Development and Micro Manufacturing of Coronary Stents in Hungary

Barnabás Szabó [1], János Dobránszky [2], László Major [3], Zsolt Nyitrai[4]

[1] Budapest University of Technology and Economics, Department of Materials Science and Engineering. 1111 Budapest, Goldmann tér 3. Hungary

[2] Research Group for Metals Technology of HAS–BUTE. 1111 Budapest, Goldmann tér 3. Hungary

[3] CardioVascular Interventions Public Benefit Company. 1123 Budapest, Alkotás utca 50. Hungary

[4] Minvasive Ltd. 2360 Gyál, Gárdonyi Géza utca 65.

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Abstract. Revascularisation by endovascular implant (stent) has great importance in the treatment of coronary artery diseases. Stents are high-technology implants that are the creation of the knowledge of health sciences, physics, chemistry, material science and engineering. Its development can be carried out only by the involvement of these areas of knowledge. Hungary has a stent production since 1995, which is the only one in the new EU member countries. The aim of the project that has been started within the frameworks of the National Research and Development Program, is the development of a new stent family based on the results of the material science researches have started for 10 years and the clinical and production experiences of experts, which could result an equivalent Hungarian product to the market leader products in case of several product lines. The original wire-mesh cut for those replaced welded stents made of wire later from tubes laser cutted ones. The stents are made of biocompatible materials: 316LVM stainless steel, Co-Cr alloys and nitinol. Stents made from wires are produced by weaving, or reeling and resistance projection welding. Nowadays, stents are produced mostly by high-precision laser cutting. These were large steps forward in the development of production technology, following the appearance of balloon catheters. Independently of what kind of manufacturing process is used, it has to be very precise because a connecting goal of the development is to increase the biocompatibility of the stents with surface treatment and to create a coating that is able to carry drug on the smooth surface. The paper presents the antecedents, achievements and main future objectives in micro manufacturing speciality of that special medical device, that is just before the surface treatment and coating process of the stent.

Introduction

Stents are biocompatible implants that have mesh structure and are able to sustain vessel walls. Stent endoprotheses have been used by cardiovascular therapy for ten years to substitute serious “by-pass” operations in case of coronary-artery disease with cheaper, quicker operations that do not wear the patients down. The stent shown in Fig.1 is placed to the site of stenosis in compressed

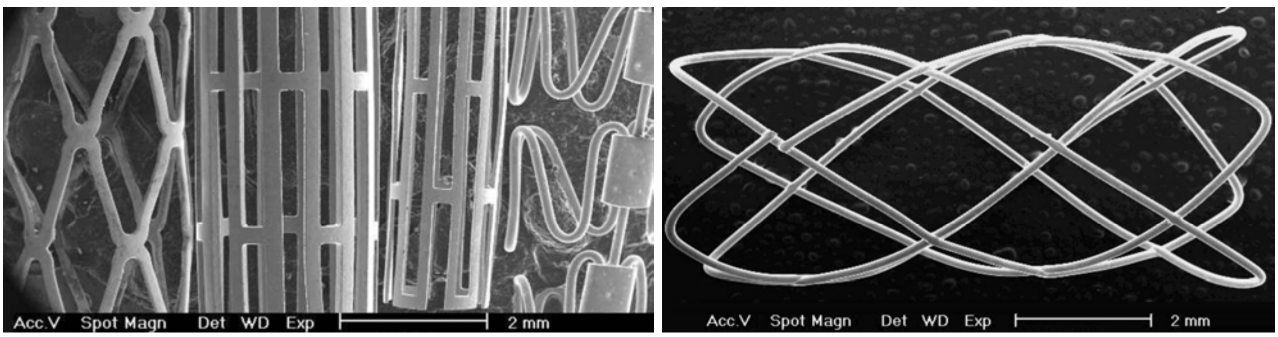

Figure 1. SEM-image of old coronary stents (left), the Hungarian *Tentaur Stent* (right)

form on a balloon catheter then with the inflation of the balloon catheter it is dilated. In the vessel treated by this method, the circulation of the blood is restored.

In case of materials being in direct contact with blood, haemocompatibility is demanded. The most important question of the quickly growing stent industry is the surface characteristic of stents. Medical science is more and more careful at stating what type of surface is ideal for a stent. The most important development trend in the last four years is the special surface treatment of stents. To produce a smooth surface that can be drug-eluted special micro manufacturing technologies - like fine laser cutting - are needed.

