

# Gastrointestinal Intervention

journal homepage: [www.gi-intervention.org](http://www.gi-intervention.org)

## Review Article

## The challenges: Stent materials from the perspective of the manufacturer



Karel Volenec, Ivan Pohl\*

### ABSTRACT

The article presents an overview of the basic data influencing the choice of materials for the manufacture of self-expanding metallic stents to be implanted into gastrointestinal tract, particularly esophageal stents. The data are evaluated primarily in terms of the manufacturer of stents. The text emphasizes not only the importance of the materials themselves, but also the biological environment in which the stent is used. Brief history of materials used in gastrointestinal stents mentions stainless steel, cobalt-chromium and nickel titanium alloys and polymers (polyester and polydioxanone). The text describes the properties of metal materials (composition, corrosion, mechanical properties) with particular focus on nickel-titanium alloy—nitinol. It lists advantages and disadvantages of nitinol. At the end of the review the authors briefly present their opinion on future materials of gastrointestinal stents and their covering.

Copyright © 2016, Society of Gastrointestinal Intervention. All rights reserved.

Keywords: Biocompatible materials; Biomedical and dental materials; Nitinol; Self expandable metallic stents; Stents

### Introduction

Selection of materials for implants, including self-expanding stents, is essential for their clinical performance and safety. This article presents an overview of the known facts concerning the fundamental characteristics of the materials for the manufacturing of metal self-expanding stents, especially for implantation into the gastrointestinal tract (GIT). Facts are presented from the perspective of the manufacturer and therefore take into account the data purely technical as well as medical. For producers are also important regulatory principles (European directives and standards), which are not mentioned in the article.

### Diversity of Body (Biological) Environment and Its Effect on the Implanted Stent

A general definition of the stent presents it as a tube-shaped device that can be inserted into a narrowed or weak anatomical passageway to hold it open. Stents became widely used in many anatomical areas, organs or organ systems (central and peripheral vascular system, extravascular organ systems—GIT; respiratory

tract, urinary tract, etc.). There are also stents, the use of which is beyond the general definition, e.g., stent supporting transjugular intrahepatic portosystemic shunt (TIPS), stent supporting drainage of the pancreatic cyst into the stomach or stent stopping the acute bleeding from the esophageal varices.

So widespread use means that stents are used in dozens of environments that differ in chemical composition, loads and speed of their change.

Duerig et al<sup>1</sup> distinguish two principal body fatigue environments: the strain-controlled and the stress-controlled. In the strain controlled environment a device is alternately deformed between two set shapes while in the stress controlled it is subjected to cyclic loading. Although the majority of fatigue environments in the body combines both above mentioned, the authors believe that the predominant is strain controlled environment due to the compliant nature of biological materials.

The GIT consists of hollow organs, in which the lumen represents different fatigue and biological environment. To avoid extensive discussion, we try to describe the environment in the esophagus and its effect on the implanted stent including interactions with stent material.

ELLA-CS s.r.o., Hradec Králové, Czech Republic

Received March 2, 2016; Revised May 20, 2016; Accepted May 30, 2016

\* Corresponding author. ELLA-CS s.r.o., M. Horákové Str. 504, Hradec Králové 500 06, Czech Republic.

E-mail address: [ivan.pohl@ellacs.cz](mailto:ivan.pohl@ellacs.cz) (I. Pohl).

pISSN 2213-1795 eISSN 2213-1809 <http://dx.doi.org/10.18528/gii160008>

© This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0>) which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

## Factors of Biological Environment in the Esophagus and Their Impact on the Implanted Esophageal Stent

Factors of biological environment in the esophagus that affect implanted stent may be divided into the following groups: anatomy including its pathological change; esophageal peristalsis; esophageal propulsive force (EPF) and substances passing through the esophagus.

The esophagus is the muscular tubular structure 25 cm long in adults. In the resting state it is collapsed. It opens to accommodate swallowed or regurgitated material. It is approximately 30 mm in its longer lateral diameter and 19 mm in its shorter anterior-posterior diameter, although it has a capability of distending to greater dimensions. The above mentioned dimensions and their pathological changes (esophageal stenosis either straight or tortuous, stable or developing; esophageal dilation, etc.) are crucial to determine the dimensions of esophageal stents and their delivery systems. Dimensions of luminal diameter of the esophagus limit deformation of the stent. Severity of the esophageal stricture determined by its internal diameter, length and ease or difficulty of its dilation correlates with the mechanical stress of the stent and thus affects its properties, including material selection.

The wavelike contractions (peristalsis) is the next important factor defining the environment of the esophageal lumen. In the body of the esophagus, swallowing is associated with an initial wave of muscular inhibition followed by a sequential activation of longitudinal and circular muscles. This is primary peristalsis (the stripping emptying wave). The peristaltic velocity is of 3 to 5 cm/sec. Due to the action of the lumen, flexible stents mimic to some extent the movement of the lumen. This reduces the risk of injury to the esophageal wall but increases the risk of migration because the stent with constant diameter along its entire axial length does not follow expansion of the esophageal diameter in full. Rudney et al<sup>2</sup> determined the average number of swallows per hour as of 122, with a wide range of swallows per hour from 18 to 400.

