Pre-surgery planning in vascular procedures: an introduction to the RT3S Project

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***Abstract*—RT3S is an EU-funded project in an area of e-health – ICT for Patient Safety. Specifically, RT3S is developing a patient-centred, probabilistic model for peripheral stent fatigue-fracture, integrated within a real-time, computer-aided surgery planning application. RT3S will provide advice on fracture risk for individual combinations of patient anatomy and stent design. Alongside the pre-operational software tool, which is addressed mainly to interventional radiologists, RT3S has also developed a training application that will be of benefit to trainee vascular interventionists and engineers in medical device companies. This paper provides an overview of the work performed during nearly three years of project activities and also addresses the motivation leading to RT3S and the expected impact.**

I. Introduction

CARDIOVASCULAR diseases (CVD), particularly coronary heart disease, stroke transient ischaemic attacks, peripheral arterial disease and the vascular complications of diabetes, are major causes of disability and death in developed countries. In the EU, CVD is the primary cause of death, accounting for 40% of deaths (over 1.9 million each year). The cost to the EU economy is estimated to be almost €196 billion/year; of which, 54% is attributable to the cost of healthcare, 24% to losses in productivity and 22% to the cost of informal care needed by suffers of the disease (European Cardiovascular Disease Statistics 2012).

Coronary artery disease and stroke present a significant problem for the EU economy and healthcare system, so it is not surprising that these areas have had, and continue to receive, significant investment. However, despite accounting for more than 25% of disability-adjusted life-years lost in the EU from CVD (European Cardiovascular Disease Statistics 2008), other vascular pathologies including those of the peripheral arteries have received less attention.

Disease of the peripheral arteries gives rise to major morbidity and mortality. More specifically, disease in the lower limb arteries is a major cause of morbidity. Around 20% of the population over 60 years old have peripheral arterial disease and symptoms can become severe and progressive in about 20% of these, causing major lifestyle limitation through pain during walking (intermittent claudication). Progressive disease can result in critical limb ischaemia, which is the major cause of amputation resulting in approximately 5,000 amputations per year in the UK. Such symptoms are more common in diabetics, smokers and those with known arterial disease elsewhere (Vascular Society of Great Britain and Ireland, 2009).

Although arterial disease is generally declining due to increased primary and secondary prevention measures this is offset, particularly in relation to distal arterial disease, by the ageing population and increasing incidence of diabetes.

There is an increasing trend towards the use of minimally invasive treatments including angioplasty and the use of arterial stents. Thus, endovascular approaches are becoming the preferred approach for the treatment of many vascular occlusive diseases. In vascular stenting, a small wire mesh tube called a *stent* is permanently placed in the newly opened artery or vein to help it remain open.

In general, vascular stenting is safe and feasible with few complications reported. However, there are concerns that, as the use of stents increases and the technology is used to treat lesions of greater complexity, the incidence of serious complications may become more frequent [1].

The RT3S Project, funded under the 7th Framework Programme of the European Commission and started in early 2011, has focused its research on predicting the risk of stent fracture by developing pre-surgery planning software for optimising the combination of patient-stent specific parameters in order to minimise the risk of stent fracture, thereby reducing the incidence of such complications.

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II. THE RT3S RATIONALE

The rate of radiological and clinical failure of endovascular procedures in the peripheral circulation depends upon many factors including the extent and anatomical distribution of disease, patient factors such as smoking, diabetes and activity levels and the symptomatic nature of the disease, in that patients with critical ischaemia have a far worse prognosis. The complication considered to be the most relevant among clinicians is re-occlusion. Typical re-occlusion rates are in the order of 10-20% for low risk patients, while high-risk patients with critical ischaemia often have re-occlusion rates of greater than 50% in the first year [2]. Drug-eluting stents, which slowly release drugs that prevent the formation of fibrosis and of clots, may reduce the incidence of this complication [3] [4] but another concern that may be relevant to re-occlusion is fatigue-failure of the stent itself.

Follow-up of arterial stents shows that stent fracture is a significant problem. Whilst fracture of short or small stents such as renal or coronary stents is relatively infrequent, fatigue-failure may be more significant for longer, more mobile, stents such as those placed in the superficial femoral artery (SFA). Exact rates are difficult to ascertain as patients with stents are rarely subjected to routine follow-up, but stent fracture rates of between 2 and 65% have been reported [5]. In the largest prospective cohort study [6], for the 121 legs treated, the overall stent fracture rate was 37%. These ranged from minor fractures of a single strut to complete separation of stent segments. Overall, structural failure was associated with a much higher rate of restenosis or re-occlusion, with a Kaplan-Meier analysis of primary patency rate at 12 months showing that those with stent fractures were nearly four times more likely to be occluded (occlusion rate 58.9% versus 15.7%, $p<0.0001$).

