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ORIGINAL ARTICLE

Transcatheter aortic valve implantation using anatomically oriented, marrow stromal cell-based, stented, tissue-engineered heart valves: technical considerations and implications for translational cell-based heart valve concepts

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BASIC SCIENCE

Abstract

OBJECTIVES: While transcatheter aortic valve implantation (TAVI) has rapidly evolved for the treatment of aortic valve disease, the currently used bioprostheses are prone to continuous calcific degeneration. Thus, autologous, cell-based, living, tissue-engineered heart valves (TEHVs) with regeneration potential have been suggested to overcome these limitations. We investigate the technical feasibility of combining the concept of TEHV with transapical implantation technology using a state-of-the-art transcatheter delivery system facilitating the exact anatomical position in the systemic circulation.

METHODS: Trileaflet TEHVs fabricated from biodegradable synthetic scaffolds were sewn onto self-expanding Nitinol stents seeded with autologous marrow stromal cells, crimped and transapically delivered into the orthotopic aortic valve position of adult sheep ($n = 4$) using the JenaValve transapical TAVI System (JenaValve, Munich, Germany). Delivery, positioning and functionality were assessed by angiography and echocardiography before the TEHV underwent post-mortem gross examination. For three-dimensional reconstruction of the stent position of the anatomically oriented system, a computed tomography analysis was performed post-mortem.

RESULTS: Anatomically oriented, transapical delivery of marrow stromal cell-based TEHV into the orthotopic aortic valve position was successful in all animals ($n = 4$), with a duration from cell harvest to TEHV implantation of 101 ± 6 min. Fluoroscopy and echocardiography displayed sufficient positioning, thereby entirely excluding the native leaflets. There were no signs of coronary obstruction. All TEHV tolerated the loading pressure of the systemic circulation and no acute ruptures occurred. Animals displayed intact and mobile leaflets with an adequate functionality. The mean transvalvular gradient was 7.8 ± 0.9 mmHg, and the mean effective orifice area was 1.73 ± 0.02 cm^2. Paravalvular leakage was present in two animals, and central aortic regurgitation due to a single-leaflet prolapse was detected in two, which was primarily related to the leaflet design. No stent dislocation, migration or affection of the mitral valve was observed.

CONCLUSIONS: For the first time, we demonstrate the technical feasibility of a transapical TEHV delivery into the aortic valve position using a commercially available and clinically applied transapical implantation system that allows for exact anatomical positioning. Our data indicate that the combination of TEHV and a state-of-the-art transapical delivery system is feasible, representing an important step towards translational, transcatheter-based TEHV concepts.

Keywords: Aortic valve • Transcatheter • Transapical • TAVI • Tissue-engineered heart valves • Marrow stromal cells

[†] Both authors contributed equally to this paper.

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) represents an efficient alternative for the treatment of valvular heart disease in the elderly [1–4], and numerous transfemoral and transapical TAVI devices are commercially available [1–9]. The concept of anatomically oriented devices has been suggested to be beneficial with regard to delivery, positioning and the avoidance of coronary obstruction (CO) [2, 5–7, 10].

Table 1: Animal data and preoperative assessment

Parameter	Mean ± SD
Body weight (kg)	57.7 ± 2.5
Diameter aortic annulus (mm)	22.9 ± 0.3
Distance to brachiocephalic trunk (mm)	42.1 ± 2.4
Diameter sinus portion (mm)	29.0 ± 1.0
Diameter sinotubular junction (mm)	24.3 ± 1.6
Height of sinus portion (mm)	14.5 ± 0.7

However, despite these rapid technological advances, the currently utilized prostheses for TAVI are bioprosthetic, containing bovine or porcine tissue, and are thus well known to be accompanied by continuous and progressive degeneration, which may be even accelerated due to structural damage in response to crimping procedures [11]. To overcome such limitations, heart valve tissue-engineering (HVTE) technologies comprising repair, regeneration and growth capacities have been repeatedly suggested. However, a translational, clinically applicable HVTE concept requires a minimally invasive approach for both cell isolation and valve delivery, ideally completely circumventing highly technical, logistical and financial efforts [12–14]. In this regard, and based on previously described techniques in the setting of tissue-engineered vascular grafts [15–18], we have recently introduced a novel, clinically relevant concept of a single-step interventional approach to implant autologous bone-marrow mononuclear cell (BMMC)-based tissue-engineered heart valves (TEHVs) into the pulmonary and systemic circulation of primates and adult sheep [12–14]. However, while these studies were primarily performed using self-made or generic, non-clinical concept stent and delivery systems, a translational, clinically HVTE approach requires the use of state-of-the-art devices, in particular when addressing the systemic circulation [12, 13].

