Patient-specific computer modeling to predict aortic regurgitation after transcatheter aortic valve replacement

Patient-specific computer modeling to predict aortic regurgitation after Transcatheter Aortic Valve Implantation

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Abstract

Objectives: To describe a patient-specific computer model that predicts aortic regurgitation (AR) after Transcatheter Aortic Valve Implantation (TAVI).

Background: Complications after TAVI may occur despite optimal operator performance . Computer simulations predicting device-host interaction and resulting AR may help to understand and anticipate such complications, thereby, improving outcome.

Methods: Pre-operative MSCT was used to generate 3Dmodels of the aortic root of 60 patients who received a Medtronic CoreValve System. Implantation of virtual valve models was simulated using finite element computer modeling. Blood flow domains including paravalvular leak channels were derived from predicted frame and aortic root deformation. Computational fluid dynamics was used to model blood flow during diastole to assess AR. Predicted and observed AR (angiography, echography) were compared.

Results: Moderate-severe AR was seen in 15 patients (25%) by angiography (Sellers AR≥2) and in 9 (15%) by echocardiography (circumference 10-29 & ≥30%, VARC-2). Box plot analysis revealed good agreement between observed and predicted AR. ROC analysis indicated 16.25 (reference angiography) and 16.0 ml/sec (reference echocardiography) as cut-off values that best differentiated patients with none-to-mild and moderate-to-severe AR. Sensitivity, specificity, positive predictive value , negative predictive value , accuracy were 0.80, 0.80, 0.57, 0.92 and 0.80, respectively (reference angiography) and was 0.72, 0.78, 0.35, 0.94 and 0.73 (reference echocardiography).

Conclusions: Computer simulation that integrates MSCT-derived patient-specific anatomy and the geometric and mechanical properties of the valve accurately predicts AR severity. This may improve outcome by helping the physician to select the type and size of valve that best fits the individual patient.

Introduction

Transcatheter aortic valve implantation (TAVI) is increasingly used to treat selected patients with aortic stenosis and has shown to improve survival and quality of life [1-5]. Yet, TAVI is associated with a number of complications that remain to be solved [6]. One of these is aortic regurgitation (AR) that frequently occurs and has been reported to be associated with increased mortality [7-11]. AR can be explained by a combination of patient- procedure- and operator related variables such as the amount and distribution of aortic root calcification, annulus dimensions, sizing and depth of implantation. Due to the large variability of the aortic root anatomy, the occurrence and severity of AR is hard to predict, indicating the need of tools that help the physician to select the type and size of valve that best fits the individual patient in addition to the optimal landing zone.

Computer simulation of a TAVI procedure that is based upon the integration of the patient-specific anatomy, the physical and (bio)mechanical properties of the valve and recipient anatomy may serve this goal [12-15]. In this paper we describe such a model for AR prediction that was validated in a series of 60 patients who underwent TAVI with the Medtronic CoreValve Revalving System (MCS).

Methods

Study population and MSCT

Sixty patients were studied who received a 26/29mm MCS and who underwent MSCT pre-TAVI for sizing using manufacturer's recommendations. Details of MSCT have been described before [16]. Briefly, MSCT scanning parameters were: 2 x detector collimation of 64 x 0.6 mm with a z-axis flying focal spot, rotation time 285 ms, tube voltage 120 kV. A spiral scan mode with

retrospective ECG triggering was used. Each tube provided 412 mAs/rot (625 mA), and full X-ray tube current (100%) was given during the 14 to 46% of the R-R-interval. End systolic datasets were reconstructed using a single-segmental reconstruction algorithm: slice thickness 1.5 mm; increment 0.4 mm; medium-to-smooth convolution kernel (B26f) resulting in a spatial resolution of 0.6-0.7 mm in-plane and 0.4-0.5 mm through-plane and a temporal resolution of 72ms.

