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Transcatheter mitral valve replacement (TMVR): annular or apical fixation ?

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Short title:

Fixation technique for Transcatheter mitral valve replacement

ABSTRACT

Aims. The aim of this study was to evaluate the impact of two different transcatheter mitral valve replacement (TMVR) fixation strategies on the neo left ventricular outflow tract (neo-LVOT) and aorto-mitral angulation (AMA) after TMVR.

Methods and results. Two different self-expandable nitinol valved stents were developed for transapical TMVR. In one group, the stents were fixed with an **annular** fixation system (**ANN** group, n=6). These prototypes were compared with an **apical** tether fixation TMVR system (**AP** group, n=11) in another group. Echocardiographic evaluation of the AMA and the neo-LVOT was conducted before and one hour after implantation. Maximal and minimal AMA (AMA_{max} and AMA_{min}) during the cardiac cycle of the AP group were significantly narrower than those of the ANN group (AMA_{max}: 39 ±8° vs. 67 ±15°, p<0.001, AMA_{min}: 33 ±10° vs. 56 ±22°, p=0.009). More severe reduction of the neo-LVOT diameter was observed in the ANN group (60 ±11% vs. 26 ±14%, p<0.001). The ANN group had a higher peak velocity through the neo-LVOT post-implantation (200 ±52cm/s vs. 108 ±15cm/s, p<0.001).

Conclusion. The apical fixation system maintains a smaller and more stable aorto-mitral angulation and a larger neo-LVOT, thereby reducing the risk of postoperative neo-LVOT obstruction in this experimental setting.

Classifications: Mitral valve disease, other, transapical, TAVI

Abbreviations: TMVR= transcatheter mitral valve replacement, LVOT= left ventricular outflow tract, AMA= aorto-mitral angulation, neo-LVOT= neo left ventricular outflow tract, LVOTO= LVOT obstruction, PVL= paravalvular leakages, CT= computed tomography, AML= anterior mitral leaflet, TEE= transesophageal echocardiography,

Condensed abstract:

The neo left ventricular outflow tract (Neo-LVOT) after Transcatheter mitral valve replacement (TMVR) influences patient´s outcome. To address this problem, positioning and fixation technique of the stented valve is crucial. Aim of this study was to evaluate the impact of two different TMVR fixation strategies on the neo-LVOT and the aorto-mitral angulation (AMA). TMVR with apical fixation resulted in smaller and more stable aorto-mitral angulation and a larger neo-LVOT than annular fixation, thereby reducing the risk of postoperative neo-LVOT obstruction in this experimental setting.

Introduction

Transcatheter mitral valve replacement (TMVR) has been developing at an unprecedented rate since the world's first-in-man on-pump TMVR in June 2012 in Copenhagen, Denmark (1). One year later, the first in-man off-pump transapical TMVR was performed by our working group (2). In recent years, to investigate the feasibility of TMVR procedure in high-risk patients with severe symptomatic mitral regurgitation, clinical feasibility trials of different types of TMVR prostheses have been carried out (3). Meanwhile, a considerable number of cases using TAVR prostheses in the mitral position within surgical rings (valve-in-ring), failed mitral bioprosthetic valves (valve-in-valve) or in cases of severe mitral annular calcification (valve-in-MAC) were reported (6-10).

However, new challenges still arise, especially for cases with a native mitral valve. The adjacent relationship between the mitral valve complex and the left ventricular outflow tract (LVOT) may be of particular importance. It has been revealed with cardiac computed tomography (CT), that the device itself and the native anterior mitral leaflet (AML) may cause LVOT obstruction (LVOTO). An increasing number of LVOTO cases have been reported and LVOTO after TMVR has gained more recognition in the literature (11,12).

The concept of the neo-LVOT emerged during the last years and was considered a predictive factor for LVOTO after TMVR (12,13). The neo-LVOT is created by the prosthesis, the AML, and the interventricular septum. Theoretically, in addition to prosthesis-related factors, aorto-mitral angulation (AMA), the thickness of the basal septum and the left ventricular size are the main factors which influence the neo-LVOT dimensions.

In the present study, we tested two mitral valved stent prototypes for the TMVR procedure. In one group the valved stents were fixed in the mitral annulus by an apical tether fixation system (AP group) which had been previously presented by our group (14-16). In the other group, the valved stents were anchored by an annular fixation system (ANN group). The aim of this study was to evaluate and compare the effects of the two fixation systems on the AMA and the neo-LVOT in an *in vivo* porcine model.

Material and methods

Mitral valved stents

In the ANN group the mitral valved stents consisted of a modified D-shaped atrial cuff D-shaped annular stent body which was fabricated with additional 20 annular lateral struts to achieve secure systolic annular fixation. This was tested before in vitro by our working group. using an *in vitro* force-measurement system (17). The height of the ventricular element was 13.6±3.6 mm and the short axis was 28.7±1.6 mm (26-30mm) in width. For reducing the risk of any PVL, the stent was covered with a polytetrafluoroethylene membrane (Figure 1). A commercially available tri-leaflet bioprosthetic valve or a native bi-leaflet valve (produced by D.S., University of Clemson) were sewn into the ventricular stent body.

In the AP group, the valved stents also included an atrial cuff and a ventricular body. The mitral valved stent consisted of a double-frame ventricular element. The outer frame of the ventricular element was designed to match the D-shape of the mitral orifice. The D-shaped outer frame gradually bent downward into a circle until connecting to the bottom of the inner frame. The diameter of the circular inner frame together with the bottom outer ring of the valved stent was 28 mm on average in width. It was designed to support the trileaflet bioprosthetic valve. The sizes of the mitral valved stents ranged from 26 to 30 mm and were selected according to the native mitral orifice for the stent fitting the mitral annulus. The average height of the stents of the AP group was 15.9±4.8 mm and the diameter of the ventricular body ring was 28.6 ±0.8 mm. The stent was also covered with a polytetrafluoroethylene membrane. A single apical tether connected to an apical epicardial fixation pad which was attached to the bottom of the stent for anchorage of the overall mitral valved stent (Figure 1).