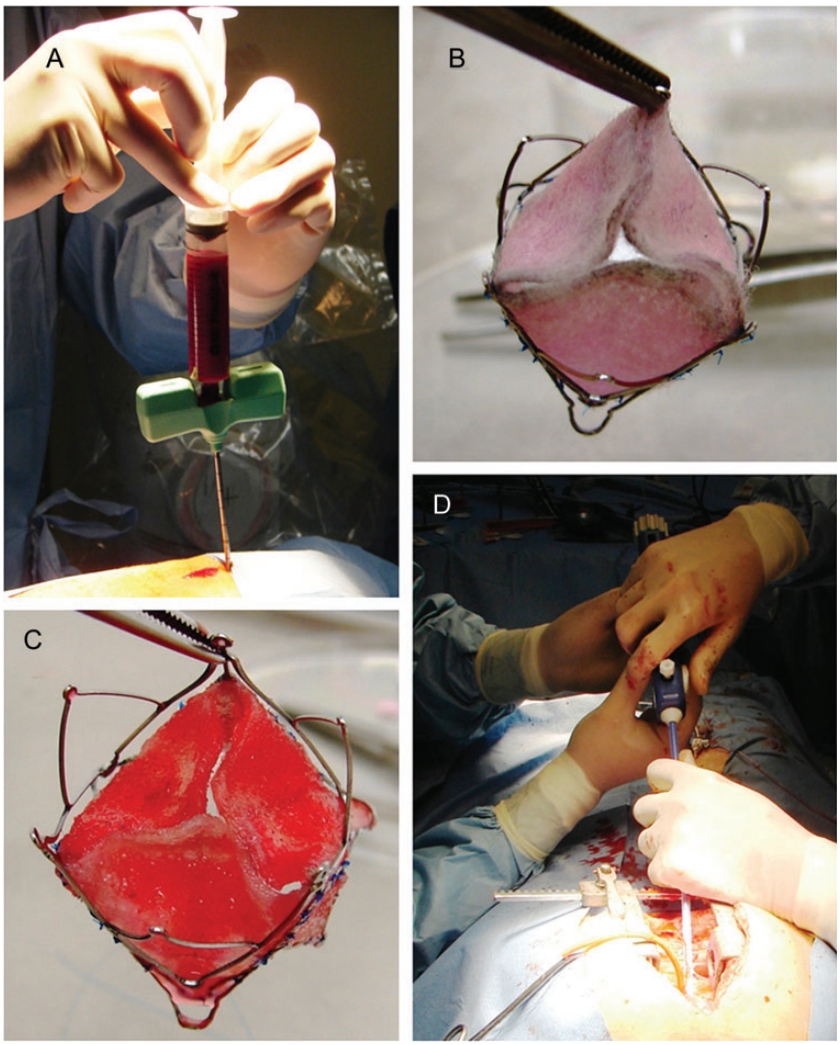

Figure 1: Bone marrow mononuclear cell isolation and TEHV preparation. Sternal bone marrow puncture (**A**) was performed before the prefabricated, stent-based polyglycolic-acid coated with 1.75% poly-4-hydroxybutyrate composite matrices (**B**) were seeded with isolated bone marrow mononuclear cells using fibrin as a cell carrier (**C**) prior to transapical delivery (**D**).

Therefore, the present study investigates the acute technical feasibility of combining the BMMC-based single-step HVTE approach with a clinically used, anatomically oriented state-of-the-art transapical stent delivery system in an adult sheep model with particular regard to TEHV *in vitro* fabrication, delivery, positioning and acute functionality.

MATERIALS AND METHODS

Experimentation approval

All animals received humane care in compliance with the 'Principles of Laboratory Animal-Care' as well as with the 'Guide for the care and use of laboratory animals' published by the National Institutes of Health (publication no. 85-23/revised 1985). All procedures were approved by the Institutional Ethics Committee (Approval-11–15).

Scaffold fabrication and integration into the JenaValve stent

Trileaflet heart valve scaffolds were fabricated from non-woven polyglycolic-acid meshes (PGA; Cellon, Luxembourg), coated with 1.75% poly-4-hydroxybutyrate (P4HB; TEPHA Inc., USA) as previously described [12–14]. Thereafter, the scaffolds were sewn onto self-expanding Nitinol stents. The scaffolds were attached to the inside of the Nitinol stent frames by single interrupted sutures.