Computer modelling

First, finite element computer models of the 26/29mm MCS were developed based on a detailed geometric evaluation of a] the frame using microscopic measurements and micro-computed tomography (resolution of 30 micron) and b] the mechanical properties of Nitinol of the herein used MCS valves using in-vitro radial compression tests at body temperature. During these tests, the frame diameter was reduced over the full frame length using a segmental compression mechanism, while the radial force was recorded (RX650, Machine Solutions, Flagstaff, US).

Next, patient-specific three-dimensional (3D) computer models of the aortic root, including the (calcified) native leaflets were constructed from clinical pre-TAVI MSCT images using image segmentation techniques (Mimics software v16.0, Materialise, Leuven, Belgium). Varying mechanical properties were then automatically assigned to different tissue regions. The model parameters related to the tissue behavior were calibrated using the MSCT datasets of 14 patients who also underwent MSCT post TAVI (i.e. back calculation).

Finite element computer simulations were then performed during which the computer generated valve frames were implanted into the patient's specific anatomy resulting in a prediction of frame and aortic root deformations. All simulations were performed using the Abaqus/Explicit v6.12 finite element solver (Dassault Systèmes, Paris, France). In each computer-

simulated implantation, all steps of the clinical or in-vivo implantation were respected consisting of predilatation, valve size selection, depth of implantation and postdilatation if applied. The depth of implantation was matched with the actual depth of implantation derived from contrast angiography performed immediately after TAVI. Simulations were repeated until the same implantation depth was obtained . For the pre- and (if applicable) post-dilatation, the same size of the balloon that was used during the in-vivo implantation was used during the computer simulation.

In a final step, the blood flow domain including the paravalvular leakage channels (if any) was derived from the predicted frame and aortic root deformation. Computational fluid dynamics was used to model blood flow during diastole and to assess the severity of aortic regurgitation after TAVI. For this purpose, a fixed pressure difference of 32mmHg was imposed from the ascending aorta to the left ventricle. The actual pressure difference post-TAVI was intentionally not used as the aim is to validate a model predicting AR based on pre-operative MSCT only (i.e. when the pressure post-TAVI is unknown). The value of 32mmHg is an average obtained from a large group of patients from our center. The resulting flow, expressed in ml/s, was compared with the clinically assessed AR. In order to illustrate the modelling of AR, one case with minimal AR and one with more severe AR are shown in Figure. 1.

In addition to the validation analysis, the potential clinical role of the model predicting AR was investigated by virtually implanting two different valve sizes, or by modelling different implantation depths for a subset of patients.

Assessment of aortic regurgitation.

Similar to the US CoreValve High Risk and the CHOICE randomized clinical studies, contrast angiography and Doppler echocardiography were used for the assessment of AR

immediately after TAVI and at discharge [5,17]. Analogous to the CHOICE study, AR severity by contrast angiography was defined by visual estimation of the contrast density in the left ventricle using the Sellers classification (0= none/trace, 1= mild, 2=moderate, 3=severe. The latter comprised grades 3 & 4 according to Sellers) [17,18]. For that purpose, an angiography protocol was used consisting of the injection of 20 ml non-diluted Iodixanol (Visipaque™) at a flow rate of 20 ml/sec via a 6 Fr pigtail that was positioned above the bioprosthetic leaflets using the optimal angiographic projection that was also used for valve implantation. Cineruns were recorded at a speed of 30 frames/sec. Two observers independently from one another scored the angiograms. In case of discrepancy, consensus was reached by consulting a senior cardiologist. The intra- and interobserver variability for the assessment of AR post TAVI according to the Sellers classification were κ 0.70 and 0.78 respectively.

Doppler echocardiography was performed before discharge. Akin the CHOICE and US Corevalve RCT, AR severity was defined by the circumferential extent of the Doppler signal at the inflow of the MCS frame in the parasternal short axis view (SAX) but using the VARC-2 instead of VARC-1 criteria [5,19]. Echocardiography was available in 56 out of the 60 patients. Distinction was made between none (grade 0), mild (<10%, grade 1), moderate (10-29%, grade 2) and severe (≥30%, grade 3) AR.