Leaving aside the secondary peristalsis, the EPF is another important factor determining mechanical stress on the stent. Hsiao et al<sup>3</sup> presents it as resulting from a large distensions of the esophagus due to an immovable bolus—stent. It consists of a single, sustained force developed by circular esophageal muscles which is significantly larger than that resulting from primary or secondary peristalsis. With respect to the esophageal lesion (no stenosis, benign and malignant stenosis), they define three types of esophageal responses to stent placement. In all three situations, the authors assume no peristalsis at upper and lower flare of the stent. In case of no stenosis they assume the EPF at the upper edge of the stent and at the base of the lower stent flare plus secondary peristalsis along the stent body. In case of benign stenosis they assume the EPF at the beginning of the stent body and at the base of the lower stent flare plus weak or no peristalsis along the stent body. In case of malignant stenosis they assume the EPF at the upper edge of the stent and at the base of the lower stent flare plus primary peristalsis along the stent body. The above mentioned model of forces developed by the esophageal wall demonstrates how difficult is to create an ideal esophageal stent.

Substances passing through the esophagus represent another factor determining internal environment interfering with implanted stent. In healthy individuals those substances are drinks, food, saliva and transient, physiological reflux of gastric contents. People consume many different foods and beverages with a large range of pH. Citrus fruits like oranges, lemons and limes are quite acidic (pH = 2.0–4.0). Carbonated drinks such as cola have a pH 4.0 to 4.5 while egg whites are slightly alkaline, with a pH of 8.0. The

pH of tap water should be between 6.5 and 9.5. Recommended daily fluid intake in adults is 2.1 to 2.3 L/day. The amount of secreted saliva is 1 to 2 L/day, pH = 6.0–7.0.<sup>4</sup> It contains 99.5% water and small amounts of other important substances such as electrolytes, mucus, antibacterial compounds, enzymes, epithelial, and bacterial cells.

Gastroesophageal (acid) reflux is in most subjects a benign physiologic process that occurs most commonly following meals. In these subjects, even repeated daily contact of the esophageal epithelium with acidic gastric contents with pH lower than 4 does not produce damage to the tissue.<sup>5</sup> Patients with gastroesophageal reflux disease experience more episodes of reflux. Many of them are prolonged because of a failure of acid clearance. The above mentioned facts demonstrate high corrosivity of the environment in the esophageal lumen that attacks the implanted stent. Thus, material resistance to corrosion is one of the basic characteristics required for esophageal stents.

## Materials Used for Manufacture of Stent Mesh

### *Materials that have been used in the past*

Due to the extensive history of stents we concentrate on the materials used for the manufacture of GIT stents, especially esophageal. The history of self-expandable metallic stents in human GIT starts from Wallstent (Medinvent SA, Lausanne, Switzerland) that was implanted in esophageal cancer by Domschke et al<sup>6</sup> in 1990. The stent was uncovered, woven in the form of a tubular mesh from surgical grade stainless steel alloy filaments. Five years later Gagneja et al<sup>7</sup> mentioned in their overview 26 published studies of esophageal stents. Three main stent types differing in material as well as design were used: uncovered and covered Wallstent (Microvasive; Boston Scientific, Natick, MA, USA), covered Z-stent (Wilson-Cook, Winston-Salem, NC, USA) and uncovered or covered Ultraflex (Boston Scientific). The authors published a table presenting the following composition of the stent mesh: Wallstent, a biomedical grade cobalt-chromium-iron-nickel-molybdenum alloy (Elgiloy Specialty Metals, Sycamore, IL, USA); Z-stent, noble stainless steel; Ultraflex, nitinol. In 2011, Martinez et al<sup>8</sup> published the article with the table listing 11 esophageal stents, which were then on the market in the US, Europe, and Asia. Four of them were made of stainless steel, six of nitinol and one (Polyflex; Boston Scientific) of polyester. Only one stent was uncovered, others were covered partially or fully. This demonstrated increasing trend of using covered stents made from nitinol. In addition, the first stent made from polyester thread and covered by silicone foil appeared on the market. Even more important position of nitinol is presented with the table published in 2013 by Song et al<sup>9</sup> that lists the self-expandable metal and plastic, esophageal stents marketed in the US, Europe, and Asia.

It starts to show a trend towards the use of biodegradable materials (BD-Stent made from polydioxanone fiber; ELLA-CS, Hradec Králové, Czech Republic).

### *The way to ideal GIT stent (material, design, and mechanical performance)*

The way to an ideal GIT stent is thorny. Laasch<sup>10</sup> describes efforts to achieve the aforementioned ideal through various designs of self-expanding enteral stents (segmented, laser-cut, woven, braided and knitted, mostly covered) and materials (metal, plastic, and biodegradable polymers).

Hirdes et al<sup>11</sup> measured radial and axial force developed by 12

self-expanding esophageal stents commercially available in 2013 (i.e., 10 nitinol stents, 1 polyester stent, and 1 polydioxanone stent). The radial force, i.e., radial resistive force (RRF) and chronic outward force (COF), was measured with respect to the method presented by Duda et al.<sup>12</sup> For axial force measurements, the samples were fixed in a set-up comparable to the previous report by Isayama et al.<sup>13</sup> Hirdes et al.<sup>11</sup> distinguished two groups with quite different radial force curves.

The first group comprises braided, nitinol self-expanding stents (Wallflex, Evolution, and Niti-S stents) and the braided biodegradable, polydioxanone stent—BD-Stent (ELLA-CS). These stents develop low initial radial force (< 150 N) that gradually decreased to 0 N at full expansion.

Ultraflex, Alimaxx, Hanaro, and Polyflex stents form the second group of stents characterized by a high radial force (300–400 N) when contracted followed by a steep drop in radial force during expansion. The high radial force may be attributed to the fact that these stent designs prevent elongation during contraction. The other factors also contribute to a higher radial force, e.g., stiffer stent material, thicker wire diameter or fully covered design.

