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Increase of coronary microvascular resistances after recanalization with Drug Eluting Stent

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1. Introduction

Drug eluting coronary stents (DES) have been demonstrated in the literature to decrease restenosis rate compared to bare-metal stents (BMS). However, the anti-proliferative drugs released by DES may facilitate distal microcirculatory dysfunction, thereby negatively affecting collateral microvessels. Considering the protective effect of well-grown collaterals, in the event of stent thrombosis, impaired collateral function could render the thrombosis much more dangerous (Meier et al., 2007; Togni et al., 2005). Besides, the results of the SYNTAX study indicate that, in patients with complex coronary disease, the need to redo the revascularization is higher when patients have been first treated with DES, as compared to patients who initially undergo coronary artery bypass surgery (CABG) (Kappetein et al., 2011).

In this paper, we present the case of a patient (P) affected by three-vessel coronary disease, previous DES implantation and in-stent restenosis. Using a simulating tool previously developed by our group, we are able for the first time to quantify the impact of the DES eluted drugs on the coronary hydrodynamic parameters of this patient. We compare his results with those obtained for a panel of 10 patients (with three vessel disease, but no stent history) published in Maasrani et al. (2011).

2. Methods

2.1. Case description

A 65 years old man with no history of myocardial infarction was referred for three-vessel disease. Five years before, he had been treated by percutaneous coronary revascularization (PCI) with deployment of DES within the midportion of the left anterior descending artery (LAD) and within the first obtuse marginal branch of the left circumflex artery (LCx). In mid-2012, the patient developed effort chest pain. Coronary angiography evidenced chronic total occlusion of the first segment of the right coronary artery (RCA), and severe intra-stent restenosis at the level of the left marginal branch, and critical stenosis of the first segment of the LAD. Indication to CABG was posed and use of the off-pump technique was planned.

2.2 Clinical measurements

Details about the surgical protocol and the per-operative clinical measurements can be found in Maasrani et al. (2011), and are briefly recalled here. A great saphenous vein graft (SVG) was anastomosed to the right coronary artery, and the pressure distal to the occlusion (P_w) as well as the central venous (P_v) and aortic pressures (P_{ao}) were measured (0G timepoint). After construction of the proximal anastomosis, and with the graft functioning, the flow within the graft (Q_{RCAg}), as well as both P_v and P_{ao} were measured (1G timepoint). Subsequently, the LAD and LCx branches were revascularized using the two internal mammary arteries. The flow within each mammary graft (Q_{LADg} and Q_{LCxg}) was then measured, with the SVG clamped (2G timepoint), as well as P_{ao} , P_v , and P_w . The 3G timepoint corresponds to the measurements when the three grafts are functioning: P_{ao} , P_v , Q_{LADg} , Q_{LCxg} , and Q_{RCAg} .

2.3 Simulating tool

Data were then entered into an analog electrical model of the coronary circulation (Fig.1) aimed at reproducing these clinical situations (Maasrani et al., 2011). In this model, the small diameter vessels like capillaries and collateral vessels are represented only by their resistance: R_{LADc} , R_{LCxc} , R_{RCAc} , and R_{col} (same R_{col} in all the collateral pathways). They are determined in a patient's specific manner. The input of the model is the aortic pressure wave, $P_{ao}(t)$. The Matlab (Simulink) simulations allow to predict flow and pressures in any branch of the model and for all surgical cases (0G, 1G, 2G, 3G). The calculated quantities are time-dependent, but we focus on average cardiac cycle values. The collected clinical data are also average cardiac cycle values.

3. Results and Discussion

The values of the capillary and collateral resistances (in mmHg.s/ml) obtained for Patient P are $R_{LADc} = 241$, $R_{LCxc} = 808$, $R_{RCAc} = 213$, and $R_{col} = 2980$. They can be compared to the mean values obtained for the group of 10 patients studied in Maasrani et al. (2011): $R_{LADc} = 159 \pm 97$, $R_{LCxc} = 125 \pm 60$, $R_{RCAc} = 125 \pm 88$, and $R_{col} = 521 \pm 282$. All the microvascular resistances of Patient P are higher than those of other patients, and especially

its R_{LCxc} and R_{col} are dramatically high. This indicates deterioration of the collateral pathways and of the microcirculatory coronary beds distal to the DES. This observation is confirmed by the analysis of the measured and simulated flow rates and pressures (Table1). The data of the case (1G) are not shown, but they lead to the same conclusions as do the results obtained in the other cases. It appears from the data of Table1 that all the flow rates calculated for Patient P are quite lower than those obtained for other patients presenting the same pathology. This may be related to the high values of the distal capillary resistances obtained for Patient P. This is especially noticeable for Q_{LCxg} and Q_{LCx} . It also appears that Patient P has no more collateral protection ($Q_{col, i=1 \text{ to } 5} < 1 \text{ ml/min}$, in any cases). This is related to the very high collateral resistances, and is consistent with the finding of low P_w values in the (0G) and (2G) cases. Moreover, even after complete revascularization (case (3G)), the total coronary perfusion, Q_t ($Q_t = Q_{LAD} + Q_{LCx} + Q_{RCA}$), remains remarkably low.

