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3-D measurement of aortic annulus dimensions using area or circumference for TAVR valve sizing. Does it make a difference?

Short title: "3-D measurements of aortic annulus."

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Abstract

Background

The use of Transcatheter Aortic Valve Replacement (TAVR) is increasing worldwide. We present our 6-year experience using 3-D TEE and investigate if different sizing methods of the aortic annulus lead to different prosthesis size that may impact on outcome.

Methods

We investigated 262 patients who underwent TAVR and had 3D TEE datasets of the aortic annulus. We have used the area-derived diameter ($D_{area}=2\sqrt{(area/\pi)}$) and the circumference-derived diameter ($D_{circ}=Circumference/\pi$) to size the prosthesis in separate populations in different time periods.

Results

The D_{circ} -method is correlated with lower incidence of paravalvular aortic regurgitation (PVAR) (OR:0.44, 95% CI: 0.23-0.85; $p=0.015$). Other factors associated with PVAR were the cover index, area-mismatch index and circumference-mismatch index.

Retrospectively, for the purposes of the study, we used the Edwards-Sapien 3 Valve 3D-Sizing Guide in all patients, to predict the hypothetical valve size with each method. In the whole population, the calculated D_{circ} was higher in all cases ($D_{circ} = 23.4 \pm 2.3\text{mm}$ vs $D_{area} = 22.9 \pm 2.3\text{mm}$; $p < 0.001$). The two methods had good agreement in predicting the valve size ($\kappa = 0.600$). 192 (73.3%) patients were assigned for the same prosthesis size, whereas 70 (26.7%) would be eligible for a

different size, of which 44 (16.7%) would definitely have had a different valve implanted.

Conclusion

Using the aortic annulus area or circumference to calculate the annular diameter provides different values. Comparing the two methods, a different prosthesis size could have been implanted in 26.7% of patients. In our series the use of circumference-derived diameter resulted in lower incidence of PVAR. The findings of this study may be independent of the imaging modality and may therefore also apply to CT based aortic annulus measurements, but this needs to be further investigated.

Key words: transcatheter aortic valve replacement (TAVR), 3D echocardiography, aortic annulus, paravalvular aortic regurgitation, aortic valve size

Abbreviations

3D: Three-dimensional

AR: Aortic Regurgitation

AS: Aortic Stenosis

AV: Aortic Valve

CI: Cover Index

CT: Computed Tomography

D_{avg} : Average Diameter

D_{area} : Area-derived effective diameter

D_{circ} : Circumference-derived effective diameter

ER: Eccentricity Ratio

LVOT: Left Ventricular Outflow Tract

PVAR: Paravalvular Aortic Regurgitation

TAVR: Transcatheter Aortic Valve Replacement

TEE: Transesophageal Echocardiography

TTE: Transthoracic Echocardiography

1. Introduction

Transcatheter Aortic Valve Replacement (TAVR) is a validated treatment for symptomatic severe aortic stenosis (AS) in inoperable or high risk surgical patients [1]. Accurate sizing of the aortic valve (AV) prosthesis is paramount to ensure acute success and a durable long-term outcome. Many procedures are performed utilising 2D transthoracic (TTE) or Transesophageal (TEE) echocardiographic measurements of the aortic annulus [2, 3]. These measurements assume that the shape of the aortic annulus is circular. However, since the aortic annulus is usually oval-shaped, it has become apparent that making a single diameter measurement from 2D images will result in erroneous dimensions.

This has led to the use of multi-slice CT and three-dimensional (3D) TEE imaging to size the aortic annulus, since they can both account for irregular, non-circular annular shapes. Planimetry of aortic annulus in 3D orientated images improves annulus measurements, and good agreement has been reported between multi-slice computed tomography and 3D TEE [4, 5]. The sizing guide for the most recent commercially available balloon-expandable valves is based on 3D annular area and 3D area-derived diameter. However, as the shape of the annulus becomes more ellipsoid, the area shrinks but the circumference remains unchanged. In this study we test the hypothesis that sizing the aortic annulus using the circumference, as opposed to the area, may lead to different prosthesis size choice, especially in patients with significantly ellipsoid shape of the aortic annulus, and we seek to investigate possible clinical implications.

