On the possible interaction mechanism between collateral vessels and restenosis

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Abstract

Several clinical studies and their meta-analysis suggest that developed collateral vessels in the heart correlate to an increased risk of in-stent restenosis. The possible physiological interaction between the collateral development and in-stent restenosis is investigated in this study. Based on existing publications, a hypothesis is suggested that the increased risk of in-stent restenosis is caused by a decrease in flow speed in the stented area, which lowers the wall shear stress there and causes a more severe tissue growth. For testing this hypothesis, an analytical model based on the hydro-electrical analogy is used. From this model, flow through the ischemic region is obtained for varying severity of stenosis and collateral flow indexes. The results suggest that even rather low collateral flow index has a considerable effect on the flow through restenosed artery for physiologically significant stenosis. This change in flow can indeed affect the wall shear stress and change the growth dynamics, so it might be necessary to account for it in models of in-stent restenosis.

Keywords: coronary arteries, in-stent restenosis, collateral circulation, wall shear stress.

1 Introduction

Cardiovascular disease and heart failure are the leading causes of death in industrialized countries [1]. In time, they might become the most widespread reasons for mortality worldwide. One particularly important type of cardiovascular disease is coronary artery disease. Restricted blood flow through the coronary usually happens because of stenosis, or abnormal narrowing of coronary arteries. One of the ways to correct a stenosis is balloon angioplasty with stent deployment. A stent injures artery walls that can lead to a maladaptive biological response in form of excessive vascular tissue growth into the lumen. The abnormal growth can produce a new stenosis (re-stenosis) [2,3]. Studying the dynamics of restenosis should lead to a better understanding of this pathology and the basic physiological processes involved.

Since restenosis is a relatively common complication, quite a lot of clinical studies of this process have been performed, for example [4,5]. The dynamics of restenosis have also been studied to some extent via in vivo experiments [6]. Yet another approach to studying restenosis is modelling it computationally. One example of this approach is the multiscale 3D in-stent restenosis (ISR) model [2].

A notable aspect of a chronic vascular disease is that it can cause development of collateral vessels which bypass the stenosis [7]. These vessels are associated with an increased risk ratio of developing a restenosis. This paper investigates the possible mechanical link between restenosis and collateral development.

2   Related works

Numerous studies concerning the growth of collateral vessels exist, which explore gradual or sudden arterial occlusions. Some of them feature dedicated in vivo experiments, and some study the circulation in patients undergoing percutaneous transluminal coronary angioplasty (PTCA). Many of these studies focus specifically on the circulation in a swine heart and find that noticeable collaterals develop if an artery is constricted or occluded [8–12], although some of them, like [11], probably overestimate the amount of collaterals (see the discussion section of [12] for further analysis). However, it seems that a typical degree of restenosis is insufficient to induce physiologically relevant collateral circulation by itself. At least, it seems to be that way in pigs, who have naturally very few collaterals and those that exist are very small [13]. Strong collateral circulation only develops if a severe (>80%) occlusion is present, and those almost never develop via restenosis in pigs [14–16].

Some studies [7,17,18] link high pre-PTCA collateral circulation with an increased risk of restenosis. Meier et al. in particular published a meta-analysis of several previous papers on this matter, reviewing seven studies, enrolling in total 1425 patients, and their study showed that patients with good collateralization showed a significantly higher chance of restenosis. While it is possible that the collaterals are simply a marker of a more severe coronary artery disease, Meier et al. mentioned a potential mechanism of interaction: similarly to a coronary artery bypass surgery (CABG), collaterals create a competing flow, which decreases shear stress in the stenosed vessel, which, in their opinion, increases the chance of cell adhesion to the vessel walls and modulates endothelial gene expression into a pro-inflammatory state. They also mention that high shear stress has an anti-inflammatory effect and reduces monocyte attraction. However, they do not mention the smooth muscle cell growth, which is considered to be a key factor in the process of restenosis or the fact that high shear stress suppresses this growth [2,3,14,19–21].

The collaterals remain partially active after recanalization [5,17,22–24] and can be further recruited as the resistance in the stented vessel grows [17,22]. Also, many patients who undergo PTCA have severe occlusions before stent implantation, up to and including total coronary occlusions (TCO). Those patients often develop significant collateral circulation to compensate for the increased resistance in the stenosed artery[4,17,22,23,25–27]. In this way, the collaterals can supply blood to the area distal to the stent. We know that the collateral resistance increases sharply during the minutes and hours right after PTCA [23,24], but the increase in the following days becomes much slower [25].