Although stent fracture may be asymptomatic, evidence suggests that it is often associated with vessel occlusion [6] [7]. Other reports indicate associations with more severe complications including vessel perforation and haemorrhage with subsequent deep vein thrombosis [8] and pseudo-aneurysm formation [9].

Re-stenosis or re-occlusion of peripheral vessels carries significant morbidity. Re-treatment by endovascular means may be impossible; in particular, where there is a residual fractured stent, bypass carries significant morbidity and may not always be feasible. There is thus a risk of severe recurrent symptoms or limb loss [10].

Current evidence regarding the rates and complications of stent fracture may be an underestimate as conventional teaching is to avoid the use of stents where there is thought to be a high risk of fracture [11]. It is thus usual to avoid the implantation of stents in areas of the femoral artery and the popliteal artery where repeated flexing can be expected. The challenges presented by femoral stenting have been recognised by regulatory agencies. In recent interview (Endovascular Today, 2007), the FDA disclosed that manufacturers of stents intended for use in the SFA face special scrutiny when seeking regulatory approval. The article stated that '... the testing requirements may change...' with '.... improvements in our understanding of the appropriate characteristics for SFA stents....'

Fatigue is a typical failure process of metallic materials subjected to cyclic loading. In many cases, a metallic component repeatedly exposed to a load lower than that required to break the component develops, over time, fractures that result from the formation and progressive accumulation of micro-damage induced by cyclic loading [12]. Placement of the stent in close proximity to leg muscles induces cyclic bending loads during daily activities such as walking. The risk of fatigue fracture is increased by the presence of residual stresses, complex geometries, and when the metal in use has a specific sensitivity to fatigue. As discussed below, in the case of peripheral stents, all of these co-factors may apply.

For most cases, the process of stent expansion inside the vessel during deployment induces significant residual stresses. Stent geometries are typically complex and, in the deployed configuration, the situation can only be worsened by the torsion present in the host vessel. In stented infra-inguinal arteries biomechanical forces such as segmental bending, compression and kinking can cause repetitive trauma to both the stent and the artery wall and may lead to arterial disruption and restenosis as well as stent fatigue fracture [13]. In a recent cadaveric study of arteries in the lower extremities, stent deformations were quantified during imposed movements [14]. The ranges of deformations measured (in axial compression and bending) were then used as input parameters for long-term *in vitro* fatigue testing of commercially available, self-expanding Nitinol stents. The results of this study suggest that stent fatigue behaviour is highly dependent upon both the type of deformation applied and the stent design.

When patient-specific and surgery-specific factors are known, by using sophisticated non-linear finite element models, it is possible to compute the stresses and strains induced by cyclic loading, and from these calculate the probability of a fatigue fracture appearing over time. Knowledge of the fatigue properties of the stent material is also required. Recently, the fatigue properties of Nitinol were measured in terms of strain-life data and strain-based constant-life diagrams for a commercially available self-expanding stent (Cordis SMART Control®) and used to calculate fatigue safety factors and predict stent fatigue resistance [15].

Data for patient-specific and surgery-specific factors emerge only during a careful planning of the intervention. In treatment planning, decisions on the use and positioning of stents are often not straightforward as there may be multiple levels of stenosis or occlusion with varying relationships to vessel anatomy. Thus, the treatment to be used and the associated risk of stent fracture should be analysed together.

The ability to compute the risk of stent fatigue fractures in different configurations, for example using multiple short stents or longer stents, or combining stenting of some areas with balloon angioplasty of others, will be invaluable to the clinician in planning patient-specific treatments.

III. The RT3S Approach

Figure 1 summarises the RT3S approach and shows the different components.

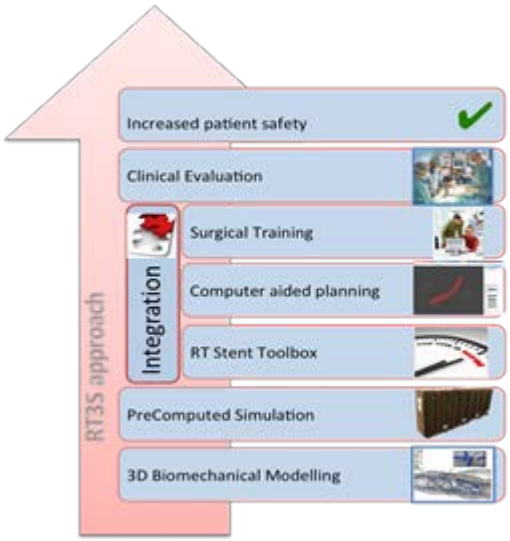

Fig. 1. Scheme of the RT3S approach.

