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ScienceDirect

Procedia Structural Integrity 15 (2019) 46–50

Structural Integrity Procedia

www.elsevier.com/locate/procedia

International Conference on Stents: Materials, Mechanics and Manufacturing ICS3M 2019

Is modeling stents still an important issue?

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Abstract

Numerical models of cardiovascular devices have always appeared in literature studies few years after their use in clinical practice. As example, FDA approval of Palmaz-Schatz stent was in 1994, while the first numerical studies on a similar stent model appeared after 1999. The same temporal delay can be observed for degradable stents, transcatheter valves or more recently for devices like the stent retrievers. This observation does not necessarily mean that numerical modeling had not been used in the design of the stents or cardiovascular devices. Companies might have used numerical tools but not published the results. Was the publication activity committed mainly to the academic world? Or was the numerical modeling an exclusive academic activity until a few years ago? Modeling has intrinsic errors, while prototyping looks immune, as it is the natural design process for a company. The real world has always attracted more attention than the virtual world. Models are useful and the gap between the industrial production and numerical tools in the designing of devices is being reduced recently. Nowadays advances in medical images and augmentation of computer power allow to think of building real-time simulations as well as patient-specific models to be used to predict the device behavior; this is a plus that numerical modeling has over the traditional design process of cardiovascular devices. Furthermore, as in the past, the identification of new unknown problems/failures will always make the usage of numerical modeling a useful tool to explain the reasons of failure. The future in modeling stents is envisioned in their use for in silico trials and in the link between biology, engineering, and science.

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2452-3216
10.1016/j.prostr.2019.07.009

Keywords: Mathematical models; Finite element models; Medical devices; Stents.

1. The introduction of stent models

Literature on medical devices generally appeared after a proof-of-concept or the clinical use of the device itself. Errors and drawbacks make the device prone to improvements or to abrupt design changes over the years.

As example, we can consider the mechanical heart valves. They were designed at the beginning of the 60ies and from the cage ball design they changed towards the tilting disk and finally to the bileaflet configuration. This process lasted for more than 20 years. Patents on mechanical heart valves increased during the years far more than the technological advances of the device. Figure 1 reports the trends in technological innovation on an ideal scale between 1 and 110 and the number of US and EU patents with the words “mechanical heart valves” in the patent title over the years. In the first life-phase of a device, the scientific research is predominant and the improvement might be enormous, while in the phase of technological and industrial research the developments are less remarkable. On the contrary, the number of patents, that reflects also the activity to protect the product from competitors, is drastically increased. At the time of development of mechanical heart valves, the computer power was limited and only a few literature papers approached the heart valve arena by means of mathematical models; however, the first modeling papers, again, appeared when the product was already established on the market.

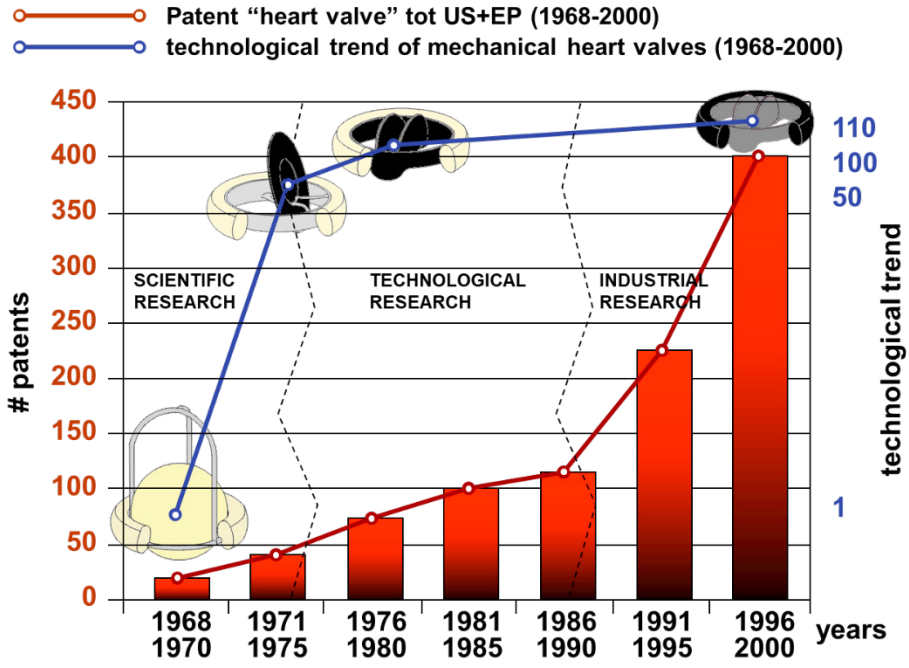

Fig. 1. Numbers of patents over the years with superimposed the innovation trends in mechanical heart valves. The phase of scientific research is followed by the technological and industrial research. In this last phase, the number of patents tends to increase mainly to protect the device from competitors (Courtesy of Riccardo Pietrabissa).