2. Material and methods

2.1. Study population

A total of 294 patients were referred to our centre for TAVR between September 2009 and May 2014. They presented with symptomatic, severe valvular calcific aortic stenosis and were reviewed by a multi-disciplinary team. A total of 11 patients were excluded from the study. Seven of those patients presented with a failing aortic valve bioprosthesis and were considered for a valve in valve procedure. One had a metallic mitral valve prosthesis which did not allow adequate TEE imaging and underwent a gated, multi-slice CT for prosthesis sizing. Three patients developed an iatrogenic ventricular septal defect or Gerbode defect and therefore paravalvular AR (PVAR) could not be accurately quantified. The implanted valves were the Edwards Sapien XT (179 patients), the Edwards-Sapien 3 (83 patients), the Boston Scientific Lotus valve (17 patients) and the Jenavalve (4 patients). The Lotus and Jenavalve valves are deployed with a controlled mechanical expansion as opposed to the Edwards balloon-expanded valves. This difference along with the different sizing recommendations may pose a bias to the explored outcome (paravalvular aortic regurgitation) and therefore the patients with a Lotus or Jenavalve prosthesis were excluded, and we only studied patients with Edwards-Sapien valves. All patients signed an informed consent for the therapeutic and diagnostic procedures, which included 3D TEE.

2.2 Echocardiographic study

Transesophageal Echocardiography was performed in all patients as part of the pre-procedural work-up to ensure suitability for the intervention, as is standard practice in our centre. In addition, all patients had peri-procedural TEE for guidance and monitoring of complications [2]. The ultrasound systems iE33 and Epiq7 (Philips Healthcare, Andover, MA, USA) with a matrix array probe (X7-2t) and the Vivid 9 (GE Healthcare, Hertfordshire, UK) with the 6VT-D transducer, to allow for 2D and 3D live images, were used. The aortic valve and the ascending aorta were studied in short axis (mid-oesophageal, 40°-70°) and long axis views (mid-oesophageal, 110°-135°) and 2D images with and without colour Doppler obtained and stored in the hospital cardiology imaging archive (Philips, Xcelera). Using the “3D zoom” feature, 3D datasets of the AV, including the LVOT and proximal ascending aorta (sinuses and sinotubular junction), were acquired. A single-beat acquisition was used.

2.3 Echo image analysis

The 3D datasets were analyzed off-line with the Philips Qlab (QLAB cardiac 3DQ, Philips Medical Systems, versions 9, 10) or online on GE machines (GE Healthcare, Hertfordshire, UK). The measurements were made in a mid-systolic frame. Three multiplanar reconstruction planes (MPR) were used. Two were bisecting the long axis of the left ventricular outflow tract (LVOT) and were orthogonal to each other in the sagittal and coronal planes. The third one was transverse to the previous ones and was intersecting the aortic valve in its short axis at the level of the annulus (Figure 1). Special care was taken to position the transverse MPR at the level just below the hinge point of all three aortic cusps. One experienced operator performed a manual

tracing of the aortic annulus in this transverse plane and also measured the maximum and minimum diameters (D_{max} and D_{min} respectively). This analysis methodology is analogous to that performed using CT datasets.

The aortic valve was assessed with both 2D and 3D echo datasets and the degree of calcification was graded as moderate or severe. There were no cases with mild valvular calcification. The AV was considered as severely calcified if all cusps demonstrated considerably increased echogenicity in more than 50% of their tip surface and there was also significant calcification affecting the commissures between cusps or there was eccentric calcification on cusps measuring more than 5mm [6] (Figure 2). The cases with lower echogenicity and thickening of the aortic cusps were graded as having moderate calcification.

The post-procedural paravalvular aortic regurgitation (PVAR) was graded by echocardiography (both TEE and TTE) according to recently published guidance [7]. Using the semi-quantitative method of circumferential extent of the PVAR jets, the quantitative width of jet at its origin and the ratio of the jet width to LVOT diameter, the PVAR was classified in a five-grade scheme (mild, mild to moderate, moderate, moderate to severe, and severe) [7].

2.4. Measurements and calculations

The effective annulus diameter was calculated from the annular area and circumference according to the equations:

$$\text{Area-derived effective diameter } (D_{area}): (D_{area} = 2\sqrt{(area/\pi)})$$

$$\text{Circumference-derived effective diameter } (D_{circ}): D_{circ} = Circumference/\pi$$

As part of our protocol we had been using the D_{area} to size the TAVR prosthesis until April 2013, whereas since then we have been using the D_{circ} to select an appropriately sized prosthesis taking into account sinus dimensions and the valve calcification. The manufacturer provides different recommendations for oversizing each valve (Sapien XT and Sapien 3). We followed these oversizing recommendations for the different valves in both groups (D_{area} and D_{circ}).