In order to be clinically useful for predicting the patient-specific surgery-specific risk of stent fracture, the prediction should be made in real time, whilst the surgeon is planning the procedure. Thus the software should enable the surgeon to simulate the effects of different parameters (stent type, positioning, a single long stent or multiple short stents, etc.), and receive warnings of above-threshold risk, with a latency time of well below one second. The simulation must be reasonably interactive, independent of whether the image data is stored on file or obtained as a live feed from the patient. Even if we consider the less ambitious objective of a quasi real-time system, where the surgeon carries out the planning and then asks the computer the risk associated with that configuration, the run time should not be much longer than 10 seconds.

State-of-the-art, 3D stent models [16] [17] [18] based on the use of the finite element model typically have an execution time of the order of the day. This is 86,000 times slower than that necessary for quasi-real-time simulation.

Among the different strategies for speeding-up predictive models, RT3S has utilised an approach based on pre-computed solutions. In RT3S, we decided to simplify the problem, reducing and parameterising the model, and to pre-compute a large number of possible solutions. These parametric simulations have been run on the HPC infrastructure available at CINECA supercomputing centre, where an IBM PLX (iDataPlex DX360M3) supercomputer equipped with 3288 cores with a total of over 10 Tb of RAM is being used.

RT3S includes AimaSimul, a software application for the preoperative planning of stenting in peripheral arteries, and the RT-STENT toolbox. The latter is based on the outputs from the response surfaces and on patient-specific images from AimaSimul, and allows the visualisation of the risk of fatigue fracture in the stent selected.

In parallel with the activities described above, a training tool for junior surgeons has been developed to provide the system with a formative environment that integrates the RT-Stent Tool Box and AimaSimul. A number of modules allow the students to review procedures and devices, to analyse patient–specific cases, and to learn how to make better decisions before undertaking practical cases.

IV. Results Achieved and Impact

A. *RT3S results*

RT3S is now in its final year, and most of the expected targets have been achieved. These are summarised below.

- Fatigue Modelling of Stent-Artery Interaction has been completed. It delivered a number of 3D finite element models of the confined expansion of peripheral stents under vessel pulsation and deformation, identified critical areas for fatigue stent fracture and defined a fatigue safety factor for different stent designs and deployment conditions. Validation of the numerical results of fatigue analyses against *in vitro* data has been successfully performed. [19], [20]
- Generation of the Probabilistic Response Model has been performed, creating and enhancing the response surface technologies and their implementation for angioplasty and stent deployment. [19]
- The development of AimaSimul is now at the beta1 version. This version is now under validation by the clinicians. Also the first version of the RT-STENT Toolbox has been released and the training application has been finalised. [21], [22]
- All the SW components are now being tested for interoperability and integrated into an overall RT3S system suitable for deployment in a clinical environment.
- In parallel a Clinical Assessment of Efficacy is being performed: an initial evaluation report on AimaSimul has been released and the user validation activities will continue until the end of the project. [21]
- An activity has been conducted on Health-Economic Analysis, to investigate the likely impact and support the exploitation of the results. A report on micro-economic analysis has been released and a second report on macro-economics is under preparation. [23]

Details on the RT3S results and all the public material released by the project are available via the project web-site www.rt3s.eu.

B. The RT3S benefits

The use of RT3S will have multiple benefits, encompassing several key social and economic aspects of life. Among direct benefits, the following are targeted:

Improvement of Patient Safety, Health and Quality of Life: The RT3S tool-set will minimise the hospitalisation period both before and after stent placement, providing a mechanism for efficient, targeted intervention and patient-specific planning.

Improvement of Healthcare Service Delivery: Surgeons and interventional radiologists will be able to examine various stenting solutions prior to, or even during, the stent placement procedure to minimise the risk of stent fracture. **Improvement of specialised clinical skills**: The RT3S training application will improve the ability of the surgeon and interventional cardiologist to select the most appropriate stent and the optimal placement during the intervention.

Indirect benefits that RT3S will bring include the following:

Improvement of stent production market quality: The wide-scale use of the RT3S system, will allow to identify common procedural factors that may be associated with stent fractures.

Reduction of healthcare costs: In the long-term, use of RT3S is expected to minimise the number of patient re-hospitalisations and secondary interventions required.

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