Statistical analysis

Categorical variables are presented as frequencies & percentages and continuous variables as mean ± SD or median [25th to 75th quartile] if not normally distributed (Shapiro-Wilk test). Data was compared using a 2-sided unpaired t test or a Mann-Whitney test, as appropriate. When comparing more than 2 groups, the Kruskal-Wallis test was used.

For the purpose of the study *(i.e prediction of AR by model)* distinction was made between

patients with none-to-mild AR and moderate-to-severe AR. Diagnostic performance of the model was measured on a per-patient basis and defined by sensitivity, specificity, positive and predictive value (PPV, NPV) and accuracy. Box plot figures were constructed to assess the agreement between the observed *(categorical classification of AR using grades 0,1,2,3)* and predicted AR *(continuous variable, ml/sec).* In addition, Receiver-Operating Curve (ROC) analysis was performed for the definition of the best cut-off value by maximizing the sum of sensitivity and specificity. IBM SPSS 21.0 (IBM Corporation, Armonk, New York, USA) was used. Statistical significance was defined as a two-tailed $p<0.05$.

Results

The clinical characteristics of the patients are shown in **Table 1.** All patients underwent transfemoral TAVI *(26 mm valve in 19 patients, 29 mm valve in 41 patients)* preceded by balloon valvuloplasty in all except 2 patients *(20 mm balloon in 11 patients, 22 mm balloon in 27 patients, 23 mm balloon in 19 patients, and 25 mm balloon 1 patient).* Three out of the 60 patients underwent balloon dilatation after TAVI *(24 mm balloon after 26 mm MCS in 1 patient, 25 and 26 mm balloon after 29 mm MCS in 2 patients)*. The depth of implantation (median, IQR) at the non- and left coronary sinus was 8 mm (6-10 mm) and 10 mm (7-11 mm) respectively.

Comparison of observed (angiography and echocardiography) and predicted AR (model)

Moderate-severe AR (Sellers AR≥2) post-TAVI was seen in 15 patients (25%) by angiography. The agreement between the observed (i.e. Sellers, angiography) and predicted AR (i.e. ml/sec, model) is shown in Figure 2 (box plot and Table 2). ROC analysis revealed that 16.25 ml/sec is the cut-off value that best differentiated patients with none-to-mild and moderate-to-

severe AR. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy were 0.80, 0.80, 0.57, 0.92 and 0.80, respectively.

By echocardiography, moderate-severe AR was seen in 9 patients (15%). The agreement between the observed and predicted AR is shown in Figure 3 (box plot and Table 2). ROC analysis revealed that 16.0 ml/sec is the cut-off value that best differentiated patients with none-to-mild and moderate-to-severe AR. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy were 0.72, 0.78, 0.35, 0.94 and 0.73, respectively.

Application

Besides mimicking the real implantation in terms of device sizing and positioning, a few alternative scenarios were investigated in a subset of cases. Figure 4 shows two cases where the model was used to investigate the impact of device sizing, whereas the impact of implantation depth is illustrated in Figure 5.

Discussion

The main finding of this study is that computer simulation using dedicated software integrating the MSCT-derived patient-specific anatomy and the geometric and mechanical properties of the valve accurately predicts the severity of AR that will occur after the implantation of the self-expanding MCS valve when measured by angiography or echocardiography.

These findings indicate both the feasibility and clinical utility of computer simulation of a TAVI procedure with the objective to improve outcome by helping the physician to select the type and size of valve that best fits the individual patient. It should be emphasized, however, that the herein proposed simulation program currently only relates to the MCS valve and can only clarify and predict outcome that is directly related to the specific device-host interaction.

AR, which was the outcome of interest in this study, also depends on the depth of implantation that in particular depends on physician's performance. As illustrated in the case study, the simulation can inform the physician which size of valve at which optimal landing zone is associated with the least amount of AR. While the choice of valve size is easy to follow in clinical practice, this is less so for the depth of implantation. The use of repositionable valve technologies, however, may overcome this technical issue, thereby, enforcing the clinical power and utility of the herein proposed simulation program [20].

