Drug eluting coating for coronary stents

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Introduction

Nowadays, when the age of bloody wars in Europe seems to be over, and we have got over all the deadly infectious diseases, the main killer of our civilization are cardiovascular disease (CVD), the product of the civilization. It is also a leading death cause on the whole globe. An estimated 17.5 million people died from cardiovascular disease in 2005, representing 30% of all global deaths. Of these deaths, 7.6 million were due to heart attacks and 5.7 million due to stroke. About 80% of these deaths occurred in low- and middle-income countries. If current trends are allowed to continue, by 2015 an estimated 20 million people will die from cardiovascular disease (mainly from heart attacks and strokes) [WHO]. Heart attacks and strokes are mainly caused by artery blockage that prevents blood from flowing to the heart or the brain. The most common cause is a build-up of fatty deposits on the inner walls of the blood vessels. The blood vessels become narrower and less flexible, symptoms also known as atherosclerosis. The blood vessels are then more likely to become blocked by blood clots. When this happens, the blocked vessels cannot supply blood to the heart and brain, which then become damaged [WHO]. The causes of CVDs are well established and well known. The most important causes of heart disease and stroke are unhealthy diet, stress, physical inactivity and tobacco use, many scientist also suspects inflammatory or auto immunological processes in the blood vessel walls. The best way to avoid CVDs is prevention, but when the artery is blocked we have to "unblock" it somehow, this treatment is known as angioplasty. There are several types of interventional procedures improving blood flow in the blocked artery, most popular are balloon angioplasty, stenting and ablation.

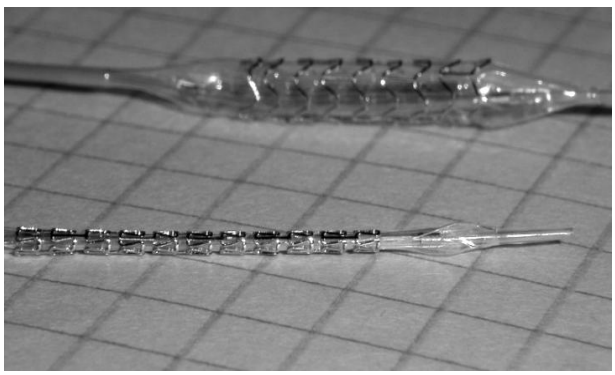

Fig. 1. Stent on the implantation balloon, before and after expansion.

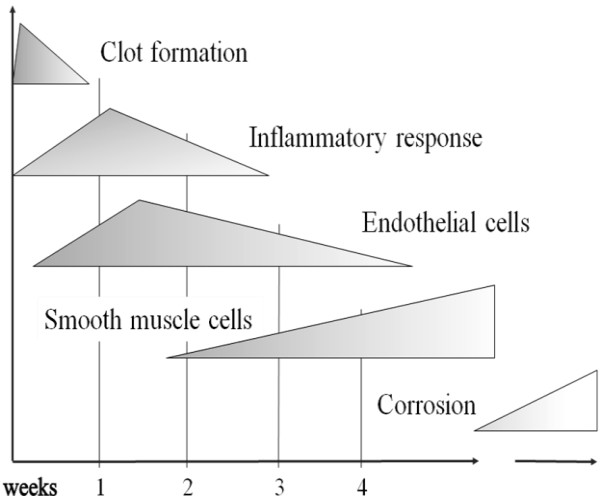

Fig. 2. Ongoing biological response after stent implantation.

During balloon angioplasty, a specially designed catheter with a small balloon tip is guided to the point of narrowing in the artery. Once in place, the balloon is inflated with a high pressure saline, expands and compress the fatty matter into the artery wall and stretch the artery open to increase blood flow to the heart. Stent is a small metal perforated tube that acts as a scaffold to provide

support inside the coronary or peripheral artery (Fig.1.). A balloon catheter, placed over a guide wire, is used to insert the stent into the narrowed coronary artery. Once in place, the balloon tip is inflated and the stent expands to open the artery lumen. The balloon is then deflated and removed while the stent stays in place permanently to hold the artery open. During first few weeks artery heals around the stent. Stents are commonly placed during interventional procedures such as angioplasty to help keep the coronary artery open. In the case of ablation or roto-ablation, a special catheter, with an anchor-shaped blades, is guided to the narrowing point in the artery. The tip spins around at a high speed and cuts away the plaque from the artery walls. The microscopic residues are washed safely away by the blood stream and filtered out by your liver and spleen. Most popular procedure, due to its safety, technical ease and good results is stenting. There are few different biological processes going on after stent implantation (Fig. 2.). Endothelial cell are necessary to cover stent struts and prevent clot formation on metal – blood interface. Unfortunately sometimes artery respond to the stent expansion and presence with a small inflammation and overgrow of the smooth muscle cells. This process leads to renarrowing of the artery in the place where the stent is implanted and is called restenosis. To prevent this a polymer coating with encapsulated drug is frequently employed to source a local drug delivery for restenosis prevention. There are an ongoing scientific debate about the efficacy of this method. A small input to this discussion is presented here.

