Journal of Theoretical Biology 429 (2017) 149–163

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/jtbi

Vascular Adaptation: Pattern Formation and Cross Validation between an Agent Based Model and a Dynamical System

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ARTICLE INFO

Article history:
Received 3 October 2016
Revised 9 May 2017
Accepted 12 June 2017
Available online 21 June 2017

Keywords:
Restenosis
Adaptation
Vein Graft
Model
Cross Validation
Pattern Formation

ABSTRACT

Myocardial infarction is the global leading cause of mortality (Go et al., 2014). Coronary artery occlusion is its main etiology and it is commonly treated by Coronary Artery Bypass Graft (CABG) surgery (Wilson et al, 2007). The long-term outcome remains unsatisfactory (Benedetto, 2016) as the graft faces the phenomenon of restenosis during the post-surgery, which consists of re-occlusion of the lumen and usually requires secondary intervention even within one year after the initial surgery (Harskamp, 2013).

In this work, we propose an extensive study of the restenosis phenomenon by implementing two mathematical models previously developed by our group: a heuristic Dynamical System (DS) (Garbey and Berceli, 2013), and a stochastic Agent Based Model (ABM) (Garbey et al., 2015).

With an extensive use of the ABM, we retrieved the pattern formations of the cellular events that mainly lead the restenosis, especially focusing on mitosis in intima, caused by alteration in shear stress, and mitosis in media, fostered by alteration in wall tension. A deep understanding of the elements at the base of the restenosis is indeed crucial in order to improve the final outcome of vein graft bypass.

We also turned the ABM closer to the physiological reality by abating its original assumption of circumferential symmetry. This allowed us to finely replicate the trigger event of the restenosis, i.e. the loss of the endothelium in the early stage of the post-surgical follow up (Roubos et al., 1995) and to simulate the encroachment of the lumen in a fashion aligned with histological evidences (Owens et al., 2015).

Finally, we cross-validated the two models by creating an accurate matching procedure. In this way we added the degree of accuracy given by the ABM to a simplified model (DS) that can serve as powerful predictive tool for the clinic.

1. Introduction

Cardiovascular disease is the leading global cause of mortality and morbidity (Roger et al., 2012; Go et al., 2014), accounting for more than 17.3 million deaths per year that represents the 31% of all global deaths (American Heart Association 2016). In 2013, nearly 801,000 people died in US from heart disease, stroke, or other heart related diseases (American Heart Association 2016). The direct and indirect costs of cardiovascular diseases and stroke total more than $316.6 billion (American Heart Association 2016).

Coronary occlusion is the most common type of heart disease (Centers for Disease Control and Prevention, 2015), and it prevents the blood from bringing nourishment to a portion of the myocardium, causing the heart attack (Reddy et al., 2015).

Coronary Artery Bypass Graft (CABG) surgery using an autologous vein graft (typically saphenous) is the most performed procedure in order to bypass the occlusion and to restore the physiological circulation (Alexander, 2005; Wilson et al., 2007).

Despite improvements in surgical techniques, the medium and long term efficacy of the procedure is far from being satisfying (Benedetto, 2016), also considering that between 3% and 12% of saphenous grafts occlude within 1 month of surgery (Joseph, 1998), a percentage that increases to 10–15% on a follow-up time of 1 year (Harskamp, 2013).

The occlusion of the vein graft is due to a series of adaptation (or arterialization) events that takes place in the post-surgical period. The variation of hemodynamic conditions, from venous to arterial flow, plays a key role in the arterialization of the graft (de Vries MR, 2016) as the exposure to the high pressure/high flow

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http://dx.doi.org/10.1016/j.jtbi.2017.06.013
0022-5193/

arterial circulation initiates two simultaneous processes: intimal hyperplasia and outward remodeling (Owens et al., 2015; Owens (2010); Lytle et al., 1985).

Intimal hyperplasia is the universal response of a vessel to injury, for which a reduction of shear stress stimulates specific grow factors to switch their status from quiescent to active. Their activation causes a highlighted division of Smooth Muscle Cells (SMC) in the intimal layer, with subsequent synthesis of ExtraCellular Matrix (ECM). These two events combined lead the tunica intima to thicken and to narrow the lumen, and even though a moderate intimal hyperplasia formation is necessary for proper arterialization and long-term graft patency (Wallner et al., 1999; Zhang et al., 2004; Zwolak et al., 1987), the patency rates of vein grafts diminish immediately after surgery from 98% to 88% within the first month post-surgery owing to acute thrombosis (De Vries, 2016).

In contrast, outward remodeling is characterized by preservation or loss of the lumen area through reorganization of the cellular and extracellular components in the media (Garbey and Berceli, 2013).

Finally, the balance between intimal hyperplasia and outward remodeling determines the success or the failure of the bypass procedure (Garbey and Berceli, 2013; Garbey et al., 2015; Roddy et al., 2003; Szilagyi et al., 1973).

In the present work we extensively used two mathematical models that replicate the phenomenon of restenosis and predict the graft adaptation outcome: a Dynamical System (DS) (Garbey and Berceli, 2013) and an Agent Based Model (ABM) (Garbey et al., 2015). Furthermore, a primary goal was to prove how we were able to replicate experimental evidences that are commonly accepted by the scientific community, such as the fact that a drastic decrease in shear stress favors an uncontrolled proliferation of cells within the tunica intima and that an increase in wall tension is responsible for the augmented proliferation of cells within tunica media (Garbey and Berceli, 2013; Garbey et al., 2015; Roddy et al., 2003; Szilagyi et al., 1973).