Cardiovascular stents were developed later than mechanical heart valves. The first stent approved by the Food and Drug Administration was dated to 1994. At the beginning of this century, drug eluting stents (DES) appeared as a consequence of the drawbacks of the bare metal stents (BMS), namely in-stent restenosis. When the event of late or very late stent thrombosis became apparent due to the localized drug release, new generation of DES were introduced with new polymeric coatings and new drugs. To overcome the limitations of DES, bioresorbable stents, either in metallic alloys like magnesium or polymeric like poly(l-lactic acid) (PLLA), were introduced and FDA approved the

first polymer biodegradable stent in 2015. Drawbacks were found also for these stents. Despite the fact that stenting is recognized as a secure and good choice, some improvements still look achievable.

Scientific paper with mathematical models began being published in the 90ies and the stent world took advantage of this unlike the mechanical heart valve research. However, again, the delay of the first numerical models appeared, with respect to existence of the stent, revels that modeling was not systematically used in the design process of stent manufacturing. The reader is referred to the reviews available in the literature (Martin and Boyle, 2011; Boyle et al., 2013) to verify that specific models appeared after the real use of the corresponding stents. Looking at the scientific literature, a simple search in the database Web of Science, with the words "finite + stent", gives an idea on how the numerical works on stents are distributed over the years (Fig. 2). The first papers are dated from the late 90ies when the stents were already in clinical use. The first numerical studies on metallic degradable materials are dated 2010 (Wu et al., 2010; Gastaldi et al., 2011; Grogan et al., 2012), but the first clinical trial presented results in 2007 (Erbel et al., 2007). From Fig. 2, it can also be seen that the numerical studies on stents have dramatically increased in the last years; a similar trend to that observed for mechanical heart valves. Mr. "Finite Stent" has a respectful indexing, which will probably increases in the years to come.

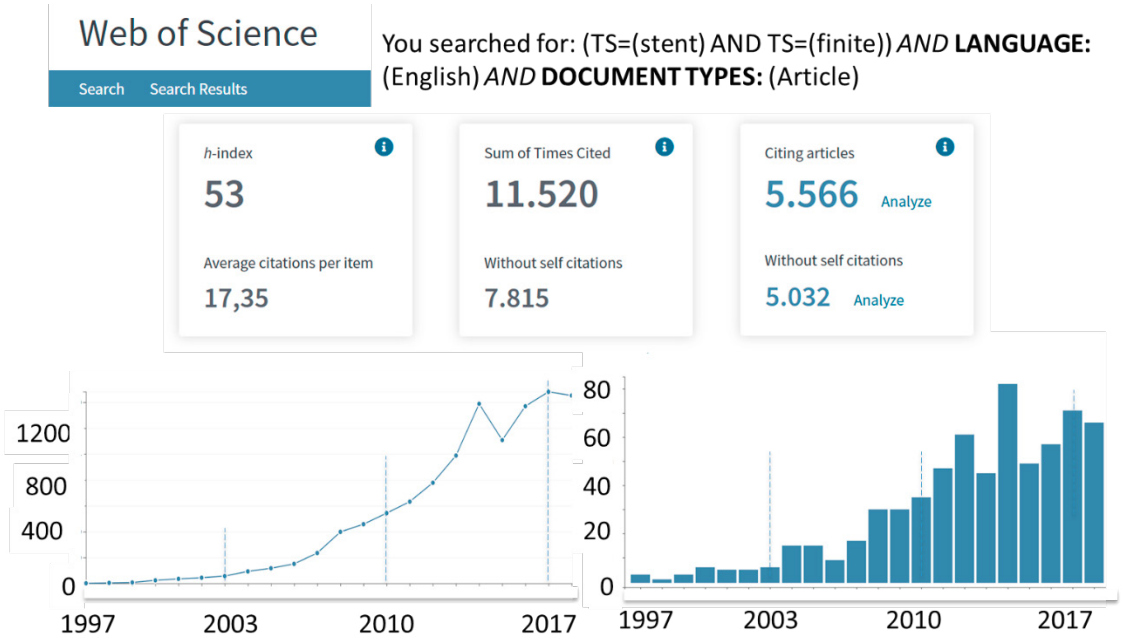

Fig. 2. Results from a search in Web of Science with the words "finite+stent". At the bottom left the citations while at the bottom right the product numbers.