Clinical applications show that there is demand for such type of stents that can be implanted to those areas where the non-flexible stents cannot be. The Hungarian *Tentaur* stent types mounted on balloon catheters are not flexible enough. To increase the flexibility new production technology is necessary (Fig.2).

The aim of the project is to develop a new stent family. The new coronary stents based on the results of the Hungarian stent development, material science researches and the clinical and production experiences of the experts of the consortium, which results an equivalent Hungarian product to the market leader products in case of several product lines.

The project even has international cooperation. The German partner is the *eucatech AG*, which is an acknowledged research, development and production company in the field of medical science and technology.

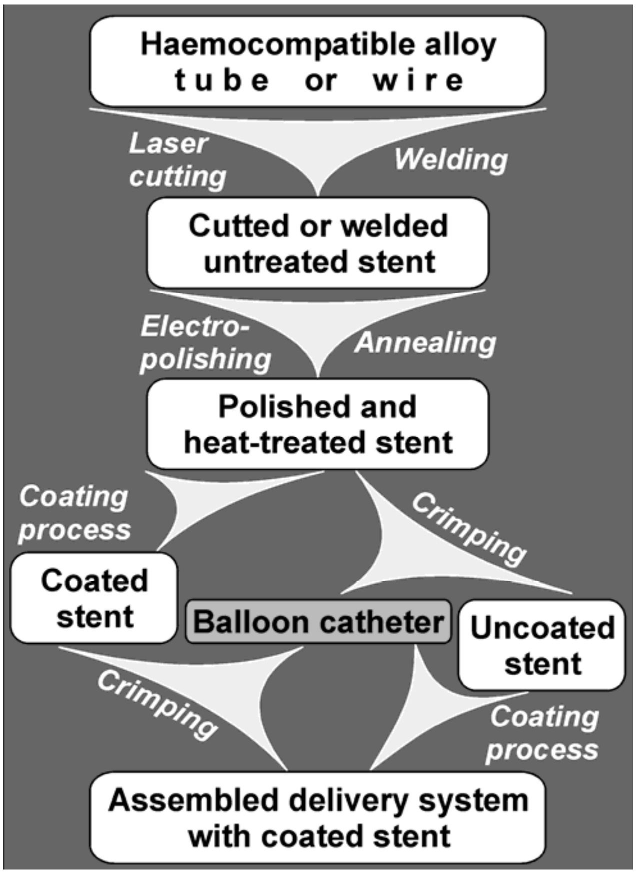

Figure 2. Schema of stent manufacturing

The research and development is made up of 4 comprehensive major tasks, of which the first 3 are presented in the paper [1]. The 4th task is the development of drug-eluting and carbon-coated stents.

Application of new substances as base material for stent production

Stents can be produced from tubes or wires. Produced by any techniques they are very precise. The mesh structure is produced from a thin wall tube by laser cut. Stents made from wires are produced by weaving, sewing or reeling and resistance projection welding. Nowadays, stents are produced mostly by high-precision laser cutting.

In the revolution of the stents different kind of materials were tested in order to get better mechanical features and physiological effects. Such a material was searched which is resistant to mechanical and biochemical effects, works for a long time in the body and does not cause any damage when deploying the vessel. Analysing the haemocompatibility and examining the manufacturing properties of the new stent materials (e.g. Co-Cr alloys, nitinol) is the way to find the perfect material for stent application [2, 3].

Several materials were tested as vessel implants or coatings; however the stainless steel (316 L, 316 LVM) is the most frequently used material, which is proved to be the most reliable, based in clinical trials. Austenitic stainless steels, especially 316L, are most widely used for implants. This group of stainless steel is nonmagnetic and possesses better corrosion resistance than others. The type 316L stainless steel may corrode inside the body under certain circumstances in blood. 316LVM (low carbon vacuum remelted) steel is used for stent production owing to its good ductility in cold worked condition coupled with remarkable corrosion resistance after annealing. This austenitic stainless steel is initially electric arc melted, then a refinement to the purity and homogeneity of the metal is done [4, 5].

Stents are also made of Ni-Ti alloys (nitinol) and Co-Cr alloys (L605, MP35N). The cobalt-chromium alloys are advantageous to X-ray opacity (Fig. 3), the huge elasticity modulus and strength makes possible to design thinner stent struts. Smaller stents with better flexibility can be produced of that kind of materials; these stents can be better deployed into the vessels. Nitinol is used for peripheral stents and not for coronary stents. Self-expanding stents are made of austenitic nitinol and balloon-expanding stents are made of martensitic nitinol.

