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Mathematical modeling of the fibrosis process in the implantation of inferior vena cava filters

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HIGHLIGHTS

- The fibrosis process of the IVC is mathematically defined using a continuum approach.
- A sensitivity study of the parameters used in the fibrosis model is performed.
- ECM turnover and endothelial denudation are determinant in the healing process.

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ABSTRACT

An inferior vena cava filter is a medical device that is implanted in the inferior vena cava and is in charge of capturing blood clots before they reach the lungs, preventing from pulmonary embolism. There are some clinical problems regarding the use of inferior vena cava filters. One of them is the difficulty when retrieving the device due to the remodeling of the vena cava. Huge effort has been made in creating computational models that reproduce tissue remodeling, but no attention has been paid to the fibrosis phenomenon occurring in the inferior vena cava. In this work, a continuum computational model that reproduces the fibrosis in the presence of an antithrombotic filter is presented. Diffusion–reaction equations are used for modeling the mass balance between species in the venous wall. The main species considered to play a key role in the process of fibrosis are smooth muscle cells, endothelial cells, matrix metalloproteinases, vascular growth factors and the extracellular matrix. The developed model has been implemented on an idealized axisymmetric geometric vena cava model. Moreover, a sensitivity analysis has been performed to study the parameters influence on the evolution of the model. Results show that the computational model is able to predict the behavior of the species considered and it captures the key characteristics of lesion growth and the healing process within a vein subjected to non-physiological mechanical forces. Our results suggests that the vessel wall response is mainly caused by the endothelium denudation area and the collagen turnover among other factors.

1. Introduction

Inferior vena cava (IVC) filters are foreign bodies against which the body reacts by trying to incorporate them into the vena cava wall, which significantly increases the difficulty of retrieval. As it has been previously observed, sometimes there is difficulty when retrieving the filter due to the apparition of fibrosis.

Several investigations have been carried out regarding the retrieval of the filter and the examination of the penetration of the filter in the IVC wall. Histological studies and laparoscopic demonstrations are the two main techniques used for these investigations. This issue was previously reported by De Gregorio et al. (2003) who observed during the removal of some IVC filters that in some cases the filter could not be retrieved due to an evident fibrotic wall reaction surrounding the anchoring hooks and any struts that had been in contact with the IVC wall. If the filter was left inside the IVC longer than 20 days, there was evidence of fibrosis with thick intimal proliferation and total filter prong involvement, which difficulted the retrieval of the filter. A laparoscopic demonstration carried out by Laborda et al. (2011) showed subintimal thickening that had embraced the filter legs. Besides, histologic examination showed that the subintimal thickening was a hyperplasia and hypertrophy of the media and adventitia layers, mainly due to proliferation of nonstriated muscle

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cells. It was also pointed out that the trayectory of the filter leg was covered with collagen formation. Proctor et al. (1998) also carried out laparoscopic examination to four sheeps with filters implanted and it was seen that some filter hooks had penetrated the muscular media of the IVC and partially or completely penetrated the adventitia. These hooks were completely encapsulated in either a fibrous capsule or a folded extension of the caval wall.

The design of medical devices could be very much improved if robust tools were available for computational simulation of tissue response to the presence of the implant (Boyle et al., 2010). The reaction to a filter by the venous tissue is a complex biological process, which is very difficult to predict from the initial stimuli described by the mechanical environment after inserting the filter. One way forward is to develop mechanobiological models that relate mechanics to biological response (i.e., injury and inflammation) in order to simulate the process over time (Boyle et al., 2011). Filter implantation causes unphysiological loading of the venous tissue, which may lead to tissue in-growth and reblockage. This phenomenon is called fibrosis.

With the emergence of tissue engineering as a promising technique in regenerative medicine, there is a genuine need for robust mechanobiological models for the analysis of tissue response (Zahedmanesh and Lally, 2012). The huge complexity of biomechanical systems has motivated tremendous efforts towards developing novel computational models for predictive purposes and also to provide a better understanding about these systems. Mechanics play a key role in regulating this adaptation. Mechanobiological models are required to capture the long-term behaviour of the system, and if such models can be successfully corroborated, it opens one way to improve the design of medical devices.