Hirdes et al.<sup>11</sup> demonstrated that majority of the stents with the high radial force develop the low axial force and vice versa. The Polyflex stent was the only stent demonstrating the high axial as well as radial force. Hirdes et al.<sup>11</sup> consider the combination of high radial and low axial force to be optimal with respect to mechanical performance of an esophageal stent (Ultraflex and Alimaxx-ES). However, the authors admit a significant role of several other variables (material used to construct the stent and its covering, diameter of the wires, the size of each cell and the angle of the crossover wires, stent flares, uncovered parts of the stent, etc.).

### **Properties of different materials and the impact on stent manufacturing**

As stated before, the materials most commonly used for the production of GIT stents include metals and their alloys (stainless steel, nitinol, Elgiloy-Phynox), non-degradable polymers (polyester), and degradable polymers (polylactide, polyglycolide, polydioxanone).

#### **Stainless steel**

Although stainless steel has long since lost its position in the construction of self-expanding metal stents for GIT, Song et al.<sup>9</sup> and the American Society for Gastrointestinal Endoscopy (ASGE)<sup>14</sup> still present in their reports a few of stainless steel stents: Esophageal Z-stent, Z-Stent with dual antireflux valve (Cook Medical Inc., Bloomington, IN, USA) and some stents from the ELLA Esophageal Stent family (ELLA-CS). They are made from austenitic 316L stainless steel.

The 316L stainless steel is defined as low-carbon, nickel-chromium-molybdenum steel with the following chemical composition: Fe 63 wt%, Ni 10–14 wt%, Cr 16–18 wt%, Mo 2–3 wt%. With respect to greatly reduced risk of intergranular corrosion Hansen<sup>15</sup> mentioned this low carbon stainless steel (maximum 0.03 wt%) with a high Mo content, classified as 316L (American Iron and Steel Institute, AISI) or 1.4404 W-Nr (DIN 17007), being the only stainless steel suitable for manufacturing the implants. However, 316L stainless steel is high susceptible to crevice corrosion as compared to the other implant alloys.<sup>15,16</sup>

Significant pitting and crevice corrosion followed by implant failure was detected in the implanted fixation plates and screws.<sup>17</sup>

The importance of these types of corrosion for clinical efficacy and safety of stainless steel stents in GIT is not known, but seems to be negligent.

Another problem in the manufacture of self-expanding, stainless steel stents is to avoid irreversible deformation of the stent construction caused by extensive change in cross-sectional dimensions during expansion to the 'working' diameter *in vivo*. This is why, intricate designs allowing such extensive deformation and avoiding the risk of extensive yielding and fracture have been developed.

#### **Cobalt-chrome alloy (Elgiloy-Phynox)**

Elgiloy (Phynox) is an austenitic cobalt-based alloy (Co 40 wt%, Cr 20 wt%, Ni 16 wt%, Mo 7 wt%). It is non-magnetic, extremely resistant to corrosion (not sensitive to corrosion by organic acids), and its behavior in inorganic acids is greatly superior to that of the best stainless steels. Furthermore, Elgiloy (Phynox) presents an excellent passivity in contact with human tissues (bio-compatibility). Thanks to its high Young modulus, very high yield strength and good fatigue strength in the stress-controlled environment, Phynox has exceptional spring properties.<sup>18</sup> Krams<sup>19</sup> mentioned that self-expanding Elgiloy stents are made from cold drawn wire that is specifically heat treated (age hardening) in order to increase its tensile and yield strength and reduce its ductility. However, Technology Status Evaluation Report on enteral stents published by the American Society for Gastrointestinal Endoscopy<sup>14</sup> in 2011 mentions only one stent made from Elgiloy—Wallstent colonic and duodenal (Boston Scientific).

#### **Nickel-titanium alloy (nitinol)**

Duerig et al.<sup>20</sup> defined nitinol as an equiatomic or near-equiatomic intermetallic compound of nickel and titanium (e.g., Ni 55 wt%, Ti 45 wt%). It undergoes a phase transformation in their crystal structure when cooled from the stronger, high temperature form (austenite) to the weaker, low temperature form (martensite). This inherent phase transformation is the basis for the unique properties of these alloys—in particular, shape memory and super-elasticity, i.e., the ability to return to its original shape upon heating after an apparent plastic deformation and to its original shape upon unloading after being strained significantly, respectively. Besides these effects, nitinol exhibits some unusual yet useful properties which are mentioned in the following text.

A manufacturer of a medical device from the nitinol has to define the nitinol specification to adequately meet the needs of the product for which it is being produced. The sensitivity of the transformation temperature to composition is so great that the active austenite finish temperature; active A(f) is used for specifying the alloy instead of the chemistry. With respect to its thermomechanical condition the nitinol wire is delivered as cold worked (as drawn or as rolled) or super elastic strain annealed. In the first case the nitinol that has not yet undergone the final strain anneal and thus does not exhibit superelastic or shape memory properties. In the second case the nitinol has been heat treated to be fully superelastic at room temperature. Depending on the final application, it may be necessary to specify some mechanical properties. These may include ultimate tensile strength and elongation to failure. For superelastic alloys loading plateau, unloading plateau, and residual plastic strain (permanent set) may also be specified.<sup>21</sup>

Robertson<sup>22</sup> described in his dissertation the principals of final heat treatment (shape set anneal) of stent wire mesh. Whether the nitinol is superelastic or shape memory, in the cold work or straightened condition, it is often necessary to form the material into a new "memory" shape. This is done by firmly constrain-

ing the material into its new shape in a fixture or on a mandrel and then performing a heat treatment. The heating method can be an air or vacuum furnace, salt bath, sand bath, heated die, or other heating method. The temperature should be in the range of 500°C to 550°C with higher temperatures resulting in lower tensile strengths. Cooling should be rapid to avoid aging effects, a water quench is recommended. In all cases, experimentation for the proper time and temperature will be required to determine the combination that gives the desired results.