For the two study groups, two self-expandable nitinol mitral stents were produced by RTM Inc., Medical Group, Germany.

Porcine in vivo model and Mitral valved stent implantation

The experimental implantations were carried out in a well-established porcine model (19, 23). Twenty female pigs of the German Landrace and Edelschwein or their cross-breeds underwent transapical off-pump mitral valved stent implantation (ANN group: n=10, average body weight: 48 ±2 kg, AP group: n=12, average body weight: 47 ±3 kg, p=n.s.). All animals received humane care in compliance with the 'Guide for the Care and Use of Laboratory Animals' prepared by the Institute of Laboratory Animal Resources, revised in 2011. The transapical TMVR procedure via a lower ministernotomy was already described in previous studies of our working group (16, 18).

Measurements

Echocardiographic evaluation of the aorto-mitral angle (AMA), the LVOT diameter (LVOTd) and doppler-derived peak flow velocity through the LVOT (V_{max}) and mitral valve inflow velocity were recorded and analyzed before and one hour after implantation using 2D and 3D TEE. The presence of PVL was also evaluated and recorded after implantation.

The AMA and the LVOTd were measured at two points of time of the cardiac cycle. First, at the end of isovolumic systole or the beginning of isobaric systole, which is the beginning of ventricular ejection. The maximal LVOTd ($LVOTd_{max}$) and the minimal AMA (AMA_{min}) can be observed during this phase of systole. The second measurement was at the end of isobaric systole, which is the point in time to record the minimal LVOTd ($LVOTd_{min}$) and the maximal

AMA (AMA_{max}). In this study, the LVOTd was measured as the shortest distance between the ventricular stent bottom rim and ventricular wall using 2D TEE in the left ventricular long axis view. The AMA was defined as the angle formed by the center axis of the aortic annulus and the mitral annulus before implantation. After stent implantation, it was defined as the angle between the center axis of the aortic annulus and the tube-shaped ventricular element of the stent (Figure 2).

Statistical analysis

All statistical analyses were performed using the statistical software package SPSS (IBM SPSS Statistics for Windows, Version 23; IBM Corp., Armonk, NY, USA). Continuous variables are expressed as mean and standard deviation and categorical data as count and percentages. Changes in echocardiographic parameters from baseline after TMVR within the two groups were evaluated with the dependent t-test for paired samples. Inter-group comparisons were conducted with the Student's t-test or Mann-Whitney-U-test for two independent samples. The probability of a type I error was set to 5% ($\alpha = 0.05$).

Results

The main results are summarized in Table 1 and 2.

Seventeen animals successfully underwent the TMVR procedures. In addition, one animal of the AP group and 2 animals of the ANN group died prior to stent implantation due to ventricular fibrillation. Two stents of the ANN group were malpositioned into the left atrium or into the left ventricle. These two animals were excluded from this study, respectively.

All animals had structurally normal hearts with no mitral or aortic valve stenosis or regurgitation. Among the 17 animals who underwent a successful TMVR procedure, peak inflow velocity across the valved stent after implantation was 120 ±9 cm/s in the ANN group and 108 ±33 cm/s in the AP group (p=0.42), reflecting a normal mitral valve inflow gradient (Table 2). Mild PVL occurred in 3 animals of the ANN group and 4 animals of the AP group.

Additionally, trace PVL was observed in 2 of 11 animals of the AP group. All subsequent animals demonstrated no PVL. Valvular leakages were not observed in the overall cohort, except two trace leakages in each of the study groups.

Intra-group comparison

In the ANN group, echocardiographic evaluation revealed an enlarged AMA at both points in time after stent implantation (AMA_{max}: p=0.002, AMA_{min}: p=0.011), while no significant differences for the post-implantation AMA data were observed in the AP-group compared to the pre-implantation data. Furthermore, in the AP group, the difference between AMA_{max} and AMA_{min} slightly decreased after implantation (p=0.01). In both groups, the neo-LVOTd was smaller than the native LVOTd at both measurement points (p<0.001).

Especially, in the ANN group, the neo-LVOTd at the end of isovolumic systole was only 39.8 ±11.5% of the native LVOTd. While in the AP group, the neo-$LVOTd_{max}$/$LVOTd_{max}$ was 74.5±13.6%. In contrast to the laminar LVOT flow at baseline, the peak velocity through the LVOT after implantation was slightly elevated in the ANN group with 200 ±52 cm/s. No relevant flow acceleration in the LVOT after TMVR was noted in the AP group 108 ±15 cm/s.

Inter-group comparison

After stent implantation, both the AMA_{max} and the AMA_{min} of the AP group were significantly smaller than those of the ANN group (AMA_{max}: p<0.001, AMA_{min}: p=0.009). Accordingly, compared to the AP group, more severe reduction of neo-LVOTd was observed in the ANN group, regardless of the absolute value or ratio (p<0.001). The ANN group had a higher peak flow velocity through the neo-LVOT post-implantation (p<0.001) (Table 2, Figure 3).

Discussion

In these porcine experiments we demonstrated for the first time that apical fixation of the mitral valve prosthesis in native mitral valves results in a smaller postoperative aorto-mitral angle (AMA) in comparison to annular fixation. Therefore, apical fixation is more favorable for achieving a larger neo-LVOT and reducing the risk of LVOT stenosis. This might have been due to the perpendicular implantation of the apically fixed stent. In contrast, the annularly fixed are self-seading after its deployment.

Since its first description in 2015, the concept of neo-LVOT after TMVR has become a concerning issue influencing the patient's outcome (11). Yoon retrospectively investigated 194 patients with TMVR for valve in valve, valve in ring, and valve in calcified mitral annulus procedures. They simulated TMVR by multidetector row computed tomography and calculated the cross-sectional neo-LVOT area. Narrow neo-LVOT (below 1.7 cm^2) was considered a predictive factor for LVOT obstruction after TMVR. This occurred significantly more often in patients with calcified native mitral valves. Moreover the data showed that patients with a neo-LVOT area ≤ 1.7 cm^2 in preoperative CT assessment had an LVOT obstruction rate of 66%, while the rate was 0.6% in patients with a neo-LVOT area >1.7 cm^2 (17). LVOTO was proven to be positively correlated with mortality after TMVR by the same study, and the problem remains unsolved with currently used TMVR prostheses.

