3D printing of the aortic annulus based on cardiovascular computed tomography: Preliminary experience in pre-procedural planning for aortic valve sizing

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Title

3D printing of the aortic annulus based on Cardiovascular Computed Tomography: preliminary experience in pre-procedural planning for aortic valve sizing.

Short title: 3D printing of the aortic annulus

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ABSTRACT

Background: to determine reliability and reproducibility of measurements of aortic annulus in 3D models printed from cardiovascular computed tomography (CCT) images.

Methods: Retrospective study on the records of 20 patients who underwent aortic valve replacement (AVR) with pre-surgery annulus assessment by CCT and intra-operative sizing by Hegar dilators (IOS). 3D models were fabricated by fused deposition modelling of thermoplastic polyurethane filaments. For each patient, two 3D models were independently segmented, modelled and printed by two blinded "*manufacturers*": a radiologist and a radiology technician. Two blinded cardiac surgeons performed the annulus diameter measurements by Hegar dilators on the two sets of models. Matched data from different measurements were analyzed with Wilcoxon test, Bland-Altmann plot and within-subject ANOVA.

Results: No significant differences were found among the measurements made by each cardiac surgeon on the same 3D model (p=0.48) or on the 3D models printed by different manufacturers (p=0.25); also, no intraobserver variability (p=0.46). The annulus diameter measured on 3D models showed good agreement with the reference CCT measurement (p=0.68) and IOH sizing (p=0.11). Time and cost per model were: model creation ~10-15 min; printing time ~60 min; post-processing ~5min; material cost ~1€.

Conclusion: 3D printing of aortic annulus can offer reliable, not expensive patient-specific information to be used in the pre-operative planning of AVR or transcatheter aortic valve implantation (TAVI).

Keywords: Aortic stenosis; Aortic Valve Replacement (AVR); transcatheter aortic valve implantation (TAVI); cardiovascular computed tomography (CCT); aortic annulus; 3D-printing.

ABBREVIATION LIST

AVR = aortic valve replacement

BA = Bland-Altman

CCT = Cardiovascular computed tomography

CoV = coefficient of variation

IOS = intra-operative sizing

RoA = region of agreement

STL = standard tessellation language

TAVI = transcatheter aortic valve implantation

TEE= trans-esophageal echocardiography

TPU = thermoplastic polyurethane

3D = Three-dimensional

TEXT

1. INTRODUCTION

Three-dimensional (3D) printing is a fast-growing technique used to transform digital models into physical objects.

The use of this technology in cardiovascular medicine constitutes a relatively new development (1,2). Three-dimensional cardiovascular models are potentially very useful in interventional cardiology, which involves the use of catheter-based procedures and requires a comprehensive knowledge of patient-specific anatomy (3). In this field, transcatheter aortic valve implantation (TAVI) has emerged as a valid alternative to surgical aortic valve replacement (AVR) (4). The safety and efficacy of the TAVI procedure are directly related to imaging and the size of the aortic valve annulus is used as a standard measurement for quantitative assessments of the site of implantation (5,6).

The pre-surgery evaluation of the aortic annulus size was historically based on trans-esophageal echocardiography (TEE) (7). Currently, however, Cardiovascular Computed Tomography (CCT) plays a pivotal role in patient selection and planning prior to TAVI (5,8). Cardiovascular Magnetic Resonance Imaging has also been proposed as a reliable alternative for aortic annulus valve sizing (9,10).

Recently, patient-specific 3D printed models of the aortic valve and aortic root complex have been proposed as a new tool for preoperative planning of TAVI (11–15) and for predicting which patients are more likely to develop paravalvular aortic regurgitation (16,17). The heart team could have benefit from having a tactile feedback of what the procedure will be like and from anatomically 3D printed models which may also be used for bench tests prior to valve implantation (2,18).

To the best of our knowledge, there are no published data regarding the validation of 3D printing in the pre-operative assessment of aortic annulus using as a benchmark both CCT and intra-operative sizing.

This paper reports the results of a study aimed to determine the reliability and the reproducibility of measurements of the aortic annulus diameter using 3D models printed from the pre-surgery CCT images of patients who underwent AVR. Each 3D diameter was compared with the references of CCT diameter and intra-operative sizing (IOS) diameter.

2. METHODS AND MATERIALS

The study was piloted in agreement with the 1964 Helsinki declaration and its later amendments and approved by the ethics committee of our institution (prot. N°0009101, January 26th, 2018).