The last step in the stent manufacture is surface finish. Nitinol can have different surface finishes as a raw material and as a finished component. The choice of surface depends on performance and cosmetic requirements for the particular application.

Current nitinol producers make nitinol with an oxide surface that varies in color from light amber to blue to a black color. This surface denotes material that was annealed in a controlled environment. Oxide surfaces are typically very smooth and may be more lubricious than other surface finishes. Prior to straightening, the nitinol wire may be chemically etched, i.e., the wire is running through an acid bath (pickled). Etched surfaces are typically rougher than oxide surfaces.

Stents and filters are usually electro-polished as a final process step. This process creates an exceptionally smooth, uniform oxide layer that improves biocompatibility and reduces corrosion.

## Why We Have Arrived at Nitinol

Stoeckel<sup>23</sup> summarized in his review seven reasons for nitinol's success in construction of medical devices: elastic deployment, thermal deployment, kink resistance, constant stress, dynamic interference, stress hysteresis (biased stiffness), and temperature dependence of stress. Nitinol exhibits also other important properties, such as magnetic resonance imaging compatibility, biocompatibility and corrosion resistance.

Thermal deployment is not but a usage of the thermal shape-memory of nitinol. A device with a transition temperature ( $A_f$ ) of 30°C can be compressed and inserted into the delivery system at room or lower temperature. It starts to expand to its preset shape when the temperature is raised to > 30°C, i.e., when the body heat warms it up. This feature of nitinol reduces the mechanical load of a delivery system with preloaded stent and enables to reduce its profile. Kink resistance prevents localization of the strain beyond the loading plateau level which is the essence of the wire kinking and stent crush. This is why the braided esophageal nitinol stents can be bent under the large angle without kinking.

Dynamic interference refers to the long-range nature of nitinol stresses. Unlike balloon-expandable stainless steel stents, self-expanding nitinol stents will always expand to their preset diameters without recoil. Although Stoeckel<sup>23</sup> presents nitinol vascular stents as an example of the dynamic interference, it can be reasonably assumed that nitinol GIT stent will also continue to gently push outward against the wall of implanted anatomic structure and follow its movements.

Biased stiffness (stress hysteresis) is a feature of superelastic nitinol, which has the most significant effect on the behavior of self-expanding nitinol stents. The hysteresis, stress-strain curve as it is described by Stoeckel<sup>23</sup> for vascular stents may be also applied to GIT stents. Once the stent reaches the diameter of the lumen of given anatomy, it starts to develop a low outward force (COF) against it. This force remains nearly constant even if the lumen would increase in diameter (dynamic interference). If it is compressed from the outside, the stent resists deformation with a higher force (RRF). The biased stiffness means that the stent ex-

erts only low outward force, but resists deformation with a much higher force.

Temperature-dependent stiffness means that the plateau stresses are strongly temperature dependent above the transition temperature of the alloy. This feature allows to modify the stiffness of a superelastic nitinol stent at body temperature by adjusting the transition temperature of the nitinol alloy. Lowering the transition temperature makes the device stiffer at body temperature.

Duerig<sup>24</sup> compared physical properties of implanted metals (stainless steel, cobalt-chrome, titanium, and nitinol). He presented nitinol as super material in many ways (high strength, very low stiffness, fatigue good in strain control, excellent resistance against corrosion and shape memory as a bonus).

Biocompatibility is one of the most important parameters of materials intended for the manufacture of implants. Its evaluation is governed by the testing according to the standard EN ISO 10993-1<sup>25</sup> and associated standards. In spite of well-known toxicity of nickel, nitinol is considered to be high biocompatible material.

Ryhänen<sup>26</sup> presented the study determining the nitinol being safe material. He tested the primary cytotoxicity of corroded nitinol and compared with that exhibited by samples of 316LVM stainless steel and pure titanium. Despite the higher initial nickel dissolution, NiTi induced no toxic effects, decrease in cell proliferation or inhibition in the growth of cells in contact with the metal surface.

The general soft tissue responses to NiTi were compared to corresponding responses to 316LVM stainless steel and Ti-6Al-4V alloy in rats during a follow-up of 26 weeks. The muscular tissue response to NiTi was clearly non-toxic and non-irritating. Ryhänen<sup>26</sup> concluded the biocompatibility of nitinol seems to be similar to or better than that of 316LVM stainless steel or Ti-6Al-4V alloy. He stressed importance of optimal surface treatment of nitinol in long-term implants.

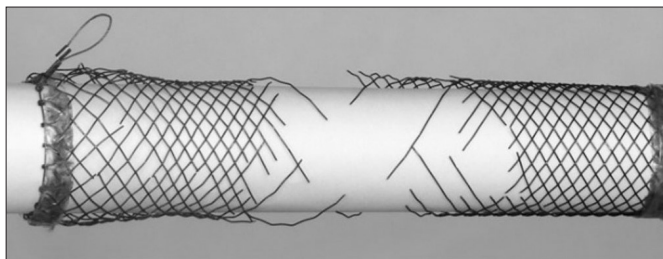
Sullivan et al<sup>27</sup> studied the effects of oxide layer composition and radial compression on nickel release in nitinol stents. They proved that additional Ni release due to stent radial compression is highly dependent on surface processing and that thicker oxide layers may be susceptible to cracking and exposing nickel-rich regions when compressed.