The neo-LVOT is considered an extension of the anatomical LVOT in the left ventricle after TMVR which is composed of the base of the interventricular septum and the mitral prosthesis with or without the AML opposing the interventricular septum. Factors influencing the width of the neo-LVOT are prosthesis-related and anatomical. It is generally accepted that the shape and size of the ventricular part of the mitral prosthesis that forms the neo-LVOT are important prosthesis-related factors. Over-height and oversize may lead to the reduction in neo-LVOT dimensions. The thickness of the base of the interventricular septum is an anatomical factor that is negatively related to neo-LVOT size (12). The problem of narrowing the LVOT when leaving the native mitral valve in place during surgical mitral valve replacement was already described by David et al (19), and was addressed by Miki and associates. They developed a technique resolving the subvalvular apparatus making a T-shaped incision on the anterior leaflet and resuturing the two halves to the annulus near their respective commissures (20). In TMVR, resection of the native valve is not possible. With respect to the innovative potential of TMVR, so far little is known about the neo-LVOT and its relevance after TMVR and the potential risk for postinterventional LVOT obstruction.

The preoperative AMA, formed by the central axes of the mitral annulus and the LVOT, is a parameter that can significantly impact the postoperative neo-LVOT dimensions. A smaller, more acute AMA may lead to lower risk of neo-LVOT obstruction (12). However, after TMVR, the atrioventricular chanal is replaced by the tube-shaped stent-loaded valved prosthesis, and the AMA is formed by the central axes of the tubular structure and the LVOT. Obviously, the direction of the new central axis is similar to that of the native mitral annulus, but the shape and fixation method may alter the AMA. Hence, both prosthetic and non-prosthetic factors influence the AMA.

In both groups of our study, the AMA changed after TMVR compared with the baseline values. However, the maximal and minimal AMA were significantly larger after implantation in the ANN group. In the AP group, changes in AMA were not significant, and the postoperative AMA was even narrower. Obviously, such a difference is related to the transapical fixation system of prostheses used in the AP group. As shown in Figure 4, because of the transapical fixation system, the central axes of stents in the AP group moved towards the apex of the left ventricle and led to a better stabilization of the axes and to lower AMA. In the AP group, the postoperative changes in the AMA during the cardiac cycle (the difference between the maximal and the minimal angulations) were lower compared to preoperative changes. This indicated that the apex fixation system led to not only a smaller but also to a more stable AMA after TMVR.

As we stated before, in the absence of an apical fixation system, the primary directions of the central axes of tubular implants and those of the baseline mitral annulus were similar, which was consistent with the designs of most current TMVR implants. However, the significant difference in changes of AMA showed the technical difficulty in maintaining a correct orientation of the central axis of implants. During the cardiac cycle, because of the prosthesis and its instability, ventricular systole and blood flow significantly disturb the AMA. During cardiac systole, the central axis of the implant changes with the mitral annulus and may sway in turbulence. If the implant is not stable, its displacement would be more evident than the movement of the native mitral annulus. Therefore, stable fixation of the implant leads to a lower change in central axis direction and the implant's central axis is more consistent with the central axis of the autologous mitral annulus. Without annular fixation, blood flow during systole may push the interior part of the stent and displace the ventricular part of stent towards the native LVOT, thus increasing the AMA significantly. Even by reducing the membrane's size on the stent to reduce the impact area or resistance, the anterior leaflet of the mitral valve covers the exterior part of the stent and is subject to blood flow, bulging toward the LVOT. In some TMVR implants, the anterior leaflet may displace the implants. As shown in Figure 5, the AML was pushed towards the aortic annulus which might be the cause of increased aortomitral angulation after TMVR. We believe that the apical fixation system not only stabilizes the implants, makes the central axis apically-oriented and reduces the AMA, but also reduces the impact of blood flow on the stent wall and further stabilizes the implant during cardiac systole. In some clinical cases the apical fixation can be done even more posterolateral to reduce the AMA. This has not been done in this study. In the AP group all apical fixations have been performed perpendicularly towards the true apex.

Aorto-mitral angulation was significantly associated with LVOTO in our experiments. Reduction in the width of LVOT was over 60% in the ANN group and only 25% in the AP group. Peak LVOT velocity in the ANN group was nearly twice as that in the AP group, and the narrowest width of LVOT was 12.9 ±8.3% of the baseline level at the end of systolic phase. This may reflect the impact of blood flow on implant displacement.

Our study indicated that the AMA plays a critical role in the appearance of neo-LVOT after TMVR. The ANN group had a much narrower neo-LVOTd, even though the height of the ventricle body of the ANN group stents were shorter than that of the AP group stents. Perhaps the TMVR designers and developers should pay more attention to narrowing and maintaining the postoperative AMA to get an ideal area of neo-LVOT.

Furthermore, a tube-shaped ventricular element maybe not the best option for the TMVR devices. Firstly, it directly narrows the LVOT. Above all, it shortens the distance between the interventricular septal bulge and the prosthesis or the AML. Secondly, its inner wall behaves like a sail in the LVOT. If the ventricular body is too high, the stent together with the AML could be pushed towards the aortic annulus. Moreover, the stent wall blocks the closing motion of the AML. It may increase the risk of systolic anterior motion (SAM) of the AML after TMVR (Figure 6). It may be an option to cut off the part of the stent in the LVOT or fix the entire AML on the stent.