4. Conclusions

The loss of collaterality and the increase in microvascular resistances following DES implantation expose the patient to a higher risk of future ischemic events. These findings unveil a complex interplay between mechanical and biological factors underlying the clinical observations from major clinical trials.

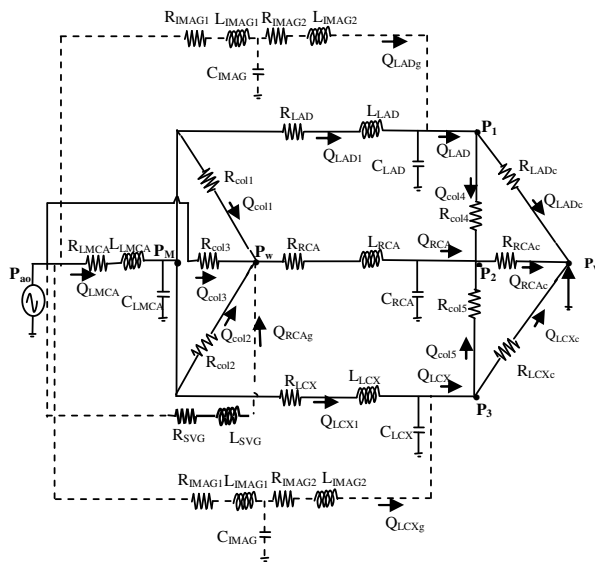


Figure 1 Analog electrical model for the coronary circulation in patients with severe stenoses on LMCA, LAD and LCx, and total occlusion of the right artery. The dotted lines represent the grafts.

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| | (0G) | (2G) | (3G) |
|----------------|----------------------------|----------------------------|----------------------------|
| P_{ao} , m | 64 <i>75.3 ± 8.0</i> | 71 <i>70.3 ± 10.8</i> | 71 <i>72.2 ± 10.1</i> |
| P_w , m | 22 <i>41.4 ± 7.5</i> | 23 <i>39.7 ± 6.6</i> | NA |
| P_v , m | 10 <i>8.2 ± 3.5</i> | 6 <i>8.3 ± 4.7</i> | 7 <i>8.1 ± 4.5</i> |
| Q_{LADg} , m | NA | 18 <i>28.3 ± 13.1</i> | 14 <i>26.6 ± 13.0</i> |
| Q_{LCxg} , m | NA | 4 <i>34.1 ± 18.4</i> | 4 <i>27.6 ± 13.4</i> |
| Q_{RCAg} , m | NA | NA | 18 <i>43.6 ± 22.8</i> |
| Q_{LAD} , s | 11.1 <i>28.4 ± 24.1</i> | 16.7 <i>37.4 ± 24.1</i> | 15.5 <i>33.6 ± 23.0</i> |
| Q_{LCx} , s | 4.6 <i>31.3 ± 23.5</i> | 5.7 <i>41.3 ± 23.0</i> | 4.7 <i>39.7 ± 28.8</i> |
| Q_{RCA} , s | 2.5 <i>15.6 ± 9.6</i> | 2.9 <i>12.8 ± 6.6</i> | 18.0 <i>44.6 ± 23.2</i> |
| Q_{RCAc} , s | 3.8 <i>19.3 ± 10.3</i> | 4.8 <i>20.5 ± 10.3</i> | 18.0 <i>43.6 ± 22.8</i> |
| Q_{col1} , s | 0.8 <i>5.0 ± 3.2</i> | 1.0 <i>4.2 ± 2.2</i> | 0.0 <i>-0.1 ± 0.2</i> |
| Q_{col3} , s | 0.8 <i>5.6 ± 3.3</i> | 1.0 <i>4.4 ± 2.2</i> | 0.0 <i>0.1 ± 0.1</i> |
| Q_{col4} , s | 0.6 <i>1.7 ± 3.6</i> | 0.9 <i>3.9 ± 1.9</i> | 0.0 <i>-0.4 ± 0.4</i> |
| Q_{col5} , s | 0.8 <i>2.0 ± 2.1</i> | 1.0 <i>3.9 ± 1.8</i> | 0.0 <i>-0.4 ± 0.4</i> |

Table 1 Measured (m) and simulated (s) data for Patient P. In italic are given the corresponding values for the group of 10 patients published in Maasrani et al. (2011). Pressures are given in mmHg, flow rates in ml/min. Q_{LAD} , Q_{LCx} , and Q_{RCA} are the flow rates in the LAD, LCx and RCA branches, as shown in Fig.1. Q_{col2} is not shown because $Q_{col2} = Q_{col1}$. NA = not applicable.