2.1. Study design

Data were retrospectively collected from all consecutive patients who underwent aortic valve replacement, according to current medical practice and inclusion criteria, from January 2017 to October 2017, and had available records of both pre-surgery annulus assessment by CCT and of intra-operative assessment. Twenty patients (table 1) were included in the study.

According to the Ethics Committee of our institution, before the CCT examination, all patients herein considered were informed about the possible use of their data for study purposes and gave written consent. Patients' information was anonymized prior to the analysis.

The 3D models were independently segmented, modelled and printed by two blinded "*manufacturers*": a radiologist (M.G.), hereafter labelled M1, and a radiology technician (G.P.) labelled M2. The operators who carried out the measurements were two cardiac surgeons: S.S., hereafter labelled O1, who carried out also the intraoperative sizing, and E.C.S., labelled O2. Both performed a set of blinded measurements of the 3D models created by M2. O2 performed also two sets of measurements on randomly rearranged new models created by manufacturer M1: all second measures were made on new models in order to avoid the possible bias of 3D-model deformation.

The comparison between the measurements of O2 on the two sets of models created by M1 and M2 allowed to estimate the inter-manufacturer variability. The comparison between the measurements of O1 and O2 on the set of models created by M2 allowed to estimate the inter-operator variability. Finally, the two measurements of O2 on the two sets of models created by M1 allowed to estimate the intra-operator variability.

2.2. Cardiovascular Computed Tomography protocol

All examinations were performed using a 64-slice LightSpeed VCT scanner (GE Healthcare Technologies, Waukesha, WI) using retrospective ECG-gating (peak mA was 40-80% of the R-R interval). Tube current and voltage were 250-600 mA and 100-120 kV, respectively; gantry rotation was 350 ms and slice collimation was 64 × 0.625 mm. Contrast medium was administered using the Smart Prep technique. An injection volume of 80–90 ml and a flow rate of 5 ml/s were used (Ultravist 370, Bayer Shering, Berlin, Germany).

2.3. 3D modeling and 3D printing

Images were reconstructed at the end-diastolic phase (80% of the R-R interval) and used to create the 3D model of the aortic root. OsiriX MD 9.0 (Pixmeo, Geneva, Switzerland) was used to segment the images. The blood pool of the aortic root was semi automatically segmented from the left ventricular outflow tract (about a cm under the plane of the aortic annulus) to the sinotubular junction using threshold values adjusted for each patient to include contrast media, annular calcium and valve leaflets. Segmented data sets were then converted to a 3D printable standard tessellation language (STL) file. A state-of-the-art open source software (Meshmixer 3.4, Autodesk, San Rafael, California, U.S.) for working with triangle meshes was used to refine and sculpt the 3D model in order to make it 3D printable. Once the geometry of the mesh was cleaned and free of errors, the 3D models were exported through the preferred slicer software (Ultimaker Cura 3.1, Geldermalsen, Netherlands) to the fusion deposition modelling printer (Ultimaker 2 Extended+, Geldermalsen, Netherlands) for printing (layer height: 0.1 mm; wall thickness: 1.2 mm; nozzle size: 0.4 mm; speed: 15 mm/s; temperature: 230°C). An ultra-flexible, extremely strong filament made from a specially formulated thermoplastic polyurethane (TPU) material (Ninjaflex®, Ninjatek, Mannheim, Pennsylvania, U.S.) was used for printing [Density: 1.19 g/cm3; Tensile Strength Yield: 4 MPa; Tensile Strength, Ultimate: 26 MPa; Tensile modulus: 12 Mpa; Elongation at Yield: 65%; Elongation at Break: 660%; Toughness: 82.7 m*N/m^3 x10^6; Hardness 85 Shore A; Impact Strength (notched Izod, 23C): 4.2 kJ/m^2 Abrasion Resistance (mass loss, 10,000 cycles): 0.08 g]. The processes of 3D modelling and 3D printing are shown in figure 1.

2.4. CCT measurements

CCT data were processed using the Advantage Windows Workstation (version 4.4, GE Healthcare). The CCT images were reconstructed and measured at the end-diastolic phase (80% of the R-R interval) to be consistent with the 3D models. The annular plane was considered to be the virtual ring formed by the lowest hinge points of the valvular attachments to the aorta (5,19).