The Eccentricity Ratio (ER) was calculated as $ER = 1 - (D_{\text{min}}/D_{\text{max}})$ [8, 9]. The average diameter (D_{avg}) was derived by the sum of D_{max} and D_{min} divided by two. We calculated the cover index (CI) using the average annulus diameter in the equation [10]:

$$CI = 100 \times (\text{Prosthesis Diameter} - \text{TEE Average Annulus Diameter}) / \text{Prosthesis Diameter}$$

Finally we used the 3D tracing of the aortic annulus to calculate the Mismatch Indices such as:

Area Mismatch Index = TEE planimetered annulus area – prosthesis area [6],
and

Circumference Mismatch Index = TEE planimetered annulus circumference – prosthesis circumference.

For the purposes of this study we retrospectively, performed a theoretical prosthesis sizing utilizing the 3D sizing guide for a new generation balloon-expandable valve (The Edwards-Sapien 3 Valve) to determine the prosthesis size in the whole population. We used this sizing guidance for both D_{area} and D_{circ} measurements. This

aimed to investigate the hypothesis that in the same individuals, the diameter derived by the aortic annulus circumference may result in a different prosthesis size compared to the area-derived diameter. This was a hypothetical retrospective comparison after the TAVR procedure, and it was not used for clinical decision making.

Finally, we assessed the interobserver variability of aortic annulus measurements. For this purpose, we asked a second experienced operator to retrace twenty cases. The second operator was blind to the exact 3D datasets and the frames used by the first operator as multiple datasets were acquired per patient. He also performed independently the alignment of axes in the multiplanar reconstruction planes.

2.5. Statistical analysis

Statistical analysis was performed using SPSS for Windows (version 20.0, IBM Corporation Software Group Somers, NY, USA). Continuous variables were summarised as mean \pm standard deviation. The continuous variables were normally distributed based on histograms. Differences between paired samples of continuous variables were tested using the paired t-test and between independent samples utilizing the unpaired student t-test. The comparison of two methods to determine the prosthesis size was performed with Cohen's kappa. Uni- and multi-variable logistic regression analyses were used to assess the correlation of several parameters with paravalvular aortic regurgitation. We have used a binary variable for PVAR in the analysis: "no PVAR" and "mild or greater PVAR". The goodness of fit of the model was tested with the Hosmer-Lemeshow test and was found to be adequate. The multicollinearity of the variables was tested with linear regression and an R square value

above 0.7 was considered suggestive of positive correlation. The interobserver variability was investigated with the intraclass correlation coefficient for a two-way mixed model. Statistical significance was considered for a two-tailed p-value < 0.05.

3. Results

3.1. *Baseline characteristics and outcome*

We divided the study population into two groups based on the method used to size the AV prosthesis (D_{area} vs D_{circ}). The baseline characteristics of the two groups are presented in Table 1. One hundred and thirty-nine patients (53.1%) had mild AR at pre-assessment, 9 had moderate AR and none had severe. The majority of patients received 23 and 26 mm valves (114 patients; 43.5% and 108 patients; 41.2% respectively); 37 patients (14.1%) had a 29mm valve implanted and 3 patients had a 20mm valve (1.1%). In 79 (30.2%) patients a transapical/transthoracic approach was used, whereas 180 (68.7%) had a transfemoral procedure and in 3 patients (1.1%) the valve was implanted through transaortic access. Post-procedure, 96 (36.6%) patients had mild paravalvular AR (PVAR) and 10 (3.8%) had mild to moderate. In terms of simplicity these 106 patients formed a common group of “mild or greater” PVAR. There were no patients with moderate, moderate-to-severe, or severe PVAR.

3.2. *Sizing AV prosthesis using the annular circumference vs area.*

Applying retrospectively the manufacturer’s guiding size for the new generation balloon-expandable valve in all patients, the two methods (D_{area} and D_{circ}) had good agreement in predicting the valve size (kappa=0.600). 192 patients (73.3%) were assigned for the same valve size prosthesis by both methods (Table 2). However,

70 patients (26.7%) were allocated to a different size group. 26 of those patients (9.9%) would be eligible for a different size as they were allocated in the overlapping groups (23 or 26mm and 26 or 29mm groups). Importantly, 44 patients (16.7%) would definitely have had a different valve implanted. All patients assigned to a different group would have had a larger prosthesis based on the D_{circ} compared to D_{area} , including 22 (8.4%) patients who would have been excluded from TAVR if prosthesis selection would have been performed based on D_{area} (diameter < 20.0mm). This is not surprising, as in the whole study population the effective diameter by circumference was higher in all cases compared to area-derived diameter ($23.4 \pm 2.3\text{mm}$ vs $22.9 \pm 2.3\text{mm}$; $p < 0.001$). There were no patients considered to have too big annulus diameter for TAVI prosthesis, as calculated by both methods.