Also, in order to meet the goal of tailored or patient-specific treatment planning, all clinically available valves should be incorporated in the simulation program that also should have the capacity to predict all clinically relevant device-host related interactions or complications. The most recent valve technologies are reported to be associated with substantially less AR but possibly with a higher than expected or accepted incidence of new conduction abnormalities [20].

The simulation program should therefore follow suit and provide a comprehensive output containing all outcomes that are relevant to the patient and physician.

The current validation is not without limitations in particular since we used contrast angiography and echocardiography for the assessment AR. These widely used clinical tools have clear limitations and are inferior to MRI for the assessment of AR (21,22). MRI should, therefore, have been used but is logistically demanding and difficult to perform in patients who underwent TAVI. It should be acknowledged that we used the same methods and definitions (albeit VARC-2 instead of VARC-1) as the pivotal studies including the CHOICE study that exclusively compared valve performance between the MCS and ESV valve (2-5,17). Yet, we did not use an independent core laboratory neither for contrast angiography nor echocardiography (CHOICE study only for contrast angiography). This and the fact that the present population consists of patients who were not enrolled in a randomized clinical trail (i.e. less selected) may explain the differences in AR between this and the pivotal studies.

Similar to the CHOICE study, we found a higher frequency of moderate-severe AR after contrast angiography than echocardiography (15 vs 9 patients). This in combination with sample size may explain why only a trend was found in the diagnostic performance of the software when differentiating none-mild vs moderate-severe AR by echocardiography. Despite this, the box plot analyses indicate that the software is capable of differentiating none-mild and moderate- severe AR. This is relevant as most studies indicate that moderate-severe AR is associated with impaired prognosis.

The present study is a proof of concept and is indicative of the clinical utility of

preprocedural computer simulation. Patient-specific preprocedure planning or personalized medicine is asked by health care authorities confronted by increasing health care costs as a result of ageing and increasing treatment modalities also for older patients. (23,24). The herein proposed method may serve this goal since and – at variance with surgical valve replacement – there is no direct vision of the target zone and no excision of calcium that intrinsically is associated with a higher degree of unpredictability of valve geometry and function. The software - by nature - assesses device-host interaction that in addition to patient-, procedure-, and operator-related factors determine or explain outcome. In addition to its clinical translation, simulation programs may also help the (further) improvement of currently available devices.

Conclusion: Computer simulation using dedicated software integrating the MSCT-derived patient-specific anatomy and the geometric and mechanical properties of the valve accurately predicts the severity of AR. This may improve outcome by helping the physician to select the type and size of valve that best fits the individual patient.

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Table 1: Clinical characteristics

mean ± SD median [25th -75th percentile] n (%)	N=60
Clinical Characteristics	
Age (y)	81 ± 6
Male	26 (43)
Height (cm)	165 ± 9
Weight (kg)	69 ± 12
Body mass index (kg/m^2)	25.0 [24.0-27.0]
Body surface area (m2)	1.7 ± 0.2
Logistic Euroscore	15.3 [10.2-22.0]
Agatston score	2039 [1468-2841]
Calcium volume	1614 [1125-2081]
Calcium mass	417 [309-586]
Procedural Characteristics	
Balloon pre-dilation N (%)	58 (96.7)
Balloon pre-dilation size N (%)	
- 20 mm	11 (18.9.)
- 22 mm	27 (46.6)
- 23 mm	19 (32.8)
- 25 mm	1 (1.7)
Balloon Post-dilation N (%)	3 (5.0)
Balloon Post-dilation size N (%)	
- 24 mm	1 (1.7)
- 25 mm	1 (1.7)
- 26 mm	1 (1.7)
Valve size N (%)	
- 26 mm	19 (31.7)
- 29 mm	41 (68.3)
Depth of Valve Implantation (mm)	
- Left Coronary Sinus	8 [6-10]
- Non-coronary Sinus	10 [7-11]
Aortic regurgitation post-implantation by aortography N (%)	
- None/trace	14 (23.3)
- Mild	31 (51.7)
- Moderate	8 (13.3)
- Severe	7 (11.7)
Aortic Regurgitation post-implantation by echocardiography N (%)	
- None/trace	22 (36.7)
- Mild	25 (41.7)
- Moderate	7 (11.7)
- Severe	2 (3.3)
- Unknown	4 (6.6)