Drug and polymer choice

The drug and the polymer choice for coronary stent coating is not an easy task. The influence of few chosen drugs on endothelial cells (good) and smooth muscle cells (not good) is shown in figures 3 and 4 (data from Abbott Laboratories).

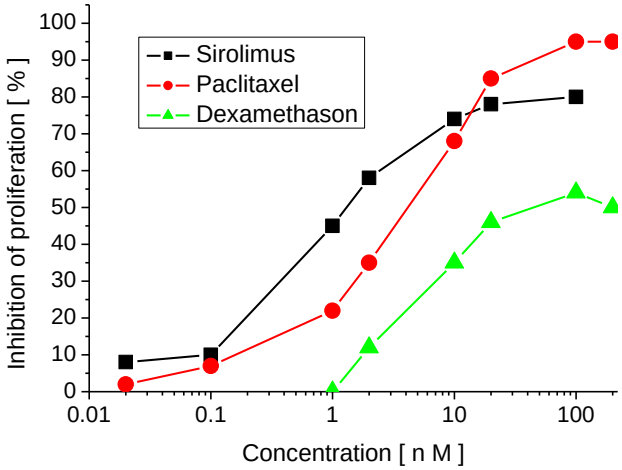

Fig. 3. Influence of drugs on smooth muscle cells grow.

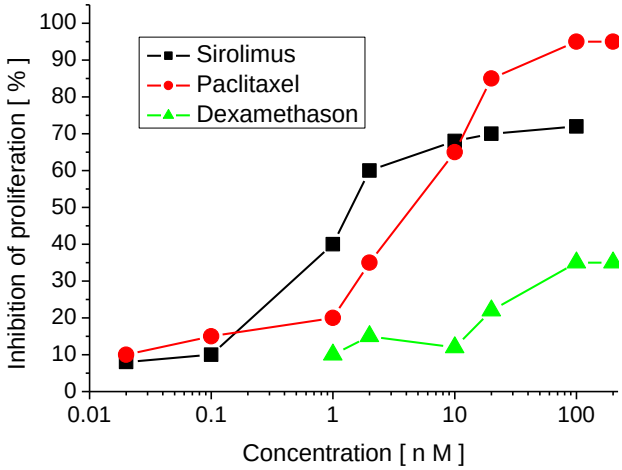

Fig. 4. Influence of drugs on endothelial cells grow.

As it can be seen on both pictures drugs influences both types of cells. Sirolimus and Paclitaxel are more potent as compared to Dexamethason, we decided to employ Paclitaxel. As a matrix polymer to encapsulate drug, a medical grade polylactic acid of 200 kDa from Boehringer Ingelheim has been employed. Stents were coated by deep coating in the drug (1%) polymer (5%) solution in chloroform. Biodegradation of the coating was tested in the phosphate buffered saline solution at 36^{O}C with 0.1% of sodium azide to prevent bacteria growth.

Results

Coating degradation results after 2 and 8 weeks in PBS are shown in the figure 5 and 6.

Fig. 5. Biodegradation of the coating after 2 weeks in PBS.

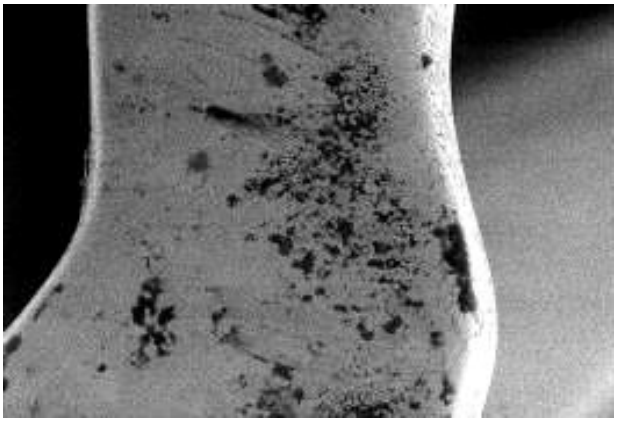

Fig. 6. Biodegradation of the coating after 8 weeks in PBS.

As it can be seen polymer degrades nicely and after 8 weeks degradation in vitro only a small residues are visible on the stent surface. Also drug release rate was estimated in vitro and results are shown in the figure 7.