Sullivan et al<sup>27</sup> referred to the US Pharmacopeia that suggested a permissible daily exposure for nickel as a metallic impurity in drug products as of 0.5 µg/kg/day. This is greater than the highest Ni release (9 µg/day) for peripheral endovascular stents in the Sullivan's study. However, the authors admit that larger stents or stents in an overlapped condition may generate higher nickel release rates than those reported in this study.

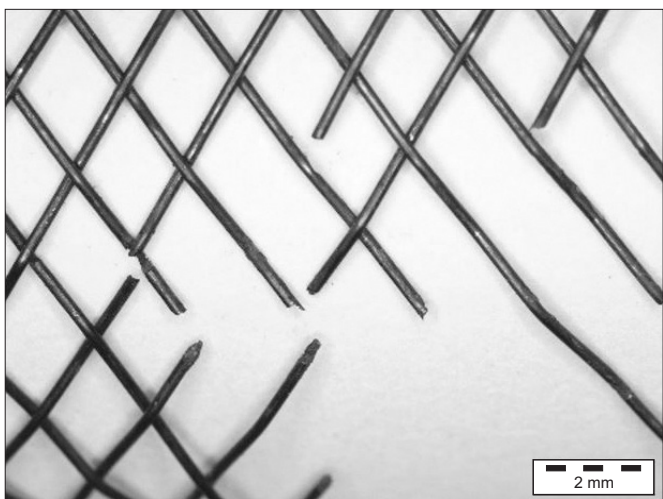
## The Problems Associated with Use of Nitinol as Material for Implants

With respect to the above mentioned features the nitinol seems to be an ideal material for stents. However, the real situation of its clinical use is much more complicated.

The properties of the stent, including its resistance to fatigue and corrosion, are determined not only by the material (nitinol), but also by original material form (e.g., wire, tubing), fabrication technology (e.g., laser machining, braiding, knitting) its design-stent geometry (rings, helix, coil, unconnected, open cell, etc.) as demonstrated by Stoeckel et al<sup>28</sup> with "stent design pyramid". If inappropriately chosen for a given application or body environment, each of these parameters may weaken the performance or



**Fig. 1.** Massive destruction of the wire mesh of nitinol braided esophageal stent (Esophageal Stent; ELLA-CS). The two-layer polyethylene covering was cut away except that on stent flares.

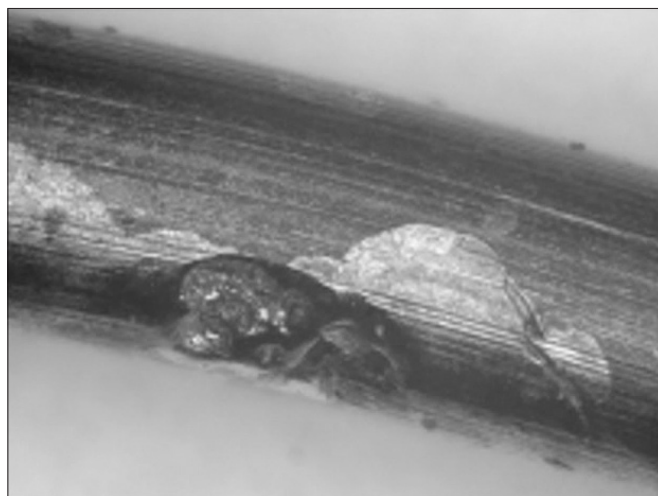


**Fig. 2.** Macroscopic details of the stent mesh breakage. Note the location of the damage to the stent integrity at the wire crossings.

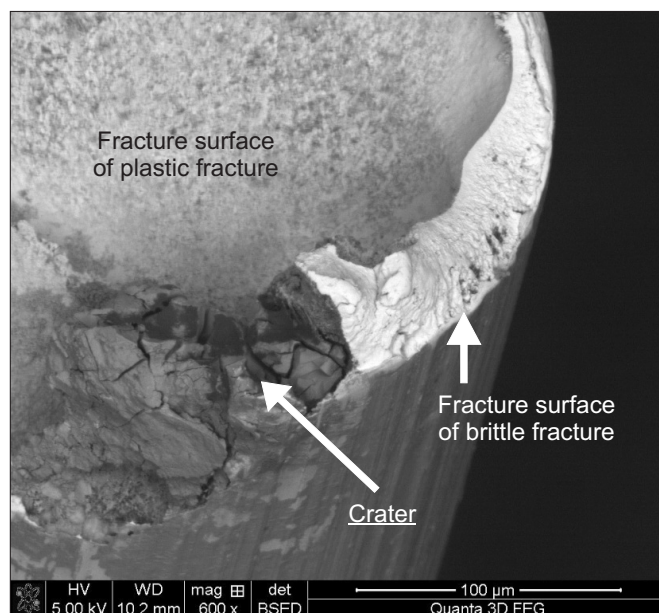
safety of the stent.

Leaving aside the complications that generally accompany the clinical use of esophageal nitinol stents (migration, bleeding from eroded artery, pain, over-growth, etc.), we experienced a single but significant complication that really surprised us. One patient experienced massive destruction of wire mesh in central portion of the self-expanding nitinol esophageal stent (Esophageal Stent; ELLA-CS) after a 6-month period of implantation (Fig. 1, 2).