2.5. Intraoperative measurements

All intraoperative annulus sizing of our study population were performed by S.S. (O1) during the course of aortic valve replacement by means of Hegar millimetre dilators, sizes 15–30 mm (Aesculap, Tuttlingen, Germany) in the arrested heart after resection of the aortic cusps and complete decalcification of the annulus (figure 2, left panel). The fit of the largest possible dilator was defined as optimal and this measure was used as the standard reference.

2.6. 3D model measurements

Three-dimensional model measurements were performed by means of Hegar millimetre dilators, sizes 15–30 mm (Aesculap, Tuttlingen, Germany) in the 3D printed models. The fit of the largest possible dilator was defined as optimal and this measure was used (figure 2, right panel).

2.7. Statistical analysis

The CCT measurements did not pass the Shapiro-Wilks normality test, so, for uniformity, also the 3D and IOS sets of measurements were expressed as median, 1st quartile Q1 and 3rd quartile Q3. The existence of statistical differences was investigated with non-parametric tests: Wilcoxon's test for n=2 correlated variables and Friedman's test for n=3.

For paired data, the within-subject ANOVA was used to compute the intraclass correlation coefficient ICC (0-1), and the Cronbach's coefficient η^2 (0-1) of pairs of measurements: the closer ICC and η^2 to 1, the better the agreement. The Bland-Altman (BA) plot was constructed as a graph in which the horizontal axis expresses the reference measurements and the vertical axis expresses the difference Δ between tested approach and reference. The limits of agreement, determined by the mean value of Δ ± 1.96 times the standard deviation of Δ identify the region of agreement (RoA) that includes 95% of the differences. The accuracy of the measurements is greater whenever RoA has smaller width and is more symmetric with respect to the zero line. The coefficient of variation (CoV) was computed as the ratio of 1.96*standard deviation to the mean of the reference measurements in the range of interest. Scatter plots with the associated regression coefficient b and Pearson's correlation coefficient r were used to check whether the measurements had similar trends: the closer b and r to 1, the more similar the behaviors.

The requirement for significance was $p < 0.05$. Calculations were run on Statplus:Mac version v6 (AnalystSoft, Walnut, CA).

3. RESULTS

The results on the intra and inter-operator variability and inter-manufacturer variability demonstrated good reliability and reproducibility in manufacturing and in diameter measurements (Table 2). We thus computed the average of the six measurements of the two operators, obtaining the 3D set to be compared with the outcome of the radiological golden standard CCT and of the intraoperative sizing (IOS).

3.1. Comparison of 3D model measurements with CCT and Intraoperative measurements

Table 3 reports the descriptive statistics for the three data sets, illustrated in the box plot of Figure 2. The Friedman's non-parametric test for three correlated distributions excluded the existence of significant differences among them ($p = 0.52$).

The reliability of the 3D measurements was further investigated by analyzing separately the pairs 3D-CCT and 3D-IOS. The former comparison was aimed to verify the ability of the 3D models to faithfully reproduce the "parent" CCT images as far as annulus diameter; the latter to assess the agreement between the measurements on the 3D model and the measurements on the real annulus during surgery.

The outcome of four independent statistical procedures applied to 3D vs CCT and to 3D vs IOS are shown in Table 4. All results vouch for a very good agreement within the two pairs: in both comparisons, intraclass correlation coefficient ICC, Cronbach coefficient η^2, regression coefficient and Pearson's linear correlation coefficient r are very close to 1, the mean differences (3D-CCT) and (3D-IOS) are very close to zero, the regions of agreement are narrow and the coefficients of variation are small.

The Bland-Altman plot for the 3D versus CCT comparison is shown in Figure 3. Figure 4 gives a comprehensive illustration of the agreement among the three sets of measurements. The top panel is the Bland-Altman plot of the difference of the 3D and CCT measurements from the IOS measurements. We could represent them in the same plot because (3D-IOS) = -0.35±0.88 mm ($p=0.11$) and (CCT-IOS) =-0.30±1.12 ($p=0.68$). The bottom panel is the scatter plot of 3D and CCT diameters versus the corresponding IOS diameters. The two plots illustrate the good agreement among the three measurements and the absence of systematic drifts due to possible manufacturing biases.