The healing response after arterial injury has been well characterized in various animal models (Grines et al., 1993; McBride et al., 1988; Pepine et al., 1990). Atherosclerosis and hypertension are two of the most popular subjects on mechanobiologic modeling, but in-stent restenosis has recently been also a common subject of interest (Boyle et al., 2011; Zahedmanesh and Lally, 2012).

To our knowledge, the phenomenon of fibrosis has escaped the attention of researchers. The creation of a mechanobiological model related to the use of IVC could help in understanding the long-term effects of perturbing the mechanical environment of the inferior vena cava and could aid in the creation of new solutions to avoid this problem in the future.

In short, we present a mechanobiological model which deals with the apparition of fibrosis in the inferior vena cava. The biological processes that lead to fibrosis have been mathematically defined and the constants which define the biological interaction between the different species have been obtained from experimental studies from the literature. Furthermore, a sensitivity study of the constants defined has been performed to take into account for their variability and dispersion.

2. Hypothesis of the model

Fibrosis of the IVC is, basically, a process in which there is a creation of new tissue surrounding the filter struts as a consequence of the damage on the wall. The damage is caused by the penetration of the filter struts to the media and adventitia layers.

The process begins immediately after the initial injury and may last for weeks or months. This growth response that leads to the development of a neointimal thickening, also known as neointimal hyperplasia. Neointima formation in response to injury can be simplified into five distinct phases and can be seen in Fig. 1:

1. Quiescent or contractile smooth muscle cells (SMCs) and endothelial cells (ECs) populate the vena. If the tissue is uninjured SMCs remain in a contractile phenotype.
2. Filter hook insertion induces the inflammation through injury/damage. During the expansion of the filter, high stresses induced by the filter cause injury to the vein, which leads to a cascade of inflammatory events.
3. Vessel injury leads to the activation of SMCs, which are in the contractile phenotype, to a synthetic phenotype. The ECs surrounding the damage area die and the extracellular matrix (ECM) is disrupted/degraded. In addition, there is a significant adventitial angiogenesis.
4. This change of phenotype is followed by migration and proliferation of synthetic SMCs towards the intima, which respond to growth factors and secrete ECM, leading to neointimal tissue formation.
5. The disruption of cell contact inhibitors results in rapid EC replication from the untraumatized segments. ECs migrate and proliferate re-establishing a layer of new endothelial cells surrounding the damage. Provided the source of injurious factors recedes, and the lumen does not occlude, the cells in the lesion can resort back to contractile and the lumen area equilibrates.

The steps followed for the considered process of fibrosis are summarized in Fig. 2.

Three cell types (cSMCs, sSMCs and ECS) and three extracellular components (Extracellular matrix (ECM), matrix metalloproteinases (MMP) and vascular growth factor (VGF)) were considered for the model. Cell types relevant to most mechanobiological models have a limited set of behaviours: proliferation, migration, differentiation, absorption/expression of chemicals and apoptosis, while substances belonging to the vessel wall can be produced or degraded.

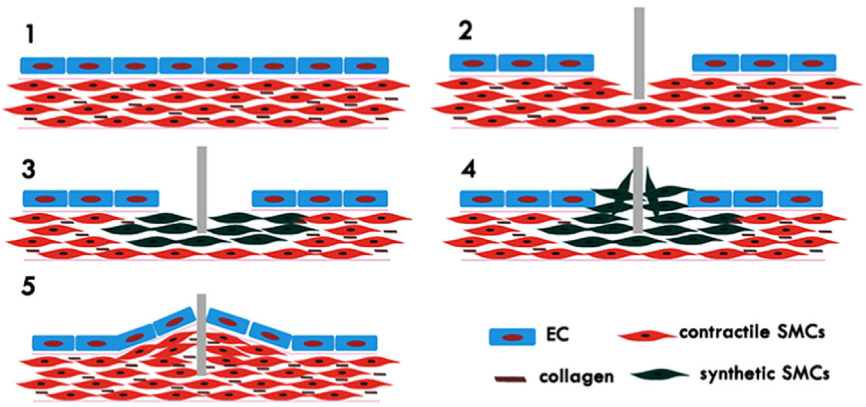

Fig. 1. Development of fibrosis following filter deployment (Adapted from Zahedmanesh et al. (2014)).