Based on the studies described here, one can come to the following conclusions. First, the collateral flow is statistically linked with the incidence of restenosis [7]. Well-developed collaterals can also supply a significant amount of blood to the ischemic tissue in humans [4,23,25,26], and even in pigs with their less-developed collateral circulation they can, given enough time to grow, supply enough blood in the resting state even if the artery is completely occluded [10–12]. As the restenosis develops and its resistance increases, more and more blood would go through the collaterals, decreasing the wall shear stress in the stent and forming a sort of a positive feedback loop (if the collateral resistance doesn't go up as well in the weeks following the PTCA). It is possible that even if

right after recanalization there is no competing flow through the collaterals, it can arise as the tissue grows around the stent and its resistance becomes hemodynamically significant. In this case, the competing flow might dampen the wall shear stress and push the growth over 50% area into a clinically recognised restenosis territory.

Even when the artery is recanalized, in some cases enough collaterals stay open to facilitate a significant flow in case of a brief reocclusion [4,5,17,22–26,28]. It is hypothesized that in some cases, there would be a notable competing flow through these collaterals even in absence of reocclusion [7].

If this is the case, the flow through the stenosis and the wall shear stress inside it would decrease, which, according to our ISR model [2,14,21], would allow the smooth muscle cells in the stented walls to proliferate further, leading to a restenosis [3,14,20,21]. Other possible mechanisms of restenosis mention for instance monocyte adhesion, but the general consensus is that lower shear stress leads to a stronger restenosis [29]. In turn, a more severe restenosis would cause more blood to go through the collaterals instead of the stenosed vessel, causing further collateral growth.
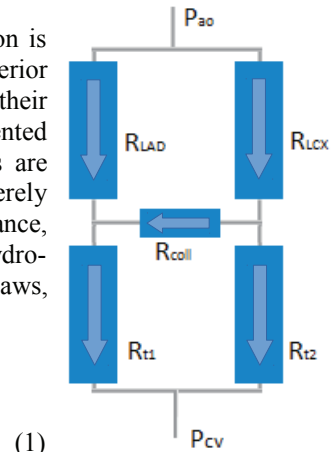
To sum this up, a possible cause and effect interaction of collaterals and restenosis can be proposed: increased collateral flow slows down the increase of the wall shear stress in the restenosis area, meaning that even in the presence of functional endothelium it takes more time and a more narrow vessel until nitric oxide is produced and stops smooth muscle cell proliferation, resulting in a more severe restenosis. To see if this increase in flow is big enough for a difference in collateral flow index (CFI) to affect the restenosis, an analytical estimation is performed.

3   Analytical estimation

In this section a proof-of-concept analytical estimation of the relation between the collateral development and the flow through the stenosed region is presented. This estimation is based on the hydraulic resistance model of blood vessels. Flow pulsatility and vessel compliances are ignored for simplicity's sake.

For this estimation, the following model of left ventricle perfusion is used: the ventricle is perfused via two major coronary arteries (left anterior descending artery, LAD and left circumflex artery, LCX) and their corresponding capillary beds. Each of these four elements is represented by a hydraulic resistance, and the resistances of the capillary beds are much greater than the arterial resistances, unless the artery is severely occluded. A collateral network, represented by a single resistance, connects the distal parts of LAD and LCX (fig. 1). By using the hydro-electrical analogy and writing out the analogue of Kirchhoff's circuit laws, we can come to the following system of equations:

Figure 1: Coronary network used for the estimation. Arrows show positive flow directions (eq. 1)

$$
\begin{aligned}
Q_{LAD} + Q_{coll} &= Q_{t1} \\
Q_{LCX} - Q_{coll} &= Q_{t2} \\
R_{LAD} \cdot Q_{LAD} - R_{coll} \cdot Q_{coll} - R_{LCX} \cdot Q_{LCX} &= 0 \\
R_{LCX} \cdot Q_{LCX} + R_{t2} \cdot Q_{t2} &= P_{ao} - P_{cv} \\
R_{LAD} \cdot Q_{LAD} + R_{t1} \cdot Q_{t1} &= P_{ao} - P_{cv}
\end{aligned}
\tag{1}
$$

Here P_{ao} denotes the aortic pressure, and P_{cv} denotes central venous pressure. Q and R are, respectively, flows and resistances of the corresponding parts of the vasculature (see figure 1 for reference).