The literature contains recommendations (5) for the choice of valves based on the assessment of the aortic annulus size. We performed valve sizing for CoreValve and Sapien XT valve using the CCT and the 3D model measurements. We found perfect agreement between the indication of the two techniques, as it was expected since the maximum difference in the diameter estimate was ±1mm.

3.2. Time – cost analysis

The segmentation plus post-processing time was approximately 10-15 minutes per model. Estimated printing time for a single model was about 60 min. 10 aortic root models could be printed at one time and it took a total of 9 to 10 h to print these ten 3D phantoms simultaneously. Post-print processing took approximately 2 minutes. Each measurement took approximately 2 minutes. Overall, the total "observer-time" for a single final printed model was approximately 15-20 minutes.

The cost of one reel of TPU is about 65€ for 1000 gr. The weight of a single model is 4-6 gr. and therefore the printing materials cost in each phantom was approximately 1€.

4. DISCUSSION

Our study investigated the performance of 3D models of aortic root printed from CCT images as a tool for preprocedural evaluation of the aortic annulus size for a sample of 20 patients with severe aortic stenosis.

We showed that 3D models of aortic root from CCT images were able to yield annulus measurement characterized by low intraobserver and interobserver variability with good agreement with CCT and intraoperative measurements.

Moreover, 3D printing gives the operator optimal illustration and spatial appreciation of cardiovascular structures, allowing advanced procedural planning. A life-size, patient-specific model, not only gives haptic feedback to the surgeon or interventional cardiologist but also permits decision-making on device choice and appropriate size, a possibility to simulate the implant, as in the operating theater, evaluating the best operative approach and the more accurate positioning of the implant. It may also be a great tool to improve the physician-patient communication during the explanation of the procedure (20).

Inter-manufacturer reproducibility is a basic requirement for 3D model generation. Even if the process can be partly automated, it nevertheless requires great care. Errors can be generated during any step of the process, including image acquisition, segmentation and post-processing, as well as 3D printing (21). Careful judgment is often required when setting threshold values and when adjusting segmentation contours. The radiology technician involved in our study was trained from a radiologist expert in 3D file generation and this allowed us to obtain a very low inter-manufacturer variability through the whole 3D printing process, from image acquisition to 3D model measurement.

To reproduce the real anatomy of the aortic root is a challenging task. It is well known that the morphology of the annulus exhibits conformational pulsatile changes throughout the cardiac cycle due to deformation and stretch. Suchà et al. (22) affirmed that the selection of the cardiac phase in which the annulus shows the largest dimensions seems to prevent prosthesis undersizing, but that the maximal phase is patient specific. These data were recently underlined by Murphy et al. (23) who reported that the systematic differences between systolic and diastolic annular measurements have implications for device sizing with potential for valve under-sizing if diastolic annular dimensions are employed. The expert consensus document from SCCT on imaging before TAVI (24) indicates that imaging of the aortic root and annulus in systole may be preferable over diastole because of the slightly larger annular sizes noted in systole, but they also underlined that it is crucial to ensure adequate image quality even if systolic imaging is used. This last affirmation was consistent with Kasel et al.'s state-of-the-art paper (5), which recommended using the phase of the cardiac cycle with the best image quality. Three-dimensional models can be printed in either systole or diastole; however, since the intraoperative measurements were performed in the arrested heart, which is in diastole, we decided to print the 3D model in the diastolic phase and to be consistent with that we also measured the aortic annulus on CCT images at the end-diastolic phase.

Another critical point of TAVI preprocedural assessment is the distribution of aortic valvular and LVOT calcification (25). We did not evaluate this with our models because they were segmented including contrast media, annular calcium and valve leaflets, but this was for being consistent with the surgical measurement which was taken after complete decalcification of the annulus. However, it has been previously demonstrated (16, 17) that 3D printed models could provide a feasible, non-invasive technique to evaluate the physical interplay of the aortic root, valve leaflet, calcification and implanted valves and that this may complement traditional techniques used for predicting which patients are more likely to develop paravalvular aortic regurgitation.

Elasticity and thickness of the 3D model are two other issues. There are no direct measurements made of these two characteristics in the annulus. There is a report about the elastic modulus of the aorta being roughly 9 MPa in circumferential orientation (26), varying with wall thickness, disease state and aneurysmal dilation. The aortic annulus, however, has a fibrous, and thus stiffer, structure, corresponding to a higher elastic modulus. For this reason, the material chosen for manufacturing the 3D model has elastic modulus around 12 MPa, which presumably better reproduces the anatomical conditions of patients with aortic degeneration, particularly the older ones. The 1.2 mm thickness of the model represented the best possible compromise to balance the elasticity of the model and the risk of rupture.