Limitations of the study

Though the study might have limitations in the relatively small sample size, the large animal model offers the chance to create reproducible conditions, that should be evaluated further in a clinical setting. Furthermore, as the neo-LVOT is not a strictly simple circular structure and dependent from many anatomical structures like the interventricular septum, the AML and the atrioventricular prosthesis. The visualization of the Neo LVOT would have been more precise by using additional 3D TEE in our experimental study. Nevertheless, for the AMA measurements and functional data the 3D TEE wouldn't have given additional data.

Conclusions

In conclusion, our experiment demonstrates for the first time that an apical fixation system maintains a smaller and more stable AMA and a wider neo-LVOT, thereby reducing the risk of postoperative LVOT obstruction after TMVR.

Impact on daily practice

Narrowed neo-LVOT is associated with LVOT obstruction after TMVR. Most TMVR prostheses are balloon-expandable annular fixated and few focuses on preventing the enlargement of AMA which is a predictor of neo-LVOT. Our study demonstrated that the apical fixation system has a unique advantage in maintaining the AMA and reducing the narrowing of the neo-LVOT.

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Conflict of interest statement

Dr. Frank is a consultant of Medtronic and Edwards Lifesciences and Dr. Lutter of Abbott and Medtronic. The other authors have no conflicts of interests.

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Table 1 Intra-group comparison

TEE parameter	**ANN group** (n=6)			**AP group** (n=11)		
	Pre	**Post**	**P**	**Pre**	**Post**	**p**
LVOTd min [mm]	14.8 ±2.1	1.8 ±1.1	<0.001	15.3 ±1.6	9.0 ±3.0	<0.001
LVOTd max [mm]	19.5 ±2.3	7.6 ±1.9	<0.001	22.4 ±2.8	16.4 ±2.1	<0.001
AMA min [°]	28.1 ±4.6	56.2 ±21.7	0.011	33.6 ±7.6	33.4 ±10.0	0.958
AMA max [°]	39.5 ±4.9	67.2 ±14.9	0.002	44.7 ±8.2	39.3 ±7.8	0.136
Difference of AMA [°]	11.5 ±4.5	11.0 ±16.9	0.946	11.0 ±4.8	5.9 ±3.6	0.010

Pre: pre-implantation; Post: post-implantation; LVOTd min: minimal left ventricular outflow tract diameter; LVOTd max: maximal left ventricular outflow tract diameter; AMAmin: minimal aorto-mitral angulation; AMA max: maximal aorto-mitral angulation

Table 2 Inter-group comparison post implantation

TEE parameter	**ANN group** (n=6)	**AP group** (n=11)	p
Neo-LVOTd min [mm]	1.8 ±1.1	9.0 ±3.0	<0.001
Neo-LVOTd max [mm]	7.6 ±1.9	16.4 ±2.1	<0.001
Neo-LVOTd min/LVOTd min (%)	12.9 ±8.3	69.2 ±20.2	<0.001
Neo-LVOTd max/LVOTd max (%)	39.8 ±11.5	74.5 ±13.6	<0.001
Postoperative AMA min [°]	56.2 ±21.7	33.4 ±10.0	0.009
Postoperative AMA max [°]	67.2 ±14.9	39.4 ±7.8	<0.001
Difference of postoperative AMA [°]	11.0 ±16.9	5.9±3.6	0.345
Postoperative LVOT Vmax [cm/s]	200 ±52	108 ±15	<0.001
Mitral valved stent Vmax [cm/s]	120 ±9	108 ±33	0.421

Neo-LVOTd min: new minimal left ventricular outflow tract diameter; Neo-LVOTd max: new maximal left ventricular outflow tract diameter; AMA: aorto-mitral angulation; Postoperative LVOT Vmax: maximal velocity of the left ventricular outflow tract postoperatively; Mitral valved stent Vmax: maximal velocity across the mitral valved stent

Figure 1: **A**: An atrial view of the bi-leaflet mitral valved stent of the ANN group **B**: ventricular view of a tri-leaflet valved stent of this ANN group; **a**: Inter-commissural length of ventricular part of the mitral valved stent of the ANN group was 32 – 36 mm; **b**: Short axis length of ventricular stent body of ANN group was 28 – 30 mm; **red arrows**: the annular fixation struts on the outside of ANN valved stent **C**: Top view of implanted mitral valved stent of the AP group; **D**: Lateral view of the implanted mitral valved stent within the native mitral annulus of the AP group. The ventricular part of the mitral valved stent face towards the apical fixation system on the apex. **LA**: Left atrium; **LV**: Left ventricle

Figure 2: TEE measurement before (**A**) and after (**B**) stent implantation. **L1** or **L5**: Projection line of the aortic annulus. **L3** or **L7**: Central axis of LVOT. **L2**: Projection line of the mitral annulus. **L4**: Central axis of the mitral annulus. **L6**: Projection of the bottom rim of the stent. **L8**: Central axis of the stent. **A1**: Preoperative AMA. **A3**: Postoperative AMA. **A2**: Sharp angle between L1 and L2. **A4**: Sharp angle between L5 and L6. In terms of geometry, A1=A2 and, A3=A4. In this study, we measured A2 and A4 to obtain the value of the pre- and post-operative AMA.