Isolation and seeding of ovine autologous BMMCs

Bone marrow mononuclear cells (BMMCs) were isolated via sternal puncture as previously described and characterized in accordance with the established protocols [12–14]. Using fibrin as a cell-carrier (Sigma Chemical, USA), BMMCs were seeded onto the stented heart valve scaffolds ($1.08 \pm 0.5 \times 10^6$ cells/cm^2 valve leaflets), before the stented TEHV was crimped and inserted onto the JenaValve transapical delivery system (JenaValve, Munich, Germany).

Preoperative assessment, planning and sizing

Before implantation, all animals underwent transthoracic echocardiography in order to assess the optimal stent size. Prior to the implantation, intraoperative angiography was done to re-confirm the stent size taking into consideration the following parameters: diameters of the aortic annulus (AA), sinus portion (SP), the sinotubular junction (STJ) and the brachiocephalic trunk (BCT) as well as the distance to the BCT and the height of the SP (Table 1). Three animals received a 25-mm stented TEHV ($n = 3$), while one animal received a 27-mm stented TEHV ($n = 1$).

Transcatheter implantation of BMMC-based TEHV using the JenaValve transapical delivery system

Using the JenaValve transapical delivery system, TEHVs were transapically delivered into the aortic valve position. The valves were crimped and loaded onto a custom-made, over-the-wire JenaValve delivery system (outer diameter = 8 mm). Following a mini-sternotomy and placement of 5/0 Prolene pledgeted, purse string sutures, the apex of the left ventricle was punctured, and the TEHVs were delivered into the aortic valve position under fluoroscopic control (OECW 9900 Elite GE, Fairfield, USA) applying the previously described and anatomically oriented JenaValve transapical delivery technology. After positioning the feelers, the JenaValve stent was opened in a stepwise fashion under fluoroscopic control. After full delivery of the TEHV, the appropriate positioning, thereby fully excluding the native valve, as well as sufficient functionality of the TEHV, was confirmed by contrast angiography (CT), before the JenaValve delivery device was carefully removed.

Positioning and functionality

JenaValve stent positioning was assessed using intraoperative CT (Siemens, Munich, Germany), and *in vivo* functionality was evaluated using two-dimensional (2D) and three-dimensional (3D) echocardiography (Philips Healthcare iE33W xMATRIX Ultrasound, Netherlands).

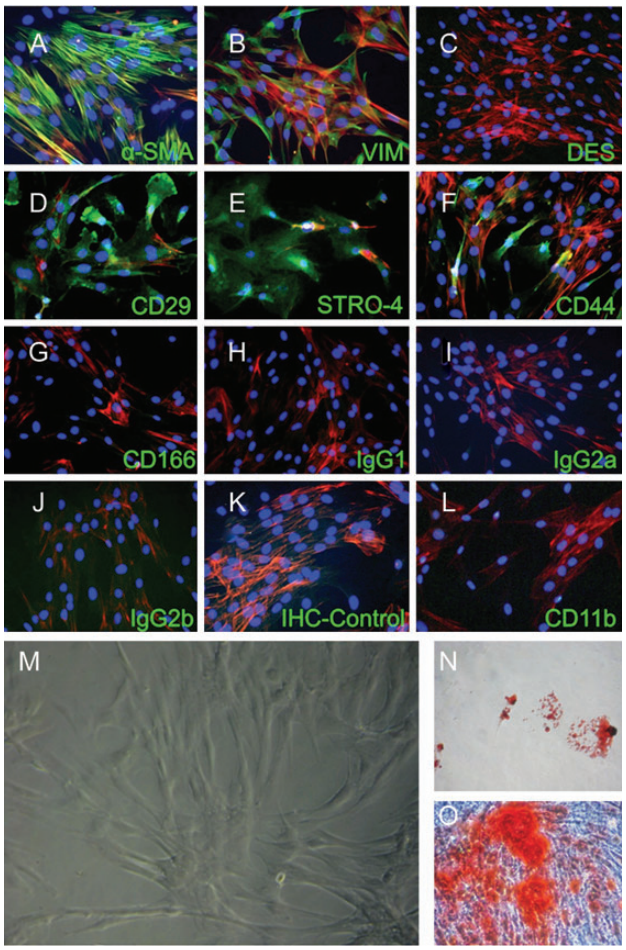

Figure 2: Cell characterization and functionality assessment. A representative patch of ovine bone marrow mononuclear cells (BMMCs) was plated and deriving ovine bone marrow derived mesenchymal stem cells (oMSCs) were characterized using immunohistochemistry for common oMSC markers (**A**–**L**). oMSCs displayed a characteristic spindle-shaped fibroblastic morphology (**M**) and functionally was proven by differentiation of a representative oMSC patch into the adipogenic and osteogenic lineage (**N** and **O**).

