Patient-specific computer simulation for transcatheter cardiac interventions: what a clinician needs to know

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ABSTRACT
Patient-specific computer simulation consists of the assessment of the interaction of the device with the host based on the integration of the detailed geometric and biomechanical properties of the device and host. Hence, it allows the prediction of valve performance (efficacy) and complications (safety) and may consequently help the physician to select the valve/device that best fits the individual patient, thereby improving outcome. There is currently little awareness and information in clinical medicine on patient-specific computer simulation. In this paper, we describe the technical background and a number of illustrations to illustrate how patient-specific computer simulation may be used for catheter-based treatment planning of acquired heart disease.

INTRODUCTION
Medicine is facing a continuous release of innovative and more powerful diagnostic and therapeutic options while the demand of healthcare authorities is to reduce expenditures.1 In addition, there is a growing call to move to patient-specific or patient-centred medicine in order to enhance immediate and long-term efficacy.2 The question is how to cope with this quandary of increasing opportunities, challenges and responsibilities. The answer is multifactorial and depends on the perspective of the stakeholder and his/her responsibility including the patient.

When it comes to the treatment of acquired valvular heart disease and other cardiac structures such as the left atrial appendage (LAA), the rapidly evolving field of minimally invasive or catheter-based treatment combined with the development of software that allows the selection of the device that best fits the individual patients with a specific acquired cardiac disease is exemplary.1

This in particular holds for transcatheter aortic valve implantation (TAVI) where randomised controlled trials have shown equivalent safety and efficacy in comparison with surgical valve replacement (SAVR) and even superiority in case of transseptal TAVI.1 4 5 In combination with its technical background and pathophysiological perspective, as in mitral-and tricuspid pathology, or from a pure anatomical perspective due to high inter-patient variability, as in the LAA.

For that purpose, patient-specific computer simulation may help and further improve the results of catheter-based treatment of acquired cardiac disease.6 In current practice the gold standard assessment for many device therapies involves the measurement of a number of parameters from a preprocedural cardiac CT scans. These are then used to determine the optimal device, its size and level of procedural difficulty. The main restriction to this philosophy of geometric sizing to guide procedures is that it fails to account for the interaction between the device and host that invariably occurs during device deployment. This introduces a significant risk of only realising complications only once they have occurred. In contrast, patient-specific computer simulation involves the application of bioengineering to the preprocedural CT scan to enable the virtual implantation (simulation) of a valve/device using finite element modelling. The principal benefit of this approach is that the geometric and mechanical properties of valve and host are incorporated enabling an assessment of the valve/device geometry in relation to the recipient anatomy. This ultimately benefits the operator and the patient by providing a better prediction as to how transcatheter heart valves and other devices are likely to behave before the actual procedure is undertaken.

The purpose of this paper is to describe the technical background of patient-specific computer simulation accompanied by a number of illustrations with the objective of creating awareness of how patient-specific computer simulation may be used in the planning of treatment of complex structural heart disease. The paper focuses on TAVI as we started the programme with TAVI and have most experience with. It goes without saying that exactly the same principles hold for other
catheter-based interventions of the heart such as of the mitral valve and LAA.

**How does it work and what are the pitfalls**

As mentioned, patient-specific computer simulation consists of the assessment of the interaction of the device with the host. For that purpose, the detailed quantitative and morphological geometry of both the patient’s target anatomy (eg, aorta, mitral, LAA) and their mechanical properties are required. The patient’s anatomy is derived from regular imaging modalities such as Multi Slice Computed Tomography (MSCT) or real time 3D echo or MRI. Although these imaging modalities are readily available in clinical practice, the key prerequisite is that they have a high image quality for the proper generation of a 3D model that meets the patient’s reality. This is of particular importance as the 3D model is used for numerical modelling and the generation of a patient-specific finite element model. The same holds for the device, either using detailed information available from the device manufacturer or microCT scanning that has higher spatial and temporal resolution than CT used in clinical practice.