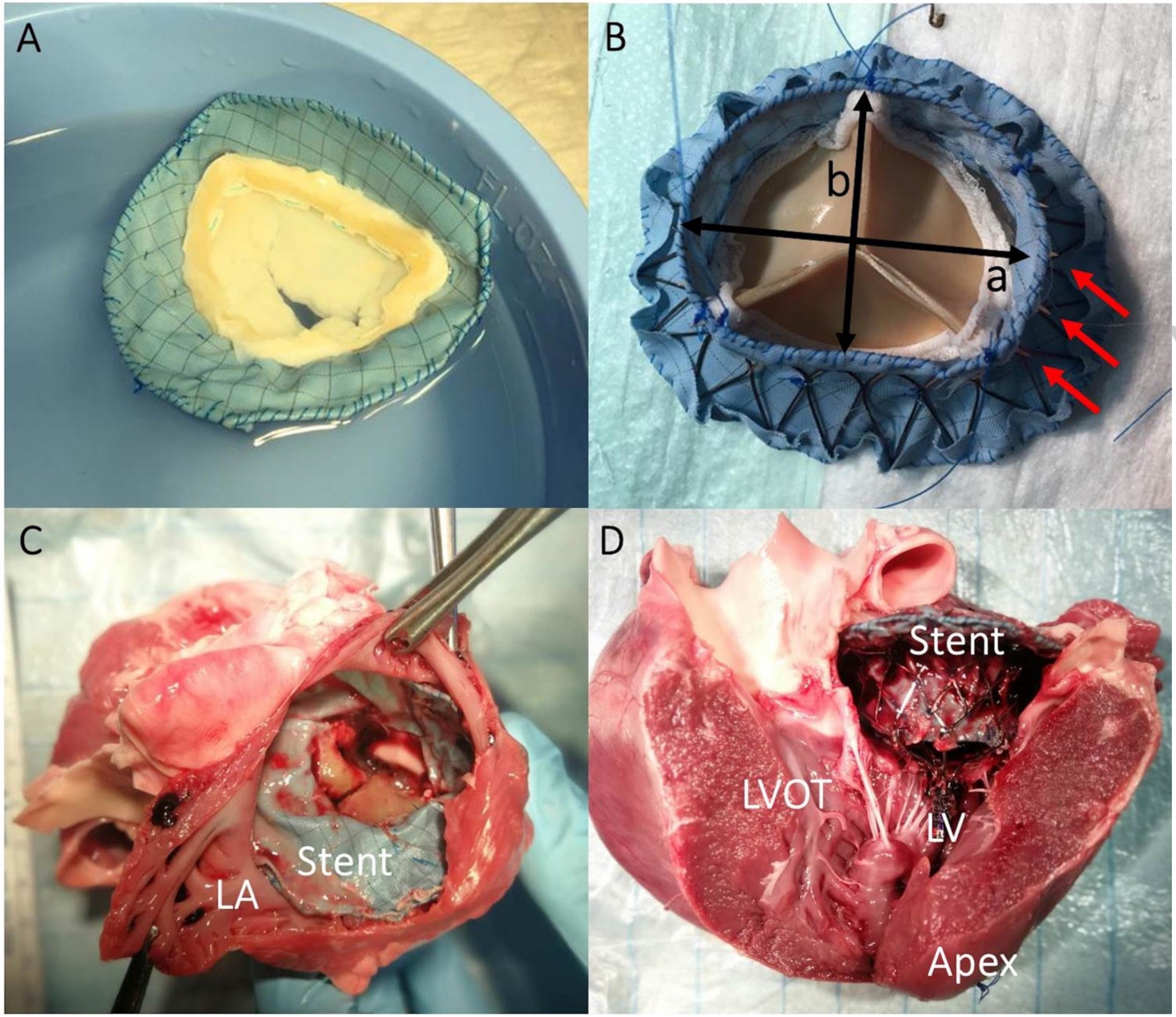
Figure 3: Inter-group comparison of echocardiographic evaluations (ANN group in blue, and AP group in green). * $p<0.01$; ** $p<0.001$. All values are mean ± SEM.

Figure 4: **A**: The left ventricle long axis view after TMVR of the AP group. The bottom of the mitral valved stent is turned toward the apical fixation pad. The aorto-mitral angulation (AMA) is small or narrowed. **B**: The left ventricle long axis view after TMVR of the ANN group. The

bottom of the stent is turned toward the interventricular septum (IVS). The aorto-mitral angulation is enlarged. **C**: Angiographic control after TMVR of the AP group. **Ao**: aorta, **LV**: left ventricle

Figure 5: The left ventricle long axis view after TMVR of the ANN group. The anterior mitral leaflet (**AML**) is pushed toward the aortic valve by the mitral valved stent and the blood flow, causes systolic anterior motion (SAM) and an occluding Neo-LVOT. **IVS**: interventricular septum