Computed tomography and gross examination

After harvest, cardiac computed tomography was performed to confirm appropriate stent positioning before the hearts were processed for gross examination.

Statistical analysis

Quantitative data are presented as mean ± standard deviation (SPSS 17.0, IBM, Somers, USA).

RESULTS

Scaffold fabrication, cell isolation and TEHV preparation

Sternal bone marrow puncture (Fig. 1A) was successful in all animals with a mean amount of 52 ± 4 ml. polyglycolic-acid coated with 1.75% poly-4-hydroxybutyrate (PGA-P4HB) composite matrices could be successfully integrated into the anatomically oriented stent system using single interrupted sutures (Fig. 1B). Bone marrow mononuclear cells (BMMCs) were isolated and seeded using fibrin as a cell carrier (Fig. 1C) before they were transapically implanted (Fig. 1D). A representative patch of ovine bone marrow mononuclear cells (BMMCs) was plated and deriving ovine bone marrow derived mesenchymal stem cells (oMSCs) were characterized using immunohistochemistry for common ovine MSC markers (Fig. 2A–L). Ovine MSCs displayed a characteristic spindle-shaped fibroblastic morphology (Fig. 2M) and functionality was proven by differentiation into the adipogenic and osteogenic lineage (Fig. 2N and O).

Transcatheter delivery of BMMC-based TEHV using the JenaValve transapical delivery system

Delivery and positioning intraoperative complications. Transapical aortic valve delivery and deployment of BMMC-based TEHV utilizing the JenaValve system could be performed successfully in all animals ($n = 4$; Fig. 3, Supplementary Video 1). In brief, the aortic root was visualized (Fig. 2A) before the loaded JenaValve device was introduced into the left ventricle and advanced into the aortic root (Fig. 3B and C). Under constant angiography guidance, the delivery process of the JenaValve delivery technology was started by positioning of the feeler arms into the deepest points of the sinuses (Step 1), which was then followed by the controlled deployment of the distal stent part (Fig. 3D–F) and completed by deployment of the proximal part