3.3. *Factors associated with paravalvular AR*

We sought to investigate factors associated with paravalvular AR (PVAR) post-TAVR in the whole cohort (Table 3). Minimum diameter, average diameter and annulus area demonstrated multi-collinearity so only the minimum diameter which showed a lower p value is shown in Table 3. Similarly, the peak and mean pressure gradients and the peak velocity demonstrated multiple collinearity and only peak velocity is included. In univariate analysis, the aortic valve area, the cover index, the area and circumference mismatch indices, the type of valve used and the method of sizing the aortic annulus were found to be correlated with PVAR. The new generation Sapien 3 valves were found to be associated with lower risk of PVAR compared to the Sapien XT valve. The sizing method using the D_{circ} as opposed to the D_{area} was related with lower risk of PVAR.

All parameters with a p value < 0.2 were included in a multi-variable model. The cover index, the area and the circumference mismatch indexes were significantly correlated to each other. We used them interchangeably in the multivariable model as they were all significantly related to PVAR in uni-variable analysis. The factors associated independently with PVAR after adjusted for aortic valve area, peak velocity, valve calcification and minimum diameter, were the cover index (OR: 0.91; 95% CI: 0.86-0.96; $p < 0.001$), the type of TAVR prosthesis and the sizing method (Table 4). The older generation valve (Sapien XT) was related with higher risk of PVAR compared to the new generation valves (OR:2.39; 95% CI:1.08-5.32; $p=0.032$). The use of annulus circumference to size the prosthesis had a more favourable outcome in terms of PVAR which was independent of other factors (OR:0.44; 95% CI:0.23-0.85; $p=0.015$). The area mismatch index was also related to PVAR (OR:2.75; 95% CI:1.64-4.63, $p<0.001$) when inserted in the multi-variable logistic regression model and the other factors (prosthesis type and sizing method) maintained correlation with PVAR. When we used the circumference mismatch index it was found to be independently associated with PVAR as well (OR:2.83; 95% CI:1.52-5.27, $p=0.001$), along with the sizing method and the type of prosthesis.

3.5 Interobserver variability

The ICC for absolute agreement of single measures for Dmax, Dmin, and Davg was 0.660 (95%CI: 0.315-0.851), 0.841 (95%CI: 0.645-0.934) and 0.813 (95%CI: 0.572-0.923) respectively. For the annulus area and circumference the ICC was 0.844 (95%CI: 0.631-0.937) and 0.856 (95%CI: 0.630-0.940) respectively.

4. Discussion

The primary findings of our study are: a) sizing the aortic prosthesis using the annulus circumference-derived diameter as opposed to area-derived diameter, would result in a potentially different prosthesis size in 26.7% of patients using a theoretical single sizing guide, b) the use of annulus circumference (D_{circ}) to size the TAVI prosthesis results in significantly lower prevalence of PVAR without additional risks compared to the sizing method using annular area (D_{area}), c) the cover index, the area mismatch index and the circumference mismatch index are all associated independently with PVAR.

Hahn et al. [11] propose a sizing algorithm using the annular area for the balloon-expandable valves and the cardiac CT expert consensus recommendations provide guidance for CT-based sizing of self-expanding valve using the mean diameter, the area or the circumference of the aortic annulus [12]. A manufacturer of a new generation balloon-expandable valve (Edwards Sapien 3) provides a sizing guide and suggests using the 3D annular area and 3D area-derived diameter to select the correct TAVI prosthesis.

We have incorporated the circumference-derived diameter into our TAVI protocol to select prosthesis size, and we tested the hypothesis that this method may have an impact on the prosthesis size when compared to an area based calculation. The aortic annulus is often not circular or more precisely is seldom a perfect circle in shape [13]. Therefore, annuli of the same area may have a different circumference depending on the annulus shape. In Figure 3 we present an example of circular and elliptical annular shapes with the same area but a different circumference. The area-

derived diameters will be identical in both cases leading to the use of an identical prosthesis size despite the different shape of the annulus. On the contrary, the circumference-derived diameters will be different in both cases which could possibly lead to the selection of a different prosthesis size. Indeed, according to our results 26.7% of 262 patients would be potentially candidates for a different prosthesis size if one method was used as opposed to the other.