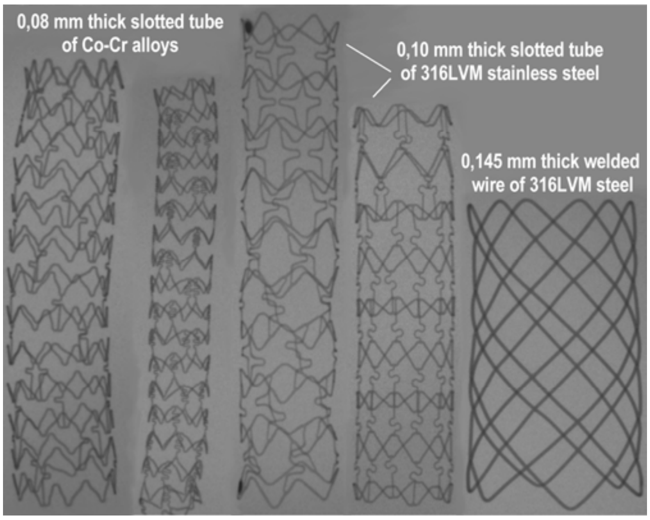

Figure 3. X-ray microscope image of five different coronary stents

Many properties are directly linked to the material. Biocompatibility, X-ray and MRI visibility, radial force, recoil, flexibility, transportability, profile and long term integrity are all depending on the mechanical and physical properties of the material. Some requirements of the materials stand opposite to the other one like holding capacity and plasticity. Plasticity of the material is important because of the flexibility of the implant. The aim is to apply materials where the same holding capacity can be reached by using the thinnest struts [6, 7].

Development of ultra-flexible stents

Developing ultra-flexible stents from tube and wire, optimising the functional attributes of them and specifying the clinical attributes of ultra-flexible uncoated stents bulk large in the project. Laser cutting gives us an adequate technology to produce ultra-flexible implants in a short time, the cutting period is depending on the length of the stent and the complexity of the design. The shape of the kerf depends on the material of the implant. A CAD-software (ProEngineer) is used for designing (Fig.4), examining and for optimising the functional attributes of ultra-flexible uncoated stents (for example: Solid Edge, CAD, FEM software). Finite element method (FEM) can help identify some valuable mechanical characteristics of stents, arteries, and their interactions, which cannot be easily obtained by routine methods. Elaborating posterior surface treatment technologies is decisive as well, because it changes the kerf width and the wall thickness of the stents.

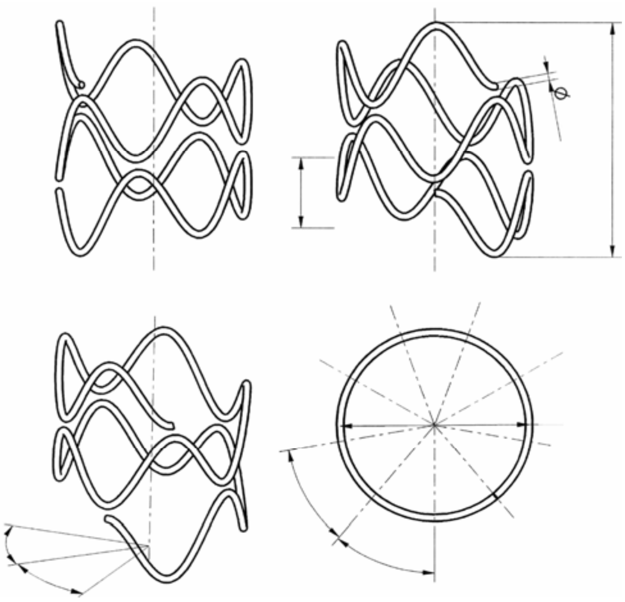
Figure 4. Ultra-flexible *TentaFlex Stent*

The testing of the properties of coated and uncoated stents, to be carried out under realistic circumstances, and the expensive pre-clinical and clinical tests which are inevitable when requesting approval from the authorities will be implemented mostly in haemodynamic laboratories. The tasks comprise experiments of sterilizing and mounting onto balloons as well as determination of radio-opacity and measurement of balloon expansion properties.

Developing the technology of mounting onto a balloon catheter, optimised to profile size and flexibility is an important subtask of this development. All partners participate in this phase of the project and will select and develop the most suitable balloon catheter and determines the optimal pressure values at balloon expanding. The experts assess the strengths and weaknesses of the new domestic stents' clinical application with comparison (benchmarking) tests.