Figure 6: **A**: In the AP group, the tether turned the stent toward the apical fixation pad, narrowed the aorto-mitral angulation (AML) and enlarged the neo-LVOT. **B**: Implanted tethered D-shaped valve stent (AP group). **C**: In the ANN group, the stent faced toward the interventricular septum (IVS), enlarged the AML. **D**: Implanted D-shaped annular fixed stent (ANN group).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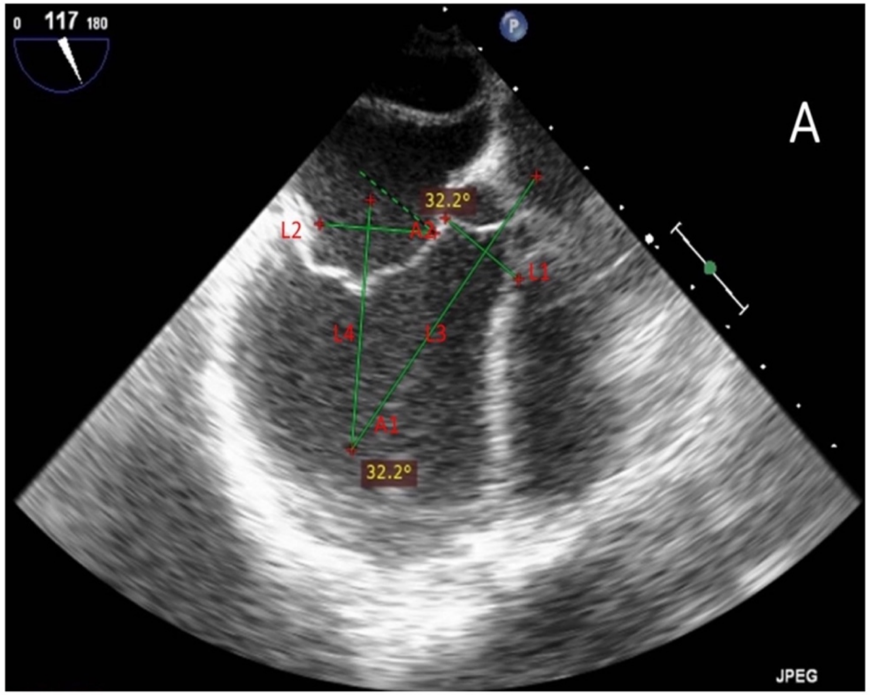
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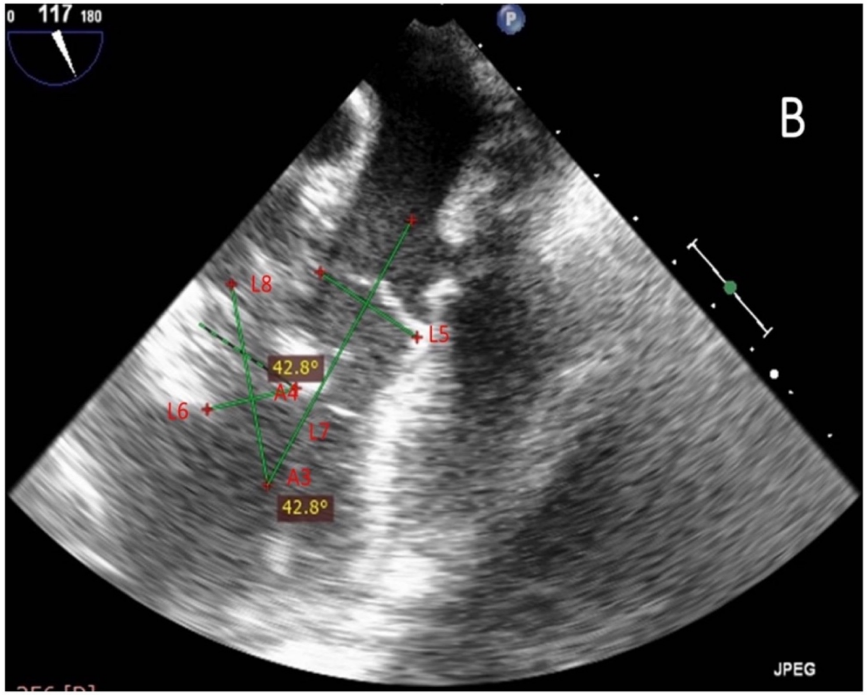
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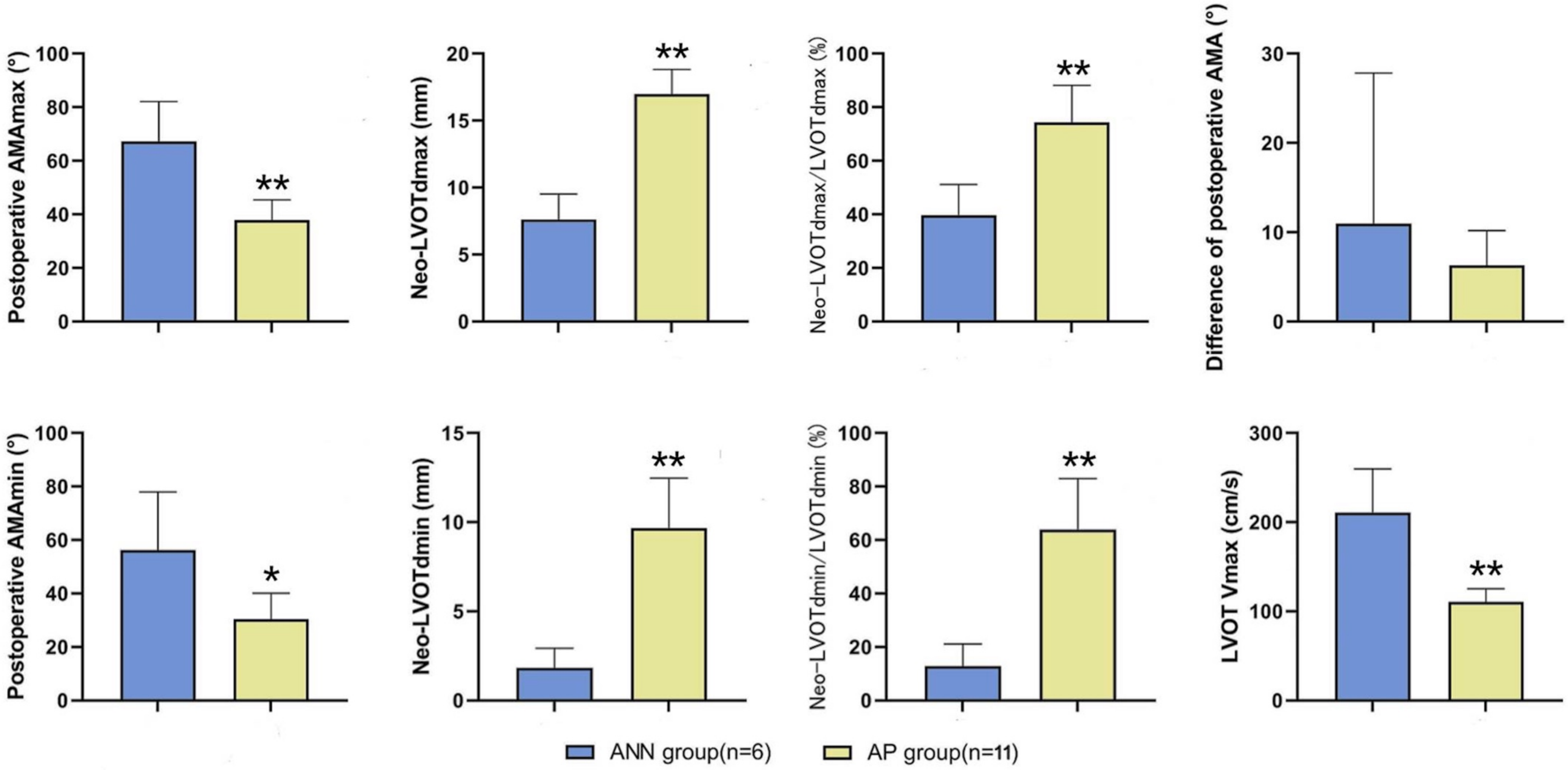