We conceived the suspicion that the damage was due to the chemical action of reflux liquid with a low pH, which came between layers of polyethylene coating of the stent, where it can not interfere with any self-cleaning mechanism. ELLA-CS organized extensive testing of wire samples taken from the failed stent. Laboratory testing was conducted by prominent Czech and foreign technical institutions and universities (The Institute of Physics Czech Academy of Science in Prague, The Institute of Chemical Technology in Prague; Materials Evaluation and Engineering Inc., Plymouth, MN, USA). We believe that the most accurate evaluation of failure mechanism was provided by The Institute of Physics Czech Academy of Science in Prague. Racek et al<sup>29</sup> proposed the mechanism for fatigue failure of superelastically cycled nitinol wires in simulated biofluids. The mechanism involves the eight steps starting from fracture of the TiO<sub>2</sub> surface layer by dense network of thin oxide cracks. These cracks are periodically open and allow repeated exposure of bare nitinol to the electrolyte (in our case to the reflux fluid). The next steps are hydrogen generation at the nitinol/liquid interface, its uptake by the bare nitinol



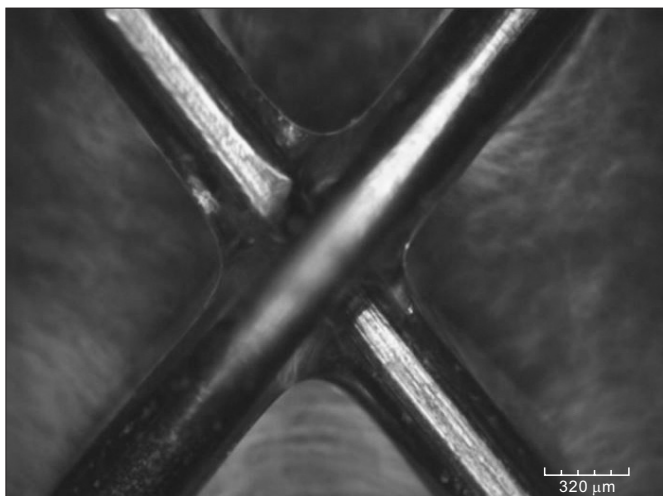
**Fig. 3.** Corrosion craters surrounded by damaged TiO<sub>2</sub> layer in the sample of wire taken from broken Esophageal Stent (ELLA-CS). Picture produced by digital microscope Keyence.



**Fig. 4.** The final stage of damage to the attacked wire. You may see three areas: The area of plastic fracture with "dimples" in the middle of the sample; Thin area of brittle fracture along the sample circumference; The area of brittle fracture at the corrosion crater with cracks. Picture produced by scanning electron microscope (Quanta 3D; FEI).

surface and transport into bulk of the wire. The mechanism is continuing by local loss of the strength of the nitinol matrix due to the hydrogen embrittlement, transfer of the oxide cracks into the embrittled matrix, propagation of selected cracks along the hydrogen traps causing ultimately the brittle fracture of the wire. Fig. 3 and 4 demonstrate starting corrosion of the wire associated with the damage of TiO<sub>2</sub> layer and final damage to the wire through brittle and plastic fractures.

Khara et al<sup>30</sup> published a case report and review of the literature dealing with esophageal stent fracture. The authors reported 8 published cases of complete esophageal self-expandable metallic stents fracture. These were all nitinol stents from different



**Fig. 5.** Image of nitinol wire crossing covered by silicone layer (confocal laser scanning microscope Lext OLS 3000; Olympus)—current nitinol esophageal stent ELLA-CS.



**Fig. 6.** Cross section of the silicone coating that enclosed the wire. Note the regular thickness of the coating round the wire. After being cut, the wire was removed from the sample (confocal laser scanning microscope Lext OLS 3000; Olympus)—current nitinol esophageal stent ELLA-CS.

manufacturers and the timing of stent fracture was anywhere from 8 to 40 weeks after initial stent placement. Half of these cases involved the Esophacoil stent, which is no longer available at the market. Partial nitinol esophageal stent fracture has been reported more commonly (33 patients in 6 references). However, most of these cases did not need any intervention. Only six cases required placement of a new stent through the lumen of the damaged stent. Khara et al<sup>30</sup> referred to diverse factors reported as potential cause of the stent fracture: the use of balloon catheter to dilate nitinol stent immediately after its deployment and laser application leading to thermal overstrain of the stent. However, other authors mention defective stent material or evaluated the fracture as spontaneous.

To prevent similar acute massive corrosion of its nitinol esophageal stents, ELLA-CS developed a method of covering the stent mesh by a silicone layer. Fig. 5 and 6 demonstrate uniform density and integrity of the silicone covering between nitinol stent arms, coats the stent wire mesh even at wire crossings. The images were taken by the laboratory of Institute of Materials Chemistry, Faculty of Chemistry of Brno University of Technology to the order of ELLA-CS.<sup>31</sup>

We do not think the hydrogen embrittlement to be the only cause of nitinol esophageal stent fractures. We believe that the nitinol stent breakage, particular the partial one, is not rare event. In our opinion it occurs occasionally, but the damage to the stent produces little or no clinical symptoms and therefore remains undetected. A lot of questions in this field leaves unanswered.