The mechanical properties of device materials or tissue are typically characterised by stress-strain analysis. Stress, defined as force per unit area, can be considered as the intensity of the internal forces within a material. As a result of stress, the device or tissue undergoes a geometric deformation from its natural or reference state and strain is defined as the deformation per unit length. Stress-strain relationship is determined in vitro when it comes to the device materials, for example, using uniaxial tensile testing. Depending on their composition, they can display very different stress-strain curves that can be classified as either elastic or superelastic (eg, certain nitinol compositions) or elastoplastic such as the composition of the frames of balloon-expandable transcatheter heart valves. For the host tissue, the data of ex-vivo animal and human necropsy analyses can be used to evaluate tissue properties or alternatively back-calculation techniques based on in-vivo medical imaging can be employed.

These geometric and mechanical properties are then translated into mathematical equations that provide the basis of the finite element modelling, which delivers the outcome of interest such as the prediction of frame geometry of the device once implanted, degree of apposition and residual leakage and/or contact pressure on host recipient tissue. This is quite an engineering endeavour since mechanical tissue properties are non-linear and anisotropic (ie, depending on loading direction) and differs from patient to patient. Furthermore, the construction of algorithms that serve a specific purpose (ie, prediction of outcome measures) needs to apply realistic boundary conditions. These are loads, displacements and constraints that determine how the 3D objects in the simulation deform and interact with each other, and with the surrounding environment that is not included in the simulation. For instance, TAVI requires the implantation of a bioprosthetic valve into the base of the aortic root, and boundary conditions will determine how and where the device will deploy within the anatomy. The same considerations hold for the development of simulation algorithms for catheter-based valve treatment of calcified mitral valve disease and become even more complex in the development of algorithms for simulation of mitral leaflet function before and after case repair (requiring leaflet pressurisation and an annular deformation).

Complex algorithms in principal approach clinical reality more than simple ones but come at the price of simulation duration that is inconvenient for clinical practice. Therefore, simpler algorithms capable of delivery at short notice (eg, TAVI 3 hours) are preferred for clinical application. These can be used for further continuous improvement and refinement by comparing the discrepancies between the predicted (ie, model) and observed (ie, MSCT postintervention) findings (ie, model training). The larger the library of data, the more refined the model becomes.
Figure 3  Finite element analysis and computational fluid dynamics assessing the location and severity of paravalvular leakage. Box plot analysis revealed that patient-specific computer simulation can discern patients with none-to-mild and more than mild paravalvular leakage. For further details, please see Ref. 21.

Figure 4  Contact pressure and pressure area in the aortic root. Predicted contact pressure and pressure area in the LVOT where the conduction system is located (square with black border below non-coronary and right coronary sinus) after TAVI. Panel left: low contact pressure and small area of contact in a patient who did not develop a new conduction abnormality. Right: opposite situation. For further details, please see Ref. 22. LOVT, left ventricular outflow tract; TAVI, transcatheter aortic valve implantation.

Clinical validation
Three multicentre observational studies have been conducted for the validation of a CE-marked patient-specific computer simulation system (TAVIguide).9 10 21 22 The first assessed the accuracy of the software to predict frame geometry and aortic leaflet displacement after valve implantation.10 Quantitative data of axial frame morphology (Minimal diameter (Dmin), Maximal diameter (Dmax), cross-sectional area and perimeter) of 33 patients treated with the Medtronic CoreValve System (MCS) and of 6 patients treated with the Edwards Sapien XT (ESV) obtained by MSCT post-TAVI (observed frame morphology & dimensions) were compared with those obtained from the computer model (predicted frame morphology & dimensions) (figure 1). Similarly, displacement of the aortic leaflet calcifications, quantified by the distance between the coronary ostia and the closest calcium nodule, was compared between MSCT and model (figure 2).

During the simulation, all steps of the clinical TAVI procedure were respected including predilatation, valve size, depth of implantation and postdilatation if applied. The depth of implantation was matched with the depth of implantation during actual valve implantation by overlaying the 3D aortic root model derived from the software after simulation of valve implantation with the one derived from MSCT post-TAVI that was used as reference. Simulations were repeated until correct alignment was obtained that was used for the validation analysis. For the predilatation and (if applicable) postdilatation, the same size of the balloon that was used during the in-vivo implantation was used during the computer simulation.