The critical question is whether the discrepancy between the two methods of annulus sizing may have an impact on clinical outcome. Our study was not designed to investigate the clinical outcome in TAVR patients, but it is well-known that under-sizing or over-sizing the prosthesis may have significant adverse results [14] and furthermore significant paravalvular AR has been reported to have negative impact on long-term outcome [15]. We investigated the prevalence of PVAR in our population and we concluded that the odds for patients who receive a prosthesis based on D_{area} were 2.4 times higher for developing paravalvular aortic regurgitation as opposed to D_{circ} . This finding is independent of other known predictors of PVAR like cover index or area mismatch index [10, 6]. However, the very limited use of new generation valves in the D_{area} group may remain a confounder. Despite the results of the multi-variable analysis we sought to investigate this further. In the D_{circ} group (N=135) we used the Sapien XT valve in 57 patients (42.2%) and the Sapien 3 in 78 (57.85%). We performed a sub-group analysis only in this group and the type of valve was not found to be related to PVAR in univariable analysis (OR: 1.32, 95% CI:0.612-2.844, $p=0.479$). Additionally, we investigated only the patients who received a Sapien XT valve (N=179). In a multi-variable model, the sizing method was found again to be

significantly related to PVAR (OR: 0.420, 95%CI: 0.199-0.884; $p=0.022$) along with the cover index (and interchangeably the area and circumference mismatch indices) (OR: 0.904; 95% CI:0.844-0.969, $p=0.004$).

There is no similar comparison between the two methods in the literature and although this is not a randomised clinical trial we believe that these findings are of great relevance to clinicians and the industry when considering prosthesis-sizing for TAVI procedures. We have recorded three cases of patients who developed complications which may be related to valve oversizing. Two of them were in the D_{area} group and 1 in the D_{circ} group. These patients were excluded from the study due to inherent difficulties in assessing the PVAR. Despite the small number of complications there was no increased risk of oversizing the prosthesis associated with the use the D_{circ} in our series. Overall, the better outcome, in terms of PVAR, of patients who had a prosthesis sized by D_{circ} , can be explained by the fact that the circumference-derived diameter corrects for the ellipsoid shape of the annulus, a factor that has been related to PVAR in previous studies [16].

Another finding of our study is that low cover index is associated with paravalvular AR in an adjusted model. This is in consistency with a previously published study by Detaint et al. [10]. Also the area mismatch index is an independent predictor of PAVR and Gripari et al [17], report similar findings using the “area cover index” defined as the percentage difference between planimetered annulus area and the nominal prosthesis area ($1 - \text{Annulus area}/\text{Prosthesis nominal area}$). Additionally, we tested the circumference mismatch index which also showed significant and independent correlation with PVAR.

Based on the results of our study it seems that the type of prosthesis is associated with PVAR. The new generation Sapien 3 valve was related to lower degree of PVAR compared to the Sapien XT valve. However, this finding is possibly related to the very small numbers of Sapien 3 valves used in the D_{area} group. Also, our study was not powered to make comparisons between valves. Therefore, these results are limited by significant statistical bias and no definite conclusions can be made.

In our study the aortic valve calcification was not correlated with PVAR. Jilaihawi et al. [18] using CT, demonstrated that valve calcification is an independent predictor of PVAR and leaflet calcium volume greater than 234 mm^3 can predict PVAR. Gripari et al. [17] demonstrated that the calcification between the right and non-coronary cusps as assessed with TEE, is an independent predictor of PVAR. However, Jilaihawi et al. [19] in another study with CT did not confirm correlation of AV calcification with PVAR using a semi-quantitative method. Santos et. al. [6] report that AV calcification in TEE was not related to PVAR using a semi-quantitative method similar to ours. These discrepancies in literature probably reflect the limitations and bias of semi-quantitative methods.

This is a single center study with the inherent limitations and bias. We have used current recommendations to assess PVAR [7], which may have some limitations as they are based in 2D color tomographic planes, therefore may not accurately estimate the 3D anatomic and spatial characteristics of the regurgitant jet. It is worth stating again, that in our population, there were no patients with moderate, moderate-to-severe or severe PVAR based on the 5-grade scheme we used [7]. A more simple system for grading PVAR could have also been used (i.e. mild, moderate