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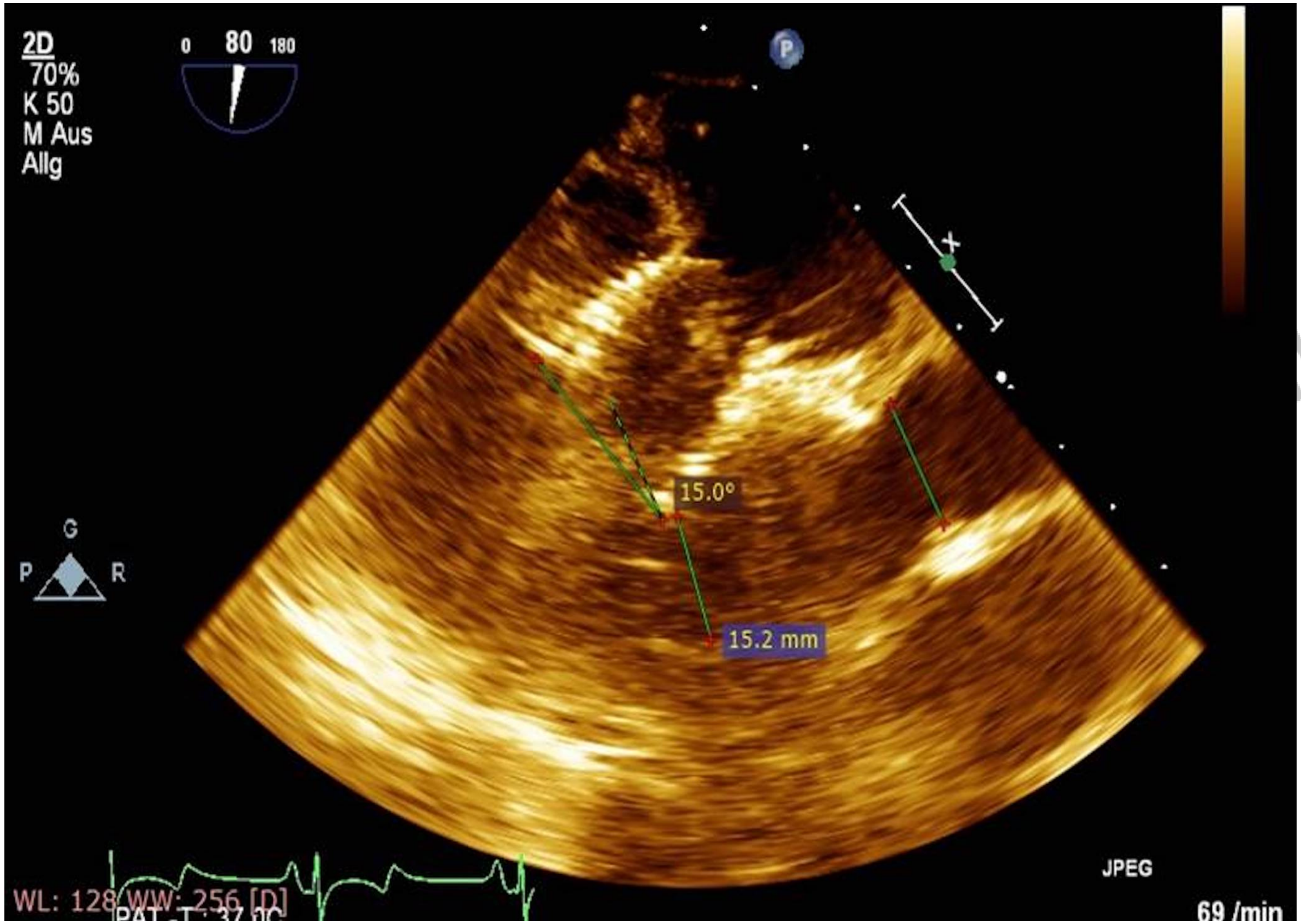
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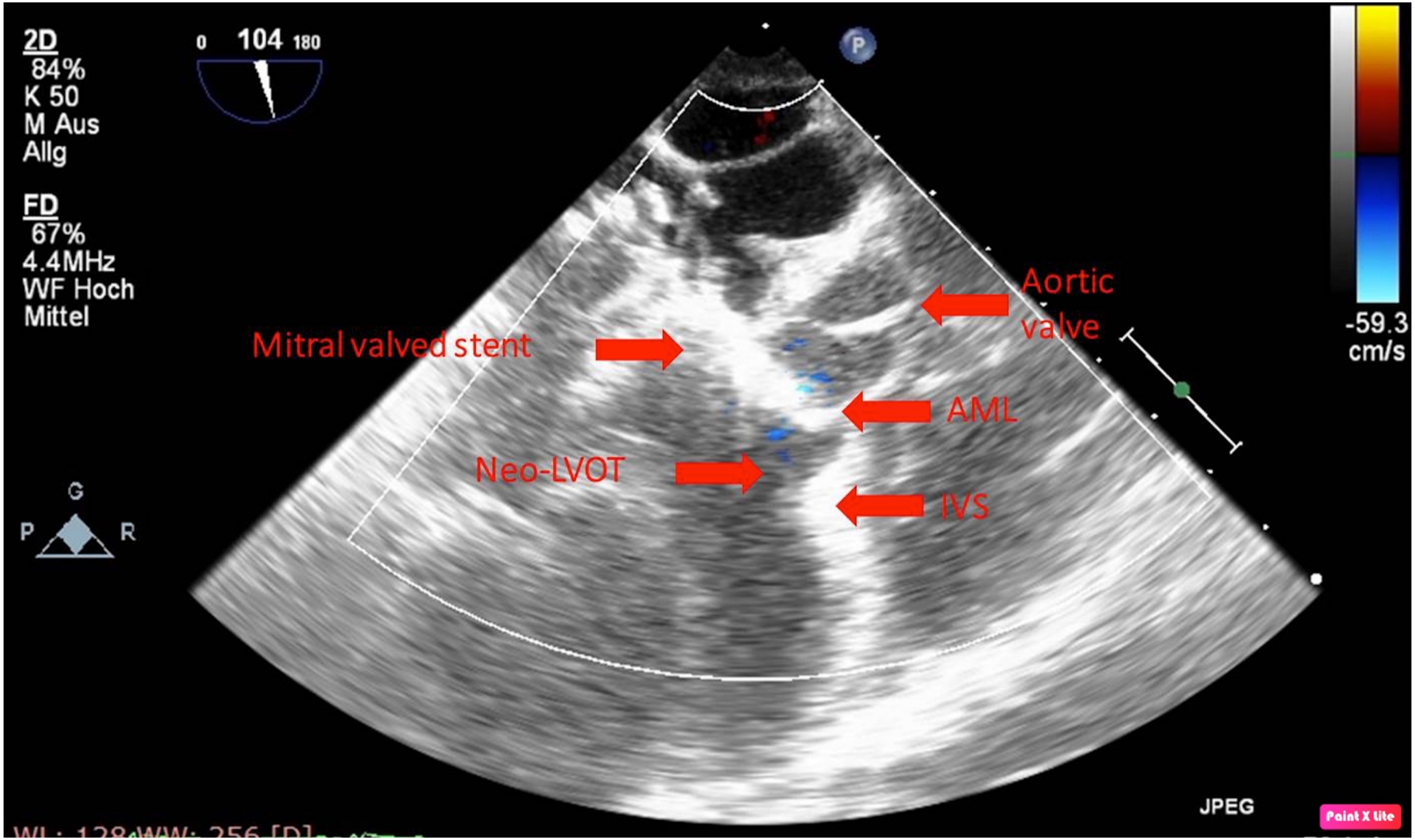