### Future Materials of GIT Stents

We trust in the future of non-degradable polymer materials, e.g., polyester which currently used in the stent Polyflex, as well biodegradable polymer materials like poly-lactic acid, poly-glycolic acid, poly-caprolactone, poly-dioxanone, poly-lactide-co-glycolide and polydioxanone (Esophageal BD-Stent; ELLA-CS). Lorenzo-Zúñiga et al<sup>32</sup> published the overview of GIT biodegradable stents concluded by conclusion on promising results of polydioxanone stent, however some aspects should be improved, e.g., premature losing of radial force, stent-induced mucosal or parenchymal injury, etc.

However, the way to widely used, standard esophageal biodegradable stent is difficult, and probably, long. This difficulty is caused by production problems such as the necessity of ensuring a high homogeneity of the starting polymer with a low content of impurities, monomer and catalyst residues. The rate of degradation must be suitably adjusted, particularly through proportion of crystalline vs. amorphous component, etc. Ensuring the biocompatibility is very complicated and expensive, especially in relation to degradation products, the speed of their formation, place of their accumulation (tissue, organ), elimination rate, etc.

There are many other problems such as the protection of the wire mesh of the stent against the unwanted degradation both during manufacture and storage. It is necessary to carefully determine the shelf life of the product. Also irreversible plastic deformation during prolonged compression of the stent is also a hard nut to crack.

It seems that the life is, as usual, ahead of regulatory activities because the majority of current regulatory documents is aimed at ensuring stability of implanted materials. A few of guidance documents issued by the U.S. Food and Drug Administration is an exception, e.g., Guidance Document for Testing Biodegradable Polymer Implant Devices.<sup>33</sup>

### Materials for Covering Enteral Stents

Song et al<sup>9</sup> list 12 self-expandable metal and plastic, esophageal stents marketed in the US, Europe, and Asia. Only two of them are presented as uncovered. The most frequently used materials are polyurethane, silicone or permalume silicone.<sup>11</sup> We consider polyurethane the most questionable material because of its predisposition to early degradation. Kim et al<sup>34</sup> questioned biodegradability of polyurethane-covered biliary stent using a flow phantom. They demonstrated that stents exposed to bile remained intact for 2 weeks. Cracks were observed at 4, 6, and 8 weeks. Their size increased gradually. After 8 weeks several large holes in the polyurethane membrane were evident.

## Current options

With respect to our experience we consider silicone of appropriate quality being the best option for GIT stent covering (mechanical properties, resistance to degradation/aging, biocompatibility including possibility of long-term implantation).

## Advantages and disadvantages

The covering provides the stent with resistance against obstruction due to an ingrowth of malignant tissue and facilitates its retrieval. At the same time, however, it produces a series of production problems. Above all, once it is placed on the mesh of the braided stent, the covering changes considerably its properties, particularly mechanical performance (dimensions, expansion force). Such changes further progress over time. It is therefore necessary to subject the stent coating to accelerated aging, determine the changes and correct them by changing the settings of the stent original properties.

## Future materials for GIT stent covering

We are developing a biodegradable polyurethane covering that should cover the biodegradable esophageal polydioxanone stent. We also assume that significant progress could produce drug-releasing coatings, e.g., releasing the drugs with anti-inflammatory effect.

## Conflicts of Interest

Karel Volenec is the director of the company ELLA-CS, Hradec Králové, Czech Republic, that develops, manufactures and sales medical devices, particularly GIT stents. Ivan Pohl works as a scientific consultant in the company ELLA-CS.