and severe PVAR), which actually may be more functional in clinical practice. The method of sizing the TAVR prosthesis is associated with PVAR in our study, but this is an observational study, with retrospective design and is therefore hypothesis-generating, which is a significant limitation. The assignment of patients to sizing method groups was not made randomly but was based on our center's protocol in two separate chronological periods. The D_{area} method was used earlier in time. Therefore, it may be claimed that the better outcome in the D_{circ} group may just reflect the learning curve of the operators, which is an important limitation. However, the team involved in the TAVI procedures in our center has remained unchanged since 2007 and there was a 2-year experience with 64 cases prior to the beginning of this study. The assessment of valve calcification was made using a semi-quantitative method, therefore was subjective and operator dependent. We did not take into account the effect of procedural factors such as balloon volume for the Sapien S3 valve and the depth of prosthesis implantation. All annulus measurements were performed in 3D TEE images and there was no direct comparison with CT measurements. However, good correlation has previously been described between 3D TEE and CT measurements [4, 5, 20]. Ng et al. [4] have demonstrated that 3D TEE underestimates the aortic annulus area compared to CT. Based on that, one may assume that the D_{circ} method cancels out this underestimation resulting in less PVAR. However, Tamborini et al. [20] showed very good agreement between 3D TEE and CT measurements. Our findings may equally apply to CT based annulus measurements, but certain conclusions cannot be made. Finally, we assessed only balloon-expandable valves (Edwards Sapien XT and Sapien 3), and extrapolation of results for self-expanding valves cannot be made. Ideally, a randomized trial with present generation prostheses

would be the best way to address our hypothesis about prosthesis sizing. However, the rapid evolution of TAVR valve types may always render such a study difficult to assess contemporary valves, unless it is designed in a multi-center fashion.

5. Conclusion

Accurate assessment of the aortic annulus is paramount for a successful result in TAVR procedures. However, there are several methods used for sizing the aortic annulus and manufacturers provide guidance based on annular area and diameter. In this study we demonstrate that if the circumference-derived diameter, was used to select the TAVR prosthesis, as opposed to area-derived diameter, one out of four patients would have had TAVR of a different sized prosthesis. The sizing method using the circumference-derived diameter results in a lower incidence of paravalvular aortic regurgitation. The correlation of the sizing method with paravalvular aortic regurgitation is independent of other factors like cover index, area mismatch index and circumference mismatch index. Our findings suggest that sizing the TAVR prosthesis by aortic annulus area measurements may have geometrical drawbacks which can be eliminated by using annulus circumference measurements. However, whether this holds true with the use of new generation valves, needs to be further investigated.

Disclosures

Prof. Olaf Wendler is a proctor for Edwards LifeSciences and has received speakers' fees from Edwards LifeSciences, Medtronic and JenaValve.

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Tables

Table 1. Baseline characteristics in the groups of the two different methods for sizing the prosthesis

Table 2. Allocation of patients in prosthesis size groups based on effective diameter derived by the circumference or the area of aortic annulus.

Table 3. Uni-variable logistic regression analysis of possible factors associated with mild or greater paravalvular aortic regurgitation following TAVR.

Table 4. Multi-variable logistic regression analysis of factors associated with mild or greater paravalvular aortic regurgitation following TAVR.

Tables

Table 1. Baseline characteristics in the groups of the two different methods for sizing the prosthesis

	Prosthesis Sizing		p value	All (N=262)
	Based on D _{area} (N=127)	Based on D _{circ} (N=135)		
Age	84.4 ± 5.9	82.5 ± 6.6	0.011	83.4 ± 6.3
Gender (male)	57 (44.9%)	69 (50.7%)	0.313	126 (48.1%)
Aortic Valve Area (cm ²)	0.70 ± 0.20	0.74 ± 0.20	0.058	0.72 ± 0.20
Peak Pressure Gradient (mmHg)	75.7 ± 22.9	73.3 ± 23.8	0.404	74.5 ± 23.4
Mean Pressure Gradient (mmHg)	42.8 ± 14.9	41.8 ± 14.1	0.564	42.3 ± 14.5
Maximum Velocity (m/sec)	4.3 ± 0.7	4.2 ± 0.7	0.268	4.3 ± 0.7
Baseline AR			0.204	
No AR	63 (49.6%)	51 (37.8%)		114 (43.5%)
Mild	60 (47.2%)	79 (58.5%)		139 (53.1%)
Moderate or Severe	4 (3.1%)	5 (3.7%)		9 (3.4%)
Severe AV calcification	44 (34.6%)	42 (31.1%)	0.543	86 (32.8%)
Maximum diameter (mm)	24.7 ± 2.7	25.1 ± 2.8	0.162	24.9 ± 2.8
Minimum diameter (mm)	20.6 ± 2.2	20.6 ± 2.5	0.909	20.6 ± 2.4
Average diameter	22.6 ± 2.3	22.9 ± 2.4	0.372	22.8 ± 2.3
Eccentricity Index (1-D _{min} /D _{max})	0.16 ± 0.07	0.18 ± 0.09	0.138	0.17 ± 0.08
Annular Area (cm ²)	4.10 ± 0.82	4.20 ± 0.84	0.361	4.15 ± 0.83
D-area (mm)	22.8 ± 2.3	23.0 ± 2.3	0.366	22.9 ± 2.3
Annular Circumference (cm)	7.28 ± 0.72	7.41 ± 0.75	0.144	7.35 ± 0.74