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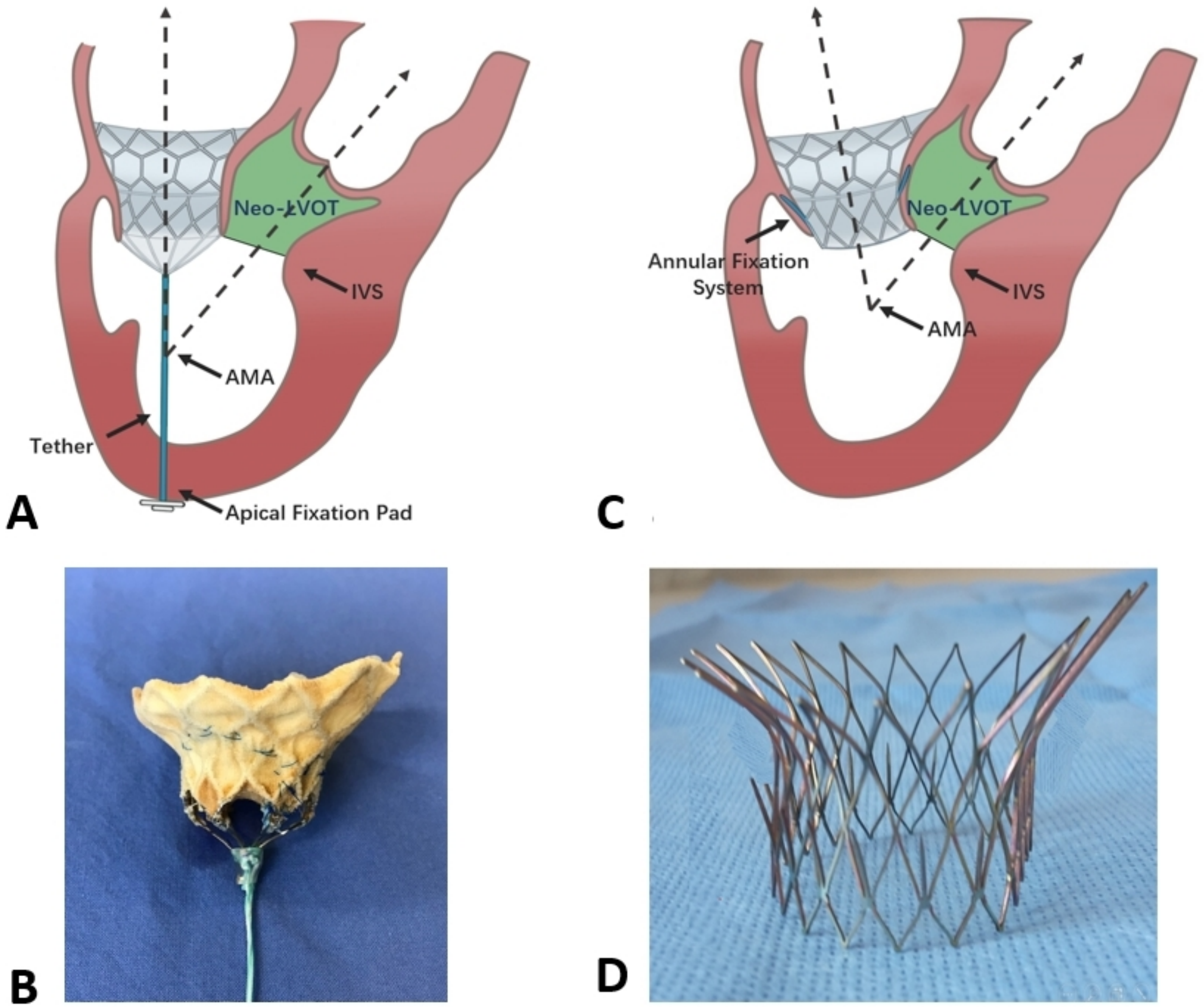
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IVS
AMA
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