercise on IVC filter interactions with the caval wall in an animal model, potentially allowing for a greater understanding of IVC filter complications in humans. Future larger-scale studies may help corroborate the results of our pilot study. Moreover, given our initial findings, human clinical studies whether retrospective or prospective may be warranted to assess the role of exercise on caval dynamics and interaction with IVC filters.

## Note

The author(s) declare(s) that they had full access to all of the data in this study and the author(s) take(s) complete responsibility for the integrity of the data and the accuracy of the data analysis. This study was approved by the International Animal Care and Use Committee (PROTO 201800124) and made possible by an internal grant provided by the Department of Radiology at our institution.

## Data Presentation

The results of this study were presented at the Society of Interventional Radiology Annual Meeting 2020.



**Fig. 2** Gross pathological examination of the excised inferior vena cava group B versus group A demonstrated increased perivascular fibrosis. (A) Group A pigs. (B) Group B pigs.

**Conflict of Interest**

None declared.

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