## References

- Duerig TW, Pelton AR, Stoeckel D. The use of superelasticity in medicine. Berlin: Metall-Verlag GmbH; 1996, p. 569–74.
- Rudney JD, Ji Z, Larson CJ. The prediction of saliva swallowing frequency in humans from estimates of salivary flow rate and the volume of saliva swallowed. *Arch Oral Biol*. 1995;40:507–12.
- Hsiao V, Keene J, Kiser J, Riccobono M, Taylor-Weiner H, Yu M. Design of improved esophageal stent with testing and model validation (Boston Scientific). 2010 SCOPE Projects. DigitalCommons Website. Available from: [http://digitalcommons.olin.edu/scope\\_2010/5](http://digitalcommons.olin.edu/scope_2010/5). Published 2010. Accessed February 11, 2016.
- Medical Physiology/Gastrointestinal Physiology/Secretions. Wikibooks Website. Available from: [https://en.wikibooks.org/wiki/Medical\\_Physiology/Gastrointestinal\\_Physiology/Secretions](https://en.wikibooks.org/wiki/Medical_Physiology/Gastrointestinal_Physiology/Secretions). Accessed February 16, 2016.
- Orlando RC. Esophageal mucosal defense mechanisms. GI Motility online Website. Available from: <http://www.nature.com/gimo/contents/pt1/full/gimo15.html>. Published 2006. Accessed February 16, 2016.
- Domschke W, Foerster EC, Matek W, Rödl W. Self-expanding mesh stent for esophageal cancer stenosis. *Endoscopy*. 1990;22:134–6.
- Gagneja HD, Singh S, Kaw M. Esophageal stents. In: Franko KL, Putnam JB, editors. Advanced therapy in thoracic surgery. 2nd ed. Hamilton: B.C. Decker Inc.; 2005, p. 520–31.
- Martinez JC, Puc MM, Quiros RM. Esophageal stenting in the setting of malignancy. *ISRN Gastroenterol*. 2011;2011:719575.
- Song HY, Kim JH, Yoon CJ. History of self-expandable metal and self-expandable plastic stent development. In: Kozarek R, Baron T, Song HY, editors. Self-expandable stents in the gastrointestinal tract. New York: Springer; 2013, p. 35–49.
- Laasch HU. Current designs of self-expanding stents. In: Kozarek R, Baron T, Song HY, editors. Self-expandable stents in the gastrointestinal tract. New York: Springer; 2013, p. 51–69.
- Hirides MM, Vleggaar FP, de Beule M, Siersema PD. In vitro evaluation of the radial and axial force of self-expanding esophageal stents. *Endoscopy*. 2013;45:997–1005.
- Duda SH, Wiskirchen J, Tepe G, Bitzer M, Kaulich TW, Stoeckel D, et al. Physical properties of endovascular stents: an experimental comparison. *J Vasc Interv Radiol*. 2000;11:645–54.
- Isayama H, Nakai Y, Toyokawa Y, Togawa O, Gon C, Ito Y, et al. Measurement of radial and axial forces of biliary self-expandable metallic stents. *Gastrointest Endosc*. 2009;70:37–44.
- Varadarajulu S, Banerjee S, Barth B, Desilets D, Kaul V, Kethu S, et al; ASGE Technology Committee. Enteral stents. *Gastrointest Endosc*. 2011;74:455–64.
- Hansen DC. Metal corrosion in the human body: the ultimate bio-corrosion scenario. *Electrochem Soc Interface*. 2008;17:31–4.
- Pilliar RM. Metallic biomaterials. Austenitic stainless steel (ASTM F 138/139, F 1314, F 1586, F 2229). In: Narayan R, editor. Biomedical materials. New York: Springer; 2009, p. 41–81.
- Wienstein AM, Spire WP Jr, Klawitter JJ, Clemow AJT, Edmund OJ. Orthopedic implant retrieval and analysis study. In: Syrett BC, Acharya A, editors. Corrosion and degradation of implant materials. Philadelphia: ASTM Special Technical; 1979, p. 212–26.
- Lamineries MATTHEY SA. Phynox. MATTHEY SA Website. Available from: [http://www.matthey.ch/fileadmin/user\\_upload/downloads/fichetechnique/EN/Phynox\\_C.pdf](http://www.matthey.ch/fileadmin/user_upload/downloads/fichetechnique/EN/Phynox_C.pdf). Published 2013. Accessed February 17, 2016.
- Krams W. Toughness evaluation of a Co-Cr wire used in an endovascular implants. In: Shrivastava S, editor. Medical Device Materials: Proceedings of the Materials & Processes for Medical Devices Conference 2003. Materials Park: ASM International; 2004, p. 308–13.
- Duerig T, Stoeckel D, Johnson D. SMA: smart materials for medical applications. In: Proceedings of SPIE 4763 from European Workshop on Smart Structures in Engineering and Technology; March 12, 2003; Geins, France. doi: 10.1117/12.508666.
- Nitinol specification guidelines. Johnson Matthey Medical Components Website. Available from: <http://jmmmedical.com/resources/120/Nitinol-Specification-Guidelines.html>. Published 2016. Accessed February 22, 2016.
- Robertson SW. On the mechanical properties and microstructure of nitinol for biomedical stent applications [PhD dissertation]. Berkeley: University of California; 2006.
- Stoeckel D. Nitinol medical devices and implants. *Minim Invasive Ther Allied Technol*. 2000;9:81–8.
- Duerig T. Metals as implantable materials. Confluent Medical Technologies Website. Available from: <https://nitinol.com/reference/metals-as-implantable-materials/>. Published 2012. Accessed February 23, 2016.
- International Organization for Standardization (ISO). Biological evaluation of medical devices. Part 1. Evaluation and testing within a risk management process. 4th ed. Geneva: ISO; 2009.
- Ryhänen J. Biocompatibility evaluation of nickel-titanium shape memory metal alloy [academic dissertation]. Oulu: University of Oulu; 1999.
- Sullivan SJL, Dreher ML, Zheng J, Chen L, Madamba D, Miyashiro K, et al. Effects of oxide layer composition and radial compression on nickel release in nitinol stents. *Shap Mem Superelasticity*. 2015;1:319–27.
- Stoeckel D, Bonignore C, Duda S. A survey of stent designs. *Minim Invasive Ther Allied Technol*. 2002;11:137–47.
- Racek J, Stora M, Šittner P, Heller L, Kopeček J, Petrenec M. Monitoring tensile fatigue of superelastic NiTi wire in liquids by electrochemical potential. *Shap Mem Superelasticity*. 2015;1:204–30.
- Khara HS, Diehl DL, Gross SA. Esophageal stent fracture: case report and review of the literature. *World J Gastroenterol*. 2014;20:2715–20.
- ELLA-CS s.r.o. Survey PRL-39-/11-VVV: qualitative and quantitative evaluation of silicone covering of SX-ELLA Stent Danis; 2011, p. 8–22.
- Lorenzo-Zúñiga V, Moreno-de-Vega V, Marin I, Boix J. Biodegradable stents in gastrointestinal endoscopy. *World J Gastroenterol*. 2014;20:2212–7.
- Guidance document for testing biodegradable polymer implant devices. FDA Website. Available from: <http://www.fda.gov/MedicalDevices/DeviceRegulation-andGuidance/GuidanceDocuments/ucm080265.htm>. Published 1996. Accessed February 25, 2016.
- Kim DH, Kang SG, Choi JR, Byun JN, Kim YC, Ahn YM. Evaluation of the biodegradability of polyurethane-covered stent using a flow phantom. *Korean J Radiol*. 2001;2:75–9.