Development of new production techniques based on laser technology

Within the frameworks of the development of new production techniques based on laser technology, laser beam welding-based manufacturing of stents produced of wire (see Fig. 5), laser cutting-based manufacturing of stents produced of tube and developing the laser-lithography and etching based technology for conventional and advanced materials are researched.

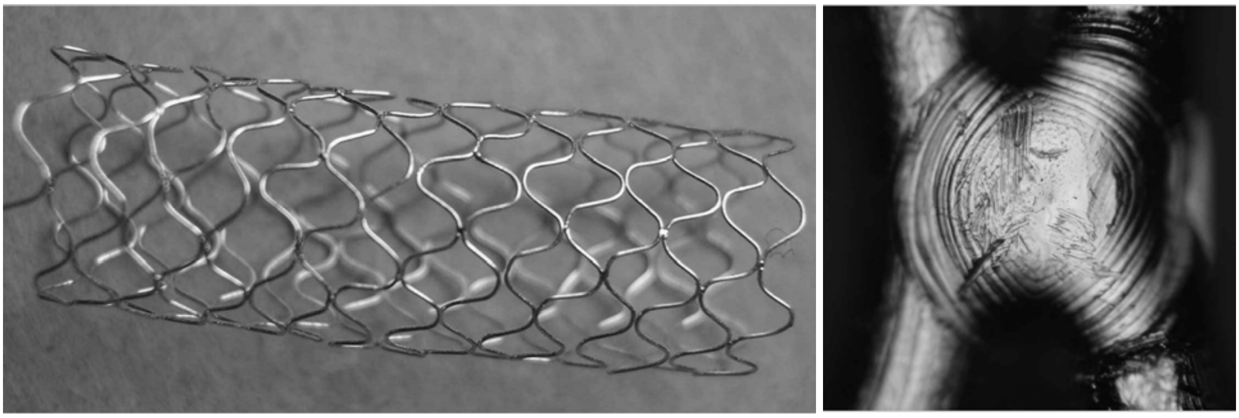

Fig. 5: Prototype of laser welded ultra-flexible stent (untreated surface)

Recently with the application of laser technology, the stent producing process has become much faster. The stent is manufactured by direct laser cutting from a single metallic tube using a finely focused Nd:YAG laser beam passing through a gas jet to impinge on the working surface of the tube as the linear and rotary velocity of the tube is precisely controlled by a high tech linear and a rotary stage. Lasers offer the manufacturing industry a fast, precise and clean process. Now it is the best way to cut tiny stents from metal tubes. Laser processing method, which produces the straight edge with desired cross section of struts, results a uniform fluid flow in the blood vessel.

A growing application of YAG lasers is cutting stents (Fig.6). It is ideally suited to producing