To date, 3D printing has been used for preprocedural evaluation of aortic root in a small number of cardiovascular cases. Firstly, Schmauss et al. (11) reported that CCT enabled creation of 3D models of the aortic annulus and surrounding structures for potentially safer valve deployment. More recently, Maragiannis et al. (27) were able to fabricate a series of fully functional aortic stenosis models implantable in flow loop, replicating the entire aortic valve complex using flexible material. Ripley et al. (16) demonstrated, in a series of 16 patients, that 3D printed models provide a feasible, non-invasive technique to assist 3D visualization of patient-specific aortic root anatomy and that measurements of annulus minimum and maximum diameter made on printed 3D models were highly correlated with annulus measurements made from corresponding 2D standard annulus measurements made on CCT by two experienced observers. Other isolated case reports (12–14) showed that patient-specific models of the aortic valve and aortic root complex could be effectively used for testing the performance of in vitro TAVI and could be particularly helpful to the heart team by providing a custom-made representation of the heart before an interventional procedure.

Although many modern clinical images can be 3D printed, limitations have been reported and include costs, time to generate models and human resources' efforts (1). However, with our approach, the 3D printing of aortic annulus could be proposed in a clinical setting in case of elective or semi-elective procedures: a whole 3D-printing process takes about 2 hours, but the “observer-time” for a single final printed model is approximately 15-20 minutes and the cost is very limited (about 1€).

Our study has some limitations. First, it is a retrospective study carried out in a single center on a limited number of patients. Second, the model creation was based only on CCT; however, this is the imaging technique of choice in TAVI pre-procedural assessment. Third, we focused on the aortic annulus dimension not considering valve anatomy, extent and distribution of valve and aortic root calcifications and shortest distance from aortic annulus to ostia of left main and right coronary arteries, which are required information in pre-procedural assessment of TAVI.

In summary, the 3D models reproduced well the CCT reference and performed well when compared to the surgical reference of intraoperative sizing. This approach may offer a reliable, not expensive, patient-specific pre-operative planning opportunity. It provides a unique interactive platform to the final user with both visual and tactile experiences, which are critical for simulation of the procedure, but not available in imaging data *per se*. With future optimizations, including development of printers and materials that better reflect the mechanical properties of the aortic annulus and associated calcifications, this developing technology may acquire an important role in the pre-procedural workup.

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FIGURE TITLE AND LEGENDS

Figure 1. Creation of the 3D model. First row: semi automatically segmentation from the left ventricular outflow tract to the sinotubular junction using threshold values adjusted to include contrast media, annular calcium and valve leaflets. Second row: Meshmixer® was used to refine and sculpt the 3D model. Third row: the 3D models were exported through Ultimaker Cura® to the Ultimaker 2 Extended+ for printing. Fourth and fifth row: 3D printed model of the aortic root in flexible material to mimic the elastic properties of the aorta.

Figure 2. Intraoperative and 3D model measurements. Left panel: intraoperative annulus sizing was performed by means of Hegar millimetre dilators in the arrested heart after resection of the aortic cusps and complete decalcification of the annulus. The fit of the largest possible dilator was defined as optimal and this measure was used as the standard reference. Right panel: Three-dimensional model measurements were performed in the same way as the intraoperative annulus sizing.

Figure 3. Comparison of the 3D model, CCT and IOS diameter measurements. The box identifies the Inter Quartile Range: the blue line inside corresponds to the median, whereas the red line corresponds to the mean diameter; the green dots evidence the outliers. The reported p value derives from Friedman's test.

Figure 4. Comparison of 3D with CCT diameter assessment. The full line is the average of the difference (3D-IOH) $\approx$ (CCT-IOH). The dot-dashed lines identify the region of agreement (RoA), symmetrical around zero.

Figure 5. Comparison of 3D and CCT diameter with IOS diameter. Top panel: Bland-Altman

plot. The full line is the average of the difference (3D-IOS) ≈ (CCT-IOS). The dot-dashed lines identify the region of agreement (RoA), symmetrical around zero. Bottom panel: 3D and CCT diameter vs IOS diameter: the full line is the bisector of the quadrant.