There are several advantages of having a tool able to replicate the main events that impact the final outcome of the procedure: i) to better understand the key events of restenosis; ii) to test in advance clinical hypotheses; iii) to anticipate the outcome of targeted therapies aimed to improve the durability of the graft.

The DS is a heuristic model and it was derived fundamentally from a conceptual diagram based on experimental observations, while the ABM is a stochastic model that starts from a bottom-up approach and implements biological knowledge at the level of the cells by using a cellular automaton principle.

Cellular automata are used as mathematical models in order to investigate the self-organization of mechanical systems (Wolfram S, 1983). A cellular automaton consists in a regular grid of cells, each of them in a specific state and each of them evolving according to defined rules (Deutsch and Dormann, 2005). The behavior of each cell is influenced by the particular states of its surrounding neighbors.

In this work, our goal was to:

1. Replicate the clinical evidences with the ABM (Fig. 1), and retrieve the pattern formations related to intimal hyperplasia and outward remodeling.
2. Define a matching procedure between the two models. This has a strong clinical interest. The DS can serve as a fast and user friendly predictive tool for the graft outcome, while the ABM is closer to the physiological realty, but it demands a high computational time and its setup is not simple. It is also easier to obtain patient specific data to set the DS than the ABM, which requires extensive biologic laboratory data.
3. Post cross-validation, verify that ABM and DS may lead to the same conclusions.
4. Distinguish and discuss where the ABM can bring understandings that are not retrievable from the DS.

2. Overview

2.1. Anatomy of a vein graft

Fig. 2 shows the anatomy of a vein graft at the time of implantation.

As described by Garbey and Berceli (2013), a graft suitable for implantation is composed of a thin intimal layer, and a thick medial layer. The first serves as blood-tissue interface, while the second provides structural support for the wall. The intimal layer is separated from the medial layer by a sheet of connective tissue, called Internal Elastic Lamina (IEL). A similar sheet separates the media from the external surface, the External Elastic Lamina (EEL).

2.2. Dynamical system (DS)

Fig. 3 shows the conceptual diagram the DS lays on. The aim of the model is to study the temporal dynamic of radius and thickness of the two innermost layers of the graft: the tunica intima and tunica media.

Graft plasticity is described as a function of local biological mechanism and of the dynamic of SMCs and the driven mechanical stimuli are wall shear stress and intramural wall tension. Each of them promotes or prevents specific cellular activities and more in detail shear forces impact events occurring in the intimal layer, while tensile forces impact events within the medial layer.

The geometrical model used to describe the vein is a straight, thick, and circumferential symmetric cylinder with internal radius $R_1$and external radius R_2, and internal pressure P_1 and external pressure P_2.

The mechanical parameters, being τ_{wall} the shear stress at the wall and σ_{wall} the wall tension, are defined according to the geometrical model chosen.

The wall shear stress is given by the formula:

$$\tau_{wall} = \mu \frac{2U}{R_1} \tag{1}$$

U is the maximum velocity of the blood (recorded at the centerline), and μ is the dynamic viscosity of blood.

The wall tension is given by the formula:

$$\sigma_{wall}(r) = \sqrt{\sigma_r(r)^2 + \sigma_\theta(\theta)^2} \tag{2}$$

$\sigma_r(r)$ is the radial tension (Kleinstreurer, 2006), where

$$\sigma_r(r) = \frac{P_1 R_1^2}{R_2^2 - R_1^2}\left(1 - \frac{R_2^2}{R^2}\right) - \frac{P_2 R_2^2}{R_2^2 - R_1^2}\left(1 - \frac{R_1^2}{R^2}\right) \tag{3}$$

and $\sigma_\theta(r)$ is the circumferential tension (or hoop stress) (Kleinstreurer, 2006), where

$$\sigma_\theta(r) = \frac{P_1 R_1^2}{R_2^2 - R_1^2}\left(1 + \frac{R_2^2}{R^2}\right) - \frac{P_2 R_2^2}{R_2^2 - R_1^2}\left(1 + \frac{R_1^2}{R^2}\right) \tag{4}$$

For simplicity, we will abandon the subscript notation τ_{wall} and σ_{wall} in favor of τ and σ.

The dynamic of the cellular events, fully described in our previous publication (Garbey and Berceli, 2013), directly impacts the radius and thickness of each compartment and is provided by the following expressions

$$\begin{cases} \dot{A}^I_{SMC} = -\gamma_1 \Delta\tau^- A^I_{SMC} \\ \dot{A}^I_{ECM} = -\gamma_2 \Delta\tau^- A^I_{SMC},\ if\ A^I_{ECM} > 0,\ \ and\ 0\ \ otherwise \\ \dot{A}^M_{ECM} = \gamma_3 \Delta\sigma A^M_{SMC},\ if\ A^M_{ECM} > 0,\ and\ 0\ otherwise \\ \dot{A}^M_{SMC} = \gamma_4\ \Delta\sigma A^M_{SMC} \\ \dot{R}_{ext} = \gamma_5\ \Delta\tau + \gamma_6\ \Delta\sigma \end{cases} \tag{5}$$