Animals trials were performed on ten pigs of 30-35 kg. Bare metal stents (BMS), polymer only coated stents (PCS) and polymer coated drug eluting stents (DES), were implanted into pigs arteries. Implantation was followed by the typical pharmacological treatment (150 mg Aspirin and 500 mg Triclopidin a day, for 4 weeks). After three months stetns were explanted and the restenosis rate was estimated, Figure 8.

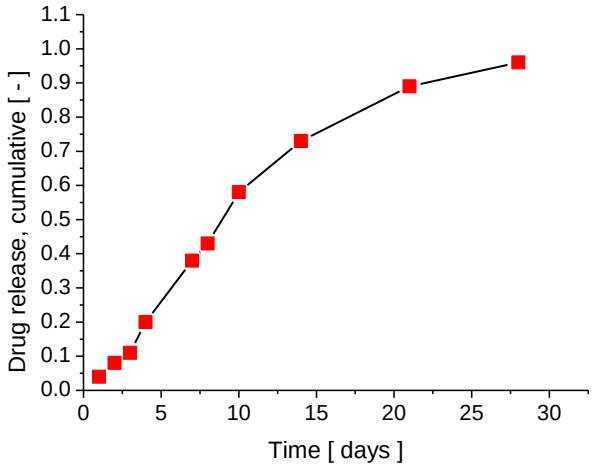

Fig. 7. Drug release rate from the stent coating, in vitro.

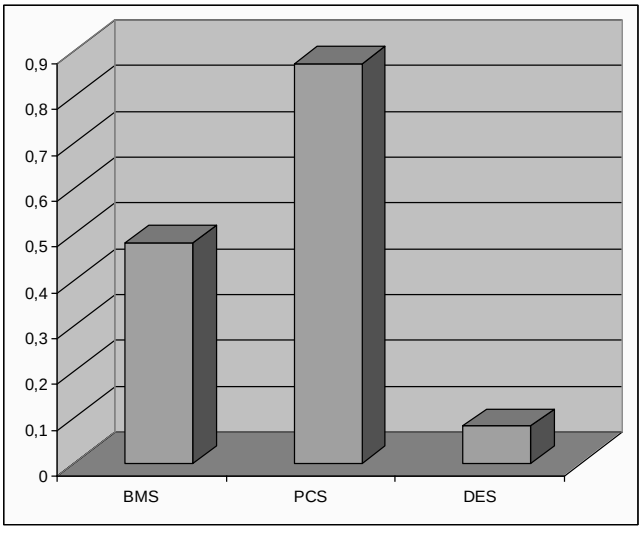

Fig. 8. Artery lumen loose after 3 months.

Histopathological investigation showed an sever inflammatory process around PCS struts, in this type of stent restenosis was also the biggest (Fig. 7).

The best results, smallest restenosis and almost no inflammatory reaction were exhibited by the artery with drug eluting stent (Fig. 8). Bare metal stent showed intermediate restenosis and inflammatory response in the artery walls. We have to bear in mind that pigs are much more sensitive for cardio vascular problems than humans, so in our case the inflammatory response would be much smaller, but that's why pigs are the best model for this type of research.

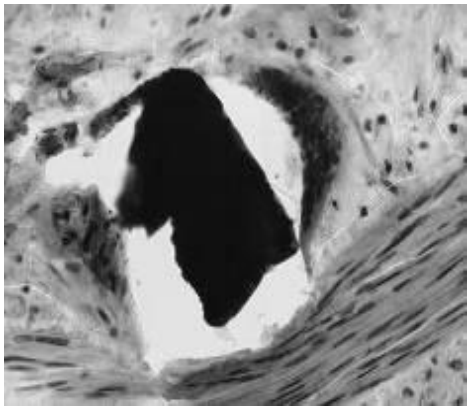

Fig. 7. Artery lumen loose after 3 months.

Fig. 8. Artery crossection of DES after 3 months.

The adverse reaction on the artery walls and the sever inflammatory response in the case of PCS, as compared to bare metal stent is probably caused by the acidic products of polymer degradation, monomeric and oligomeric lactic acid. In the case of drug eluting stent the drug itself prevents this adverse reaction.

Conclusions

Application of antiproliferative drug, Paclitaxel, decrease restenosis rate after three months in pigs. Drug eluting stents showed much smaller restenosis as compared to bare metal stents and polymer coated stents. The presence o PLA polymer on the stent struts showed a negative influence on artery walls, induce restenosis and sever inflammatory response. In the future research a new type of polymers have to be employed.

Acknowledgments

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References

WHO - http://www.who.int/cardiovascular_diseases/en/