Table 2

Observed AR	Predicted AR [ml/s]	P-value
Angiography (Sellers)		
0 (n=14)	4.3 [3.4-11.5]	
1 (n=31)	8.7 [4.4-16.0]	0.002
≥2 (n=15)	19.7 [16.7-22.2]	
<2 (n=45)	7.8 [4.0-15.8]	<0.001
≥2 (n=15)	19.7 [16.7-22.2]	
Echocardiographic (VARC-2)		
0 (n=22)	6.5 [3.6-10.7]	
1 (n=25)	13.7 [4.5-20.3]	0.012
≥2 (n=9)	17.1 [16.3-19.7]	
<2 (n=47)	8.9 [4.1-16.2]	0.070
≥2 (n=9)	17.1 [16.3-19.7]	

Figure 1: Illustration of the computer model to predict AR

The top row shows a patient in whom the model predicted perfect sealing, resulting in no streamlines from the aorta towards the ventricle. This prediction corresponds well with AR assessed by angiography and echocardiography (both grade 0). The bottom row shows a patient with more severe AR (angiography: grade 3, echocardiography: grade 2) that corresponds with the prediction of the model (16ml/s).

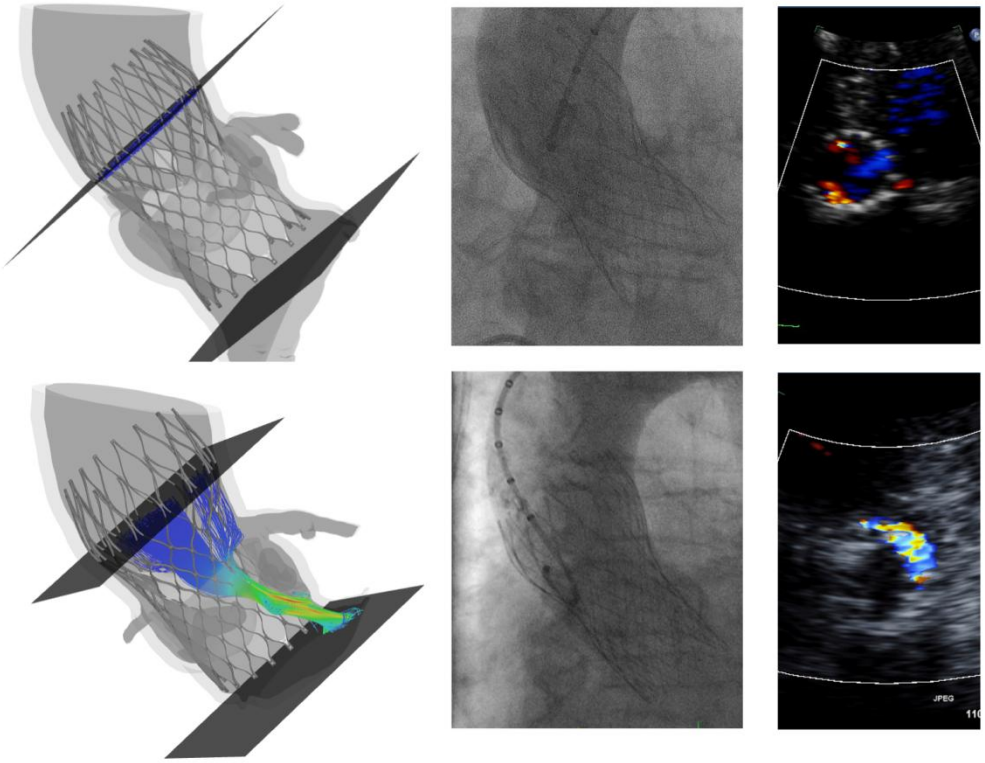

Figure 2: Box plot comparing predicted and AR by angiography

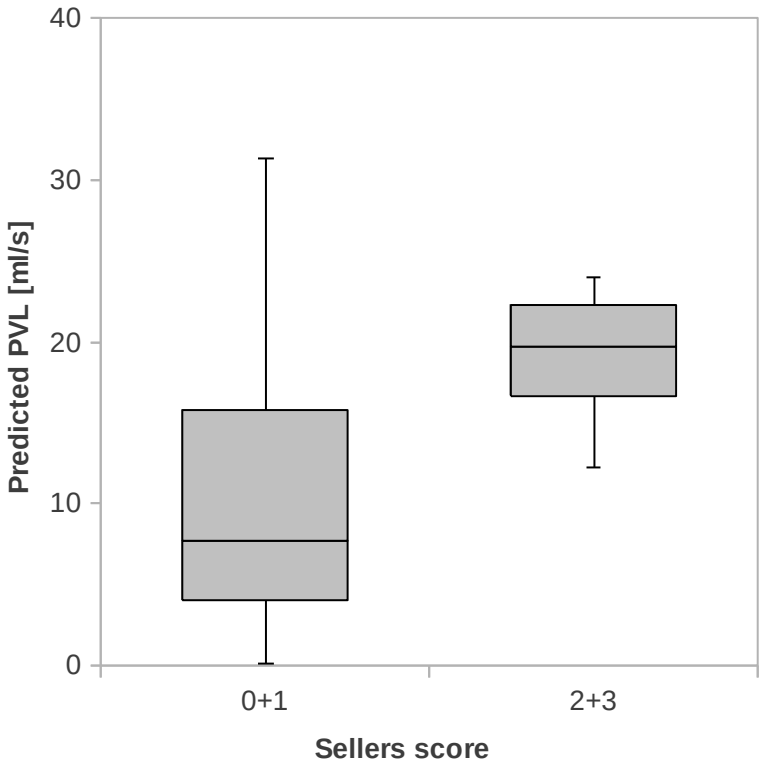

Figure 3: Box plot comparing predicted and AR by echocardiography

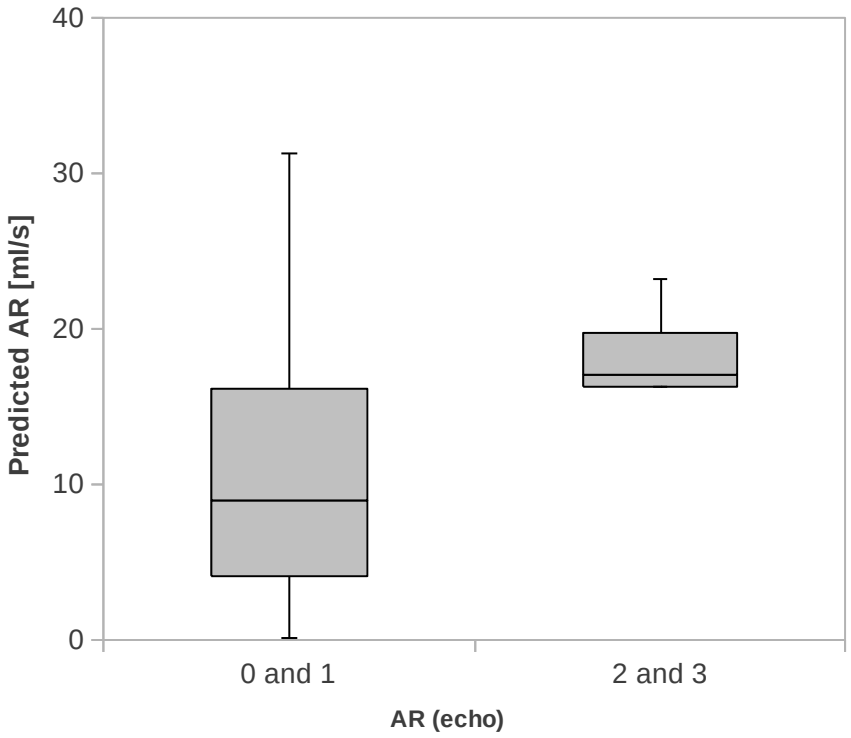

Figure 4

The top row shows first case in which a 26mm (left) and 29mm (right) MCS were implanted. The model predicts a minor impact of device sizing in this case (26mm: 4ml/s, 