2. Why are stent models still useful

Despite the fact that stent modeling is developed after the design phase of the product, there are still reasons to use stent modeling. Utility of stent modeling, in my view, is manifold, but not exclusively, to: i) design new devices; ii) analyze drawbacks of the devices; iii) predict the device performance in patient-specific anatomies; iv) conduct *in silico* trials.

2.1. Design of new devices

Structural or fluid dynamics analyses are typical of the design process, in many industrial applications. The enormous developments in computer power and numerical techniques make nowadays the use of the numerical

simulation a standard process to optimize, for example, the shape of the medical devices, in particular stents (Wu, 2010). The recent development in the additive manufacturing is another aspect to be considered. If coupled with a proper numerical design process it can reduce time and generate appropriate or personalized stents. The work by Finazzi et al. (2019) presents an example of alternative solution for the treatment of coronary bifurcation with a single stent able to treat at the same time either the main or the side branch. Numerical models might be implemented to optimize the geometry and generate an appropriate device.

2.2. Analysis of existing devices

There are many examples related to this subject. Most of the literature on stent modeling results from scrutinizing the failures of stents. The recent editorial by Edelman and Wang (2017) is a good reading in this field. As example, we can consider the polymeric bioresorbable scaffolds (BRS). When conceived, BRS were considered as an abrupt change in interventional cardiology. However, metal stents still demonstrated a superior success rate than BRS, showing substantially fewer incidences of device failure and clinical events (Kereiakes et al., 2016). The work by Wang et al. (2018) is an example where computational analyses were used to verify the mechanical performance and flaws of the polymeric stents. Structural analyses confirmed the presence of areas with localized stress concentration and microstructural damages responsible for the failure of the polymeric stents.

2.3. Patient-specific models

Usefulness of patient-specific models is ideally manifold: i) to improve diagnosis; ii) to optimize surgical treatments; iii) to predict interventional outcomes either in the immediate and/or in the long-term period; iv) to test the performance of implantable medical devices and to virtually verify the best device choice; v) to run an *in silico* trial; etc. In other words, patient-specific models aim in principle to tailor treatments and improve individual therapies.

2.4. In silico trials

Having a virtual cohort of patients (i.e. patient-specific anatomical models) with a specific disease, it is possible to run an *in silico* or virtual clinical trial. This reflects the definition of simulation experiments to be performed on each virtual patient. Examples are the comparison of an older and new design to prevent possible failure modes, the optimization of the stent frame in different anatomies or subpopulations.

The thorough design and development of these virtual trials will allow to reduce the development, testing cost and time-to-market of new endovascular devices, reduce animal testing and improving the clinical outcomes by a better understanding of the pathologies involved, the behaviour of the devices and their selection or adaptation to the current patient case. Examples of existing projects based on in silico trial are INSIST (In Silico clinical Trials for acute Ischemic Stroke) and InSilc (InSilico Trials for drug-eluting bioabsorbable vascular scaffold (BVS) development and evaluation; https://www.insist-h2020.eu/; https://insilc.eu/). The former aims to study the efficacy of the thrombectomy procedure, which is the removal of a clot from a cerebral artery, over the pharmacological treatment. The latter aims to develop a platform for designing, developing and assessing drug-eluting bioresorbable stents.

3. Conclusions

Technological advancements are always in progress and computer modelling is now more important than in the past. The identification of new unknown problems/failures will always make the usage of numerical modeling a useful tool to explain the reasons of failure. I foresee that the gap between the conceptualization of a new device and its use in clinical practice will be increasingly reduced as a result of the use of numerical models. Furthermore, the continuous and routinely use of clinical images in an engineering environment will increase the familiarity of clinicians with the results - and their interpretation - obtained from the modelling process. As a counterpart, this will also augments the link between biology, engineering and science.

Acknowledgements

The author is part of projects received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777072 and NO.777119.

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