If we solve the system (1) for the general case, we will find that the flow Q_{t2} through R_{t2} equals

$$Q_{t2}=\frac{(P_{ao}-P_{cv})\cdot(R_{coll}\cdot R_{t1}+R_{coll}\cdot R_{LAD}+R_{t1}\cdot R_{LAD}+R_{t1}\cdot R_{LCX})}{R_{coll}\cdot R_{t1}\cdot R_{t2}+R_{coll}\cdot R_{LAD}\cdot R_{t2}+R_{coll}\cdot R_{t1}\cdot R_{LCX}+R_{LAD}\cdot R_{t1}\cdot R_{t2}+R_{LCX}\cdot R_{t1}\cdot R_{t2}+R_{coll}\cdot R_{LAD}\cdot R_{LCX}+R_{t1}\cdot R_{LAD}\cdot R_{LCX}+R_{t2}\cdot R_{LAD}\cdot R_{LCX}} \quad (2)$$

This can be somewhat simplified if we make some assumptions about the resistances in question. First, in many cases LAD and LCX perfuse roughly equally sized areas [30]. For this scenario, we can assume that the terminal resistances are similar, $R_{t1} = R_{t2} = R_t$. Furthermore, there exists a relation between the collateral resistance and terminal resistance, which is measured clinically via pressure-based collateral flow index (*pCFI*) [5]:

$$pCFI=\frac{P_d-P_{cv}}{P_{ao}-P_{cv}}, \quad (3)$$

where P_d is the pressure at the distal end of the examined vessel.

For measuring pCFI, the affected artery is occluded, so the blood is only supplied through collateral network from another artery. Hence, *pCFI* can be viewed as a proportion of total and distal resistances,

$$pCFI=\frac{R_t}{R_{prox}+R_{coll}+R_t}, \quad (4)$$

where R_{prox} is the total resistance of the proximal part of the vasculature. In this model it is equal to the resistance of the supplying artery.

If the supplying artery is healthy, its resistance R_{prox} is much smaller than either of the collateral and terminal resistances. In this case,

$$R_{coll}=R_t\cdot\frac{1-pCFI}{pCFI}=a\cdot R_t. \quad (5)$$

With these substitutions, the formula (2) becomes

$$Q_{t2}=\frac{(P_{ao}-P_{cv})\cdot(R_{LCX}+a\cdot R_t+(1+a)\cdot R_{LAD})}{a\cdot R_t^2+(2+a)R_{LAD}\cdot R_{LCX}+(1+a)\cdot R_t\cdot R_{LAD}+(1+a)\cdot R_t\cdot R_{LCX}} \quad (6)$$

A stenosis in LCX would mean an increase in R_{LCX}. The severity of stenosis is measured by the fractional flow reserve index (*FFR*) [31], which is somewhat similar to *pCFI*. It is defined as the ratio of pressures distal and proximal to the vessel, in this case,

$$FFR=\frac{P_{dist}-P_{cv}}{P_{ao}-P_{cv}} \quad (7)$$

Physiologically relevant stenosis begins at *FFR* = 0.75.

For further numerical estimation of the effect of collateral resistance on flow, the following numerical values are used, based on the values from [30,32,33]. Each artery is assumed to perfuse 100 g of heart tissue, or roughly one third of the heart:

$$P_{ao}-P_{cv}=95\,mmHg$$

$$R_t=55\,\frac{mmHg\cdot s}{ml}$$

$$R_{LAD}=0.2\,\frac{mmHg\cdot s}{ml}$$

Using these values, Q_{t2} (flow through the terminals connected to the LCX) was calculated for various degrees of LCX stenosis (represented by an increase in R_{LAD}, starting from the minimal value of 0.2 mmHg·s/ml and up to 100 mmHg·s/ml. This calculation was performed for four different grades of collateral development: *pCFI* = 0.1 (undeveloped collaterals), *pCFI* = 0.5 (considered sufficient to prevent acute ischemia [34]), *pCFI* = 0.67 (very developed collaterals [25]) and *pCFI* = 0.9 (unphysiologically low resistance, useful as a borderline case).

The plot for these values is represented in figure 2. It shows that these values correspond to a slightly dilated state, resulting in blood flow slightly higher than the resting value of 50-60 ml/min per 100 g of tissue for all but the most severe cases, but much lower than the maximal value of 200-250 ml/min per 100 g.

The plot based on this analytical estimation shows that the difference in *CFI* can greatly affect the outcome of a stenosis perfusion-wise and it can even mean the difference between the tissue that gets enough blood for normal function and ischemic tissue that suffers damage because of the lack of oxygen.