D-circ (mm)	23.2 ± 2.3	23.6 ± 2.4	0.145	23.4 ± 2.3
Cover Index	8.81 ± 6.84	9.11 ± 5.90	0.710	8.96 ± 6.37
Area Mismatch Index	-0.77 ± 0.64	-0.85 ± 0.57	0.335	-0.81 ± 0.61
Circumference Mismatch Index	-0.52 ± 0.54	-0.52 ± 0.48	0.918	-0.52 ± 0.50
Valve type			< 0.001	
Sapien XT	122 (96.1%)	57 (42.2%)		179 (68.3%)
Sapien 3	5 (3.9%)	78 (57.8%)		83 (31.7%)
Transfemoral approach	72 (56.7%)	108 (80.0%)	< 0.001	180 (68.7%)
Mild or greater PVAR	70 (44.9%)	36 (26.7%)	< 0.001	106 (40.5%)

D_{area}: Area-derived diameter, D_{circ}: Circumference-derived diameter, AR: Aortic regurgitation,

AV: Aortic valve, PVAR: Paravalvular aortic regurgitation

Table 2. Allocation of patients in prosthesis size groups based on effective diameter derived by the circumference or the area of aortic annulus.

Valve size by D_{area}	Valve size by D_{circ}						Total
	Too small	23 mm	23 or 26 mm	26 mm	26 or 29 mm	29 mm	
Too small	7	22	0	0	0	0	29
23 mm	0	106	6	11	0	0	123
23 or 26 mm	0	0	0	10	0	0	10
26 mm	0	0	0	59	6	11	76
26 or 29 mm	0	0	0	0	0	4	4
29 mm	0	0	0	0	0	20	20
Total	7	128	6	80	6	35	262

Table 3. Uni-variable logistic regression analysis of possible factors associated with mild or greater paravalvular aortic regurgitation following TAVR.

Variables	OR (95% CI)	p value
Age	1.02 (0.98-1.06)	0.295
Gender (male)	0.73 (0.44-1.20)	0.210
Aortic Valve Area	0.20 (0.05-0.73)	0.015
Peak Velocity	1.45 (0.99-2.13)	0.059
Greater than mild baseline AR	1.88 (0.49-7.18)	0.355
Severe AV calcification	1.56 (0.92-2.62)	0.097
Maximum diameter	1.05 (0.96-1.15)	0.284
Minimum diameter	1.08 (0.97-1.20)	0.163
Eccentricity Index (1-Dmin/Dmax)	0.43 (0.18-10.30)	0.598
Annular Circumference	1.14 (0.82-1.60)	0.433
Cover Index	0.91 (0.87-0.95)	<0.001
Valve type (Sapien XT vs Sapien 3)	2.67 (1.50-4.75)	0.001
Sizing method (Dcirc vs Darea)	0.30 (0.18-0.50)	<0.001
Transfemoral approach	0.84 (0.49-1.44)	0.531

AR: aortic regurgitation, OR: odds ratio

Table 4. Multi-variable logistic regression analysis of factors associated with mild or greater paravalvular aortic regurgitation following TAVR.

Variables	OR (95% CI)	p value
Cover Index	0.91 (0.86-0.96)	< 0.001
Valve type (Sapien XT vs Sapien 3)	2.39 (1.08-5.32)	0.032
Sizing method (Dcirc vs Darea)	0.44 (0.23-0.85)	0.015

Figure Legends

Figure 1. Aortic annulus measurements in a 3D Trans-esophageal echocardiography dataset.

Figure 2. Long axis view of the aortic valve showing significant eccentric calcification on non-coronary cusp.

Figure 3. Typical examples of circular and ellipsoid aortic annulus shapes. Despite the difference in shape, the annular circumference is identical in both cases whereas the area is smaller in the ellipsoid shape.