Bland Altman analysis revealed a strong correlation between the observed (MSCT) and predicted frame dimensions although small differences were detected for, for example, Dmin at
the inflow (mean±SD, MSCT vs model: 21.6±2.4 mm vs 22.0±2.4 mm; difference±SD: −0.4±1.3 mm, p<0.05) and Dmax (mean±SD, 25.6±2.7 mm vs 26.2±2.7 mm; difference±SD: −0.6±1.0 mm, p<0.01). The observed and predicted distances from coronary to calcium were highly correlated for the left and right coronary ostia (R²=0.67 and R²=0.71, respectively, p<0.001). This distance was slightly overestimated by the model for both coronary arteries. Dedicated software, thus, allows accurate prediction of frame morphology and calcium displacement after valve implantation, which may help to improve outcome.

The second study focused on the accuracy of the model for the prediction of paravalvular leakage (PVL) after TAVI.21 Similar to the first validation study, preoperative MSCT was used to generate 3D models of the aortic root of 60 patients treated with a MCS valve. Implantation of virtual valve models was simulated using finite element computer modelling. Blood flow domains including PVL channels were derived from predicted frame and aortic root deformation (figure 3). Computational fluid dynamics was used to model blood flow during diastole to assess PVL. Predicted and observed PVL (angiography, echocardiography) were compared. Moderate-severe PVL was seen in 15 patients (25%) by angiography (Sellers AR≥2) and in 9 (15%) by echocardiography (circumference 10–29 and ≥30%, VARC-2). Box plot analysis revealed good agreement between observed and predicted PVL. ROC analysis indicated 16.25 (reference angiography) and 16.0 mL/s (reference echocardiography) as cut-off values that best differentiated patients with none-to-mild and moderate-to-severe PVL. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy were 0.80, 0.80, 0.57, 0.92 and 0.80, respectively (reference angiography) and were 0.72, 0.78, 0.35, 0.94 and 0.73 (reference echocardiography).

The third study assessed whether the software can predict the occurrence of conduction abnormalities after TAVI based on the analysis of contact pressure and contact pressure area in a predefined region below the non-coronary and right coronary cusp.22 Finite-element computer simulations were performed

Figure 5 Effect of valve size on contact pressure and paravalvular leakage. Representative example showing contact pressure and paravalvular leakage predicted using computer simulations after implantation of Lotus valve of two different sizes virtually implanted in the same patient. The region of the atrioventricular conduction system is represented in white.

Figure 6 Effect of valve type on paravalvular leakage. A CoreValve 26 and an Evolut Pro 26 mm were simulated in the same patient. Not unexpectedly, the Evolut Pro was associated with a lower paravalvular leakage (4.9 vs 10.2 mL/s).
Figure 7  Computer simulation for the planning of catheter-based valve implantation in patients with mitral valve disease (TMVR). Computer simulation in a patient with mitral valve dysfunction due to MAC. A 29 mm Edwards valve implantation was simulated at two different depths of implantation. A high implantation was associated with a larger neo-LVOT area in comparison to a low implantation. MAC, mitral annular calcification.
in 112 patients who had undergone Transcatheter Aortic Valve Replacement (TAVR) with the self-expanding CoreValve/Evolut R valve (figure 4). Sixty-two patients (35%) developed a new left bundle branch block or a high degree atrioventricular (AV) block after TAVR. Maximum contact pressure and contact pressure index (median [IQR]) were significantly higher in patients with compared with those without new conduction abnormalities (0.47 MPa [0.40–0.67] and 33% [22–46], respectively, versus 0.23 MPa [0.01–0.43] and 13% [0–28]). By multivariate regression analysis only maximum contact pressure (OR: 1.28, CI 1.0 to 1.6, p=0.02) and contact pressure index (OR: 1.54, CI 1.1 to 2.1, p=0.01) were identified as independent predictors for conduction abnormalities, but not implantation depth. In other words, patient-specific computer simulation revealed that maximum contact pressure and contact pressure index are both associated with new conduction abnormalities after CoreValve/Evolut R implantation and can predict which patient will have conduction abnormalities.