Furthermore, the degree of collateral development affects the flow through the stenosed vessel as well (figure 3). The difference in flow through LCX can be as high as two times for the more severe cases with R_{LCX} = 80-100 mmHg·s/ml and *FFR* = 0.3-0.4. This difference in flow can affect the wall shear stress in the stenosed region, creating a positive feedback loop and causing further growth of the stenosis, which in turn diverts more flow to the collaterals and delays the wall shear stress-provoked cessation of smooth muscle cell growth.

Of course, this very simple model can't hope to capture the true numerical relation between the

Figure 2: Flow through the terminal vessels connected to the LCX for various degrees of LCX stenosis and for different grades of collateral development.

Figure 3: Flow through the LCX for various degrees of LCX stenosis and for different grades of collateral development.

development of collaterals and the risk of developing a physiologically relevant stenosis after PCI. Rather, it shows that the relation is there and is most likely rather significant.

4 Discussion

This proof-of-concept analytical model makes quite a few simplifications. For starters, it uses a greatly reduced arterial topology. Also, it completely ignores the pulsatility of arterial flow, vessel compliance, wave reflection and other more specific features of coronary flow, such as the intramyocardial pump action, caused by the contraction of the myocardium during each systole.

Nevertheless, this analysis produced some rather interesting results and confirmed the possibility of a noticeable effect of collaterals on the flow in the restenosed artery. Right after recanalization, if it completely restores the flow through the affected artery, the flow through even the most well-
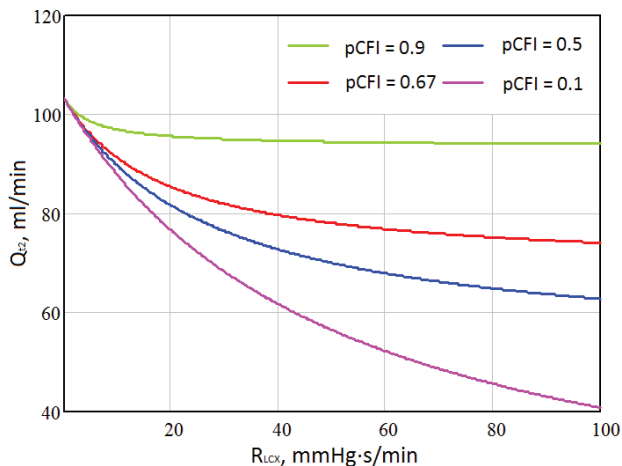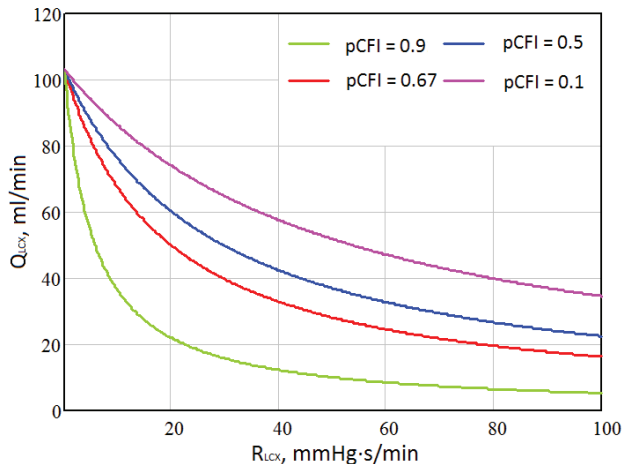
developed collaterals would be negligible. However, when the restenosis reaches higher values, a significant amount of blood supply to the potentially ischemic area is rerouted through the collateral vessels. This serves to support the hypothesis that competing flow through the collaterals causes decreased wall shear stress in the restenosis, compared to the no-collaterals case, and this decreased shear stress causes a more pronounced restenosis. It has to be noted that Meier et al. [7] suggest inflammation and monocyte adhesion as reasons of restenosis, while the ISR model by Caiazzo et al. [2] is based on SMC proliferation regulated by functioning endothelium, but the key meaning of the wall shear stress remains a common aspect.

5   Conclusions

Even the most well-developed collaterals give negligible flow immediately after a complete recanalization. As the restenosis develops, pre-existing collaterals can be recruited and decrease the flow through the lesion. For high stenosis resistances, flow decrease compared to the case with undeveloped collaterals is noticeable even for relatively low values of CFI.

It seems that for human patients the variability of the flow through the in-stent restenosis site is important, even though not all patients have a well-developed collateral network. However, this model cannot provide reliable quantitative results. For more conclusive results a more detailed model study, using a computational model of coronary network, and a comparison to clinical results are required. Potentially, with a better model and a successful validation, it might be possible to use it to account for the effect of collaterals on long-term outcomes of clinical interventions.

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