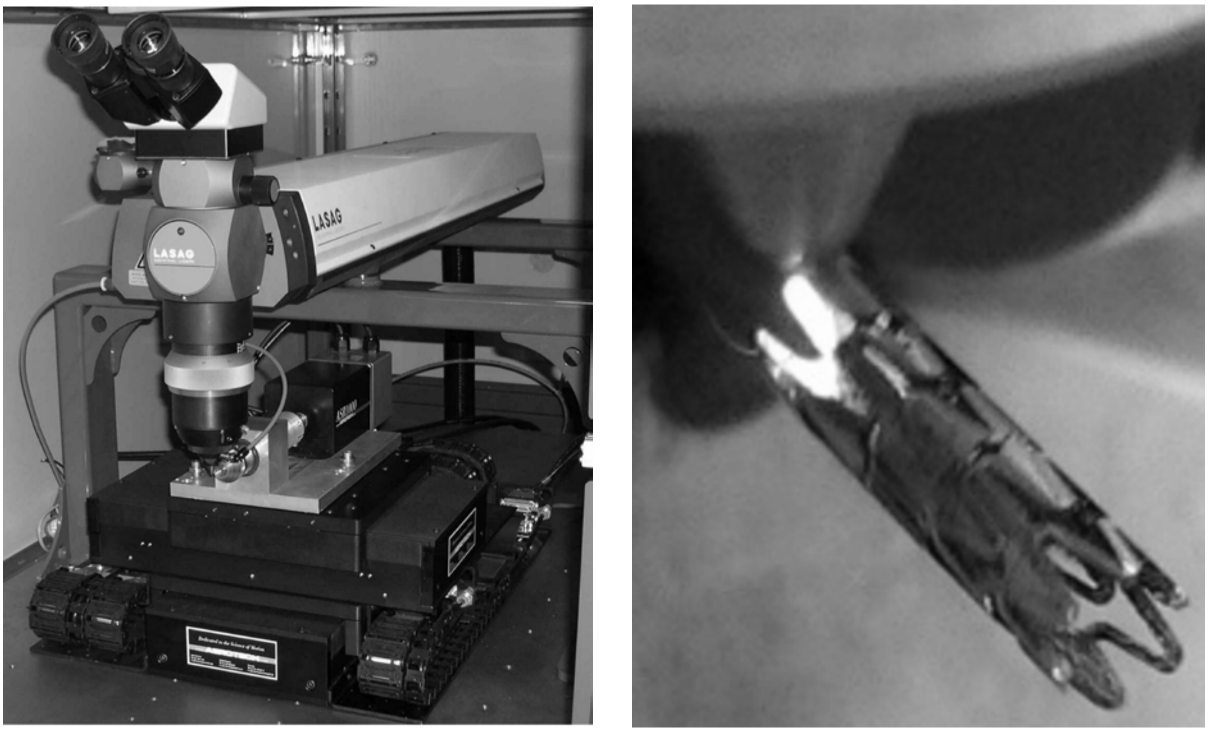

Fig.6: System for laser cutting under construction (left) the cutting process (right)

stents, because the YAG laser has the ability to cut thin walled small diameter tubes with kerf widths down to 20 μm without damaging the opposite inside wall [8, 9].

Another advantage of the YAG lasers is the minimal heat affected zone. Short pulse width is advantageous in reducing the heat-affected zone. It is less than 4 μm in common steels. A 15 mm long stent can be produced in about two minutes depending on the intricacy of the design. The typical parameters of the cutting are the spot size, output power, and repetition rate. The wavelength of the YAG lasers is 1064 nm. These fine cutting lasers are typically pulsed lasers with a high peak power range [8-10].

During the laser processing of the stent, a big problem is dross, i.e. burrs and spatter adheres to the underside of the cut. In order to overcome this problem usually pickling and electro-polishing is applied. Pickling is a type of cleaning process, whereby the underside dross or surface oxide layer is removed by chemical attack.

Factors affecting the behaviour of micro-cracks and heat-affected zone include the use of a cover gas, laser beam characteristics, cutting speed and post processing. Electro-polishing can reduce the heat-affected zone. Annealing removes the undesired effects of plastic deformation and laser cutting and electropolishing. Besides that, the roughness of the cut surface can still be reduced by using the nitrogen as assist gas instead of oxygen but at the cost of slow processing speed.

Preparing stents with mask technology and etching (Fig. 7) is another way to produce stents. It is very similar to those used in electronic technology to prepare printed wiring boards. Here the basic material is a stainless steel tube and the pattern of the mask will be projected on a cylindrical surface. The conventional etching cannot be used here; we have to use electro-chemical etching. The steps of the technology:

- Cleaning and degreasing of the surface,
- Coating of the tube surface with resist
- Drying,
- Projection of the mask on the surface with laser beam,
- Chemical or electrochemical etching of sample.

The problem of sharp edges can be solved using low current polishing after removing stent from the bar and the resist from the surface [1].

Fig.7: Processing sequences of *BorGir® Stent*

Conclusion

The development of such a medical implant is a really complex work. Researchers of the health sciences, surface physics and chemistry, material study, engineering and technology have to work on such a project. The paper lets us glimpse into some parts of a stent-research project that has the following main tasks of which the first 3 were shown in the article:

1. Application of new substances as base material for stent production.
2. Development of ultra-flexible stents.
3. Development of new production technique based on laser technology.
4. Development of drug-eluting and DLC-coated stents.

At this time point the researchers have developed a cutting machine for the laser cutting, and using many kinds of biomaterials for the investigations. The first Hungarian laser cutted raw stent will be produced in a short time, then the new developed coating methods and materials can be tested on the laser cutted stents as well. Now we use the Hungarian welded stents for the investigations, that doesn't have the flexibility of the laser cutted ones. The surface- and heat treatment parameters have to be adjusted to the cutted stents as well. The development of the new stent family will be followed by production and certification and will be finished by the obtainment of the CE mark, which supports the adaptability in the Hungarian public health. All this goes a great way to the healing of one of the most serious disease of civilization.

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