Figures

Figure 1. Aortic annulus measurements in a 3D Trans-esophageal echocardiography dataset

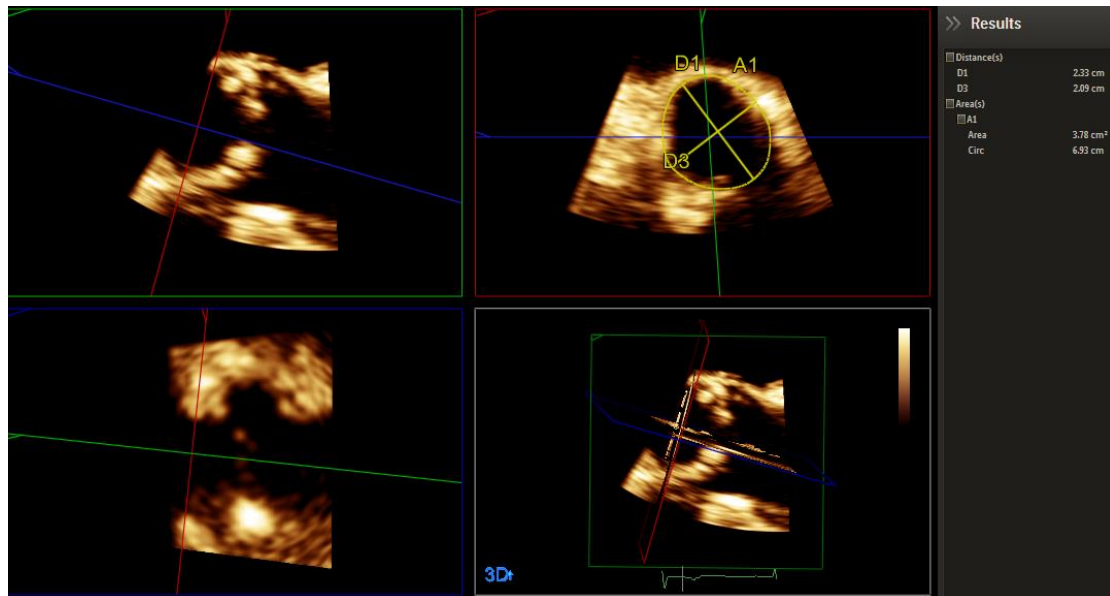


Figure 2. Long axis view of the aortic valve showing significant eccentric calcification on non-coronary cusp.

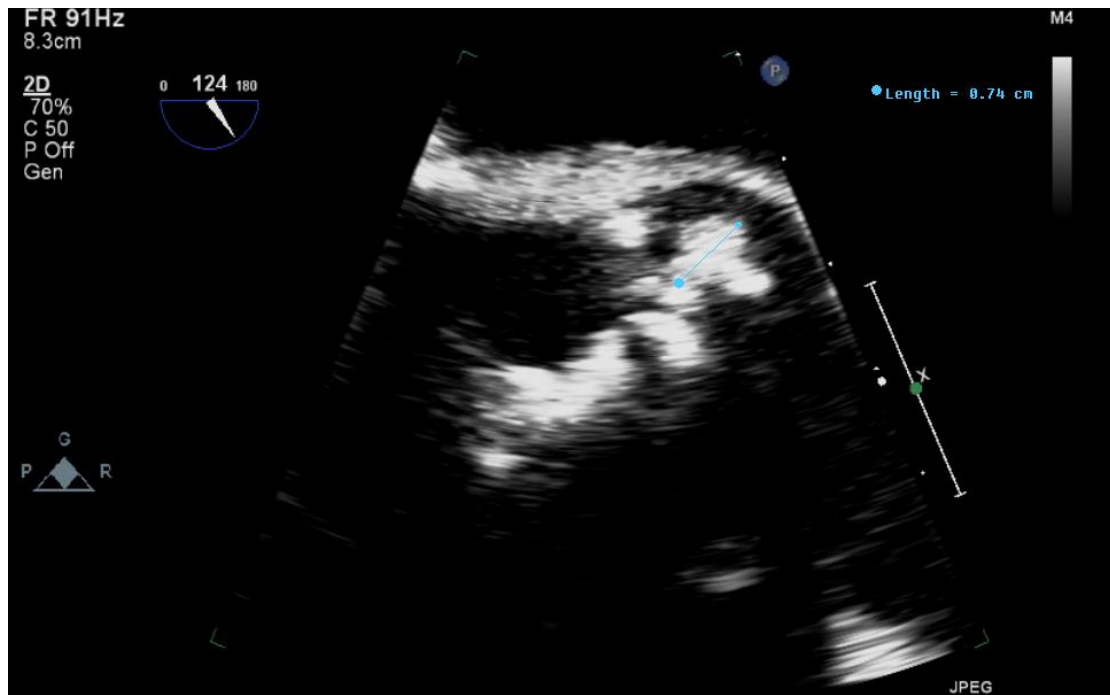


Figure 3. Typical examples of circular and ellipsoid aortic annulus shapes. Despite the difference in shape, the annular circumference is identical in both cases whereas the area is shrinking as the shape is becoming more ellipsoid.