Clinical examples

Figures 5–8 illustrate the versatility of the CE-approved TAVgL grade simulation model. While clinical experience and improved device technology have substantially contributed to improved clinical outcomes, the selection of the type and size of valve that best fits the individual patient may be even more important when moving to the low-risk patient or the so-called surgical candidate. As PVL has been addressed to a great extent, the occurrence of conduction abnormalities is the next major hurdle to overcome. The simulation model also allows preoperative assessment of the effects of alternative valve type or size at different implantation depths on contact pressure and PVL. As illustrated in figures 7 and 8, patient-specific computer simulation may be used in the planning of Transcatheter Mitral valve Replacement and for the transcatheter occlusion of the LAA.

Figure 8  Computer simulation for the planning of LAA occlusion. Implantation of a 22 mm Amplatz LAA occluder was simulated in a patient with atrial fibrillation and contraindication for oral anticoagulant therapy at two different positions within the LAA (left panel). The middle panel reflects the apposition of the device, quantified by the colour bar on the right showing the distance (mm) of the device to the surrounding LAA tissue. LAA, left atrial appendage.

DISCUSSION

The main reason why Europe at the turn of the 16th century—that was in comparison to the empires in the Middle-East and Far East an economic, cultural and scientific backwater—was able to dominate the world for more than 500 years was a change in thought.26 One started to realise and accept that—at variance with the long-standing belief in (imposed) dogmas—one knows very little, which in turn lead to a vast enterprise of exploration and investigation. A recent example of such a transition in thinking is catheter-based valve treatment.27 28 Similar to the 1500s, the proposal was initially received with considerable pessimism and even rejection. Yet, its concept and principles were so sound, that its equivalence (and possible superiority) in comparison to surgical treatment demonstrated by the landmark RCT should not have been surprising.3 4 Further innovation and experience substantially contributed to enhanced safety and efficacy and consequently to an expansion of indication (eg, intermediate risk) and subsequently treatment of the mitral valve and LAA.3 4 6–8

In this paper, we present the concept of patient-specific computer simulation and its limitations with the objective of informing the reader how such an innovative tool may help to improve outcomes of catheter-based treatment of structural heart disease (treatment planning). This field is rapidly evolving in both clinical and technical spheres—specifically, there is an incessant refinement of existing device technologies and continuous development of novel devices designed to treat a wider spectrum of cardiac pathologies. The plethora of possibilities confront the physician with the responsibility to select the device that best fits the individual patient. While outcome strongly relates to experience, it also depends on independent device-host interactions.29 30 As the range of devices and therapeutic options increase, the impact of such an interaction on outcome is likely to increase. This may be particularly relevant for the AV cardiac valves and structures such as the LAA. The AV valves have complex anatomy and function with multifaceted and heterogeneous pathophysiology. The LAA is easier to define with MSCT but is a fragile thin walled structure with high interpatient anatomic variability.

Similar to many innovations in cardiovascular medicine, novel techniques and technologies are available for clinical use but without proof of additional clinical or financial value. To address this limitation, we have added a number of case studies to illuminate the potential value of patient-specific computer simulation. As discussed, we believe that its role and value will predominantly be for the planning of catheter-based treatment of AV valves and structures such as the LAA although it still may prove to be helpful in, for instance, patients with bicuspid and other forms of aortic stenosis.

Looking ahead, the technology is also expected to play an important role in the design and development phase of novel devices—allowing the valve manufacturer to test the design concept in pathophysiological settings derived from MSCT, MRI or real time 3D echocardiography of patients with cardiac disease. Using this approach, the traditional iterative development cycle involving bench testing and animal experiments could be significantly shortened, allowing rapid generation and testing of virtual prototypes. Furthermore, moving from animal models to human trials is always associated with substantial risk since animal models often fail to reflect human pathology. Evaluation of device prototypes in a cohort of virtual human anatomies in the early stages of device development will enable the performance of virtual clinical trials, thereby significantly reducing the risks associated with first-in-human studies.

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