29mm: 1ml/s). The bottom row shows a second case where sizing has a significant impact on the predicted AR (bottom left: 26mm – 16 ml/s, bottom right: 29mm MCS – 6 ml/s).

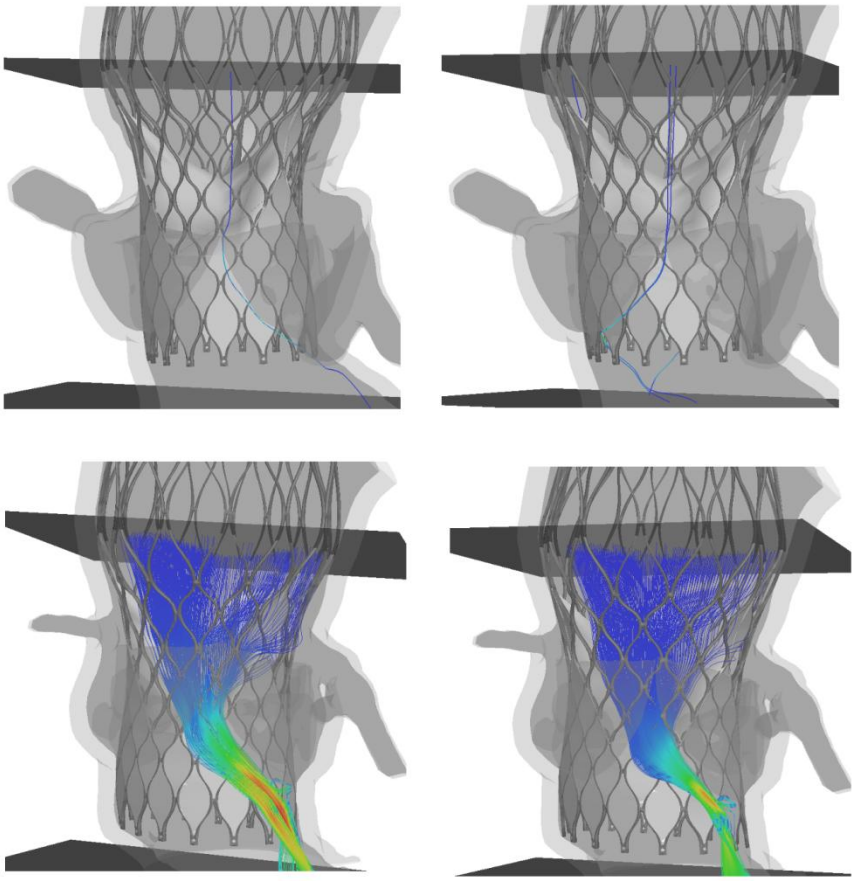

Figure 5

The top row shows a first case in which a lower implantation depth (top left) results in a higher predicted AR (32 ml/s) as compared to a higher position (top right, 17 ml/s). The second example (bottom) shows a case in which the opposite is true: the higher implantation (bottom right, 6 ml/s) results in a higher amount of AR according to the model as compared to the lower implantation depth (bottom left: 15 ml/s).