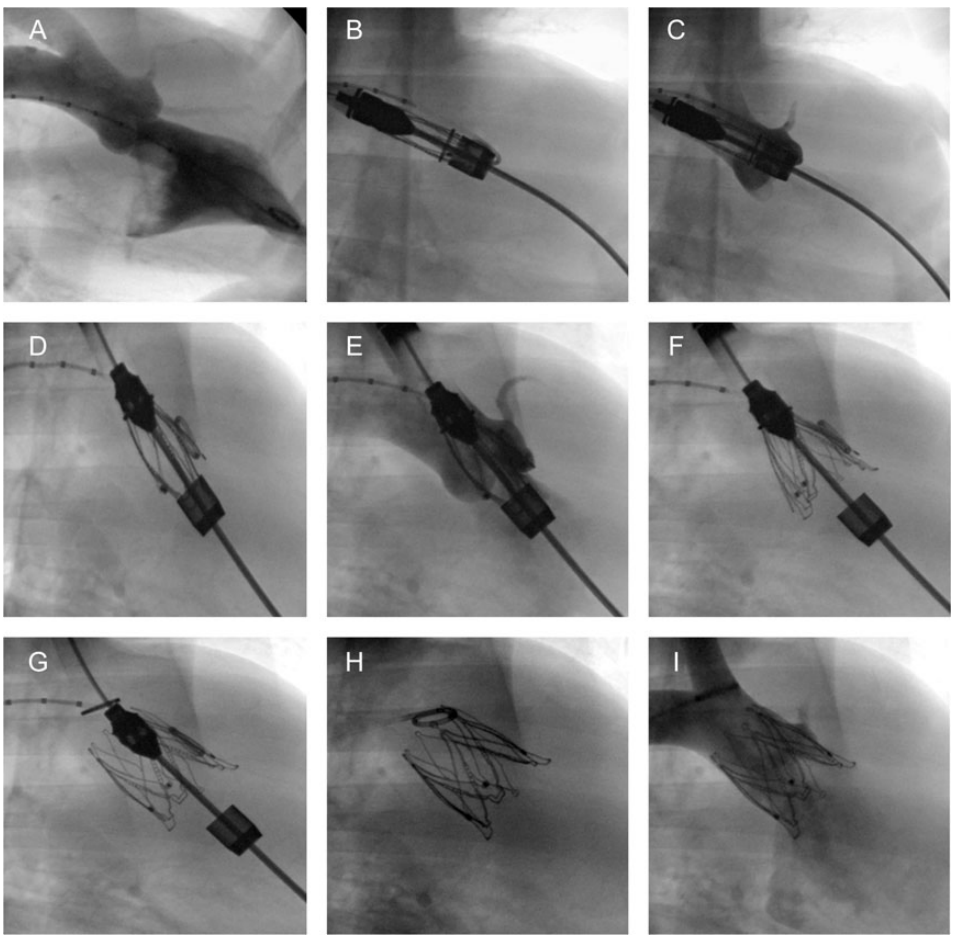

Figure 3: Fluoroscopy-guided, anatomically oriented transapical delivery of marrow stromal cell-based TEHVs into the aortic valve position. The aortic root was visualized (**A**), before the TEHV loaded JenaValve Stent System was inserted and positioned (**B** and **C**). After positioning, the feelers (**D** and **E**), the JenaValve stent was opened in a stepwise fashion under fluoroscopic control (**F** and **G**). After full delivery of the TEHV (**H**), the appropriate positioning thereby fully excluding the native valve as well as sufficient functionality of the TEHV was confirmed by CT (**I**), before the JenaValve delivery device was carefully removed.

(Fig. 3G and H). Immediately after complete deployment, appropriate perfusion of the coronaries was assessed and sufficient valve functionality was evaluated (Fig. 3I, Supplementary Video 1). During the implantation procedure, all animals were haemodynamically stable and no major complications such as bleeding or cardiac arrhythmia occurred during device removal. As in angiography, TEHV could be successfully positioned in the orthotopic aortic valve position, thereby fully excluding the native leaflets. The mean duration of the entire procedure, beginning with cell harvest until TEHV delivery was 101 ± 6 min (Table 2).

Echocardiographic assessment of TEHV. TEHV *in vivo* performance was controlled via fluoroscopy (Fig. 3, Supplementary Video 1) and echocardiography (Fig. 4, Supplementary Video 2). After implantation, all TEHV ($n = 4$) tolerated the loading pressure of the systemic circulation, and no leaflet tears or acute ruptures were detected. Sufficient leaflet mobility was present in all animals, and a sufficient opening and closing pattern along with an appropriate coaptation area was observed in two animals (Fig. 4A–F, Supplementary Video 2), while the two others displayed a single-leaflet prolapse that was related to the leaflet/valve design of the TEHV. The mean transvalvular gradient was 7.8 ± 0.9 mmHg, and the mean effective orifice area (EOA) was 1.73 ± 0.02 cm^2 (Table 2). Two animals displayed mild ($n = 1$)/moderate ($n = 1$) paravalvular leakage (PVL), and the first two animals showed moderate central aortic regurgitation (AR; $n = 2$) that was related with the scaffold design and geometry within the stent (Table 2). As a response to the central AR, the scaffold design was changed to shorter radial leaflet extensions and smaller wall-belly angles to ensure fully coaptation after delivery. No stent dislocation, migration or affection of the mitral valve was observed.

Table 2: Intraoperative data and echo findings

Parameter	Mean ± SD
Crimping time until TEHV delivery (min)	10 ± 4
Duration of the entire one-step procedure (min)	101 ± 6
TVG mean (mmHg)	7.8 ± 0.9
TVG peak (mmHg)	17.2 ± 2.2
EOA (cm^2)	1.73 ± 0.02
Central aortic regurgitation[a] (*n*)	*n* = 2
Paravalvular leakage[b] (*n*)	*n* = 2
Regurgitation of mitral valve	None
Leaflet motion[c]	Normal
Cardiac output (l/min)	5.7 ± 0.3

TEHV: tissue-engineered heart valve; TVG: transvalvular gradient; EOA: effective orifice area.
[a]Two animals presented with moderate central aortic regurgitation.
[b]One animal with mild and one animal with moderate paravalvular leakage.
[c]Two animals presented with a single-leaflet prolapse.

Post-mortem computed tomography assessment and gross examination

Optimal TEHV positioning was confirmed on post-mortem computed tomography of the excised hearts (Fig. 5A–F). Gross examination displayed the JenaValve stent with the TEHV to be well integrated into the aortic root and the left ventricular outflow tract. The leaflet structures were intact, with well-identifiable cusps, while there were no signs of leaflet thickening, shrinking or thrombus formation (Fig. 5G). Minor structural damage of one leaflet was observed in two TEHV and was either related to the procedural damage during animal harvest or related to the crimping procedures involved. In the first two animals, the leaflets were positioned in a leaflet opening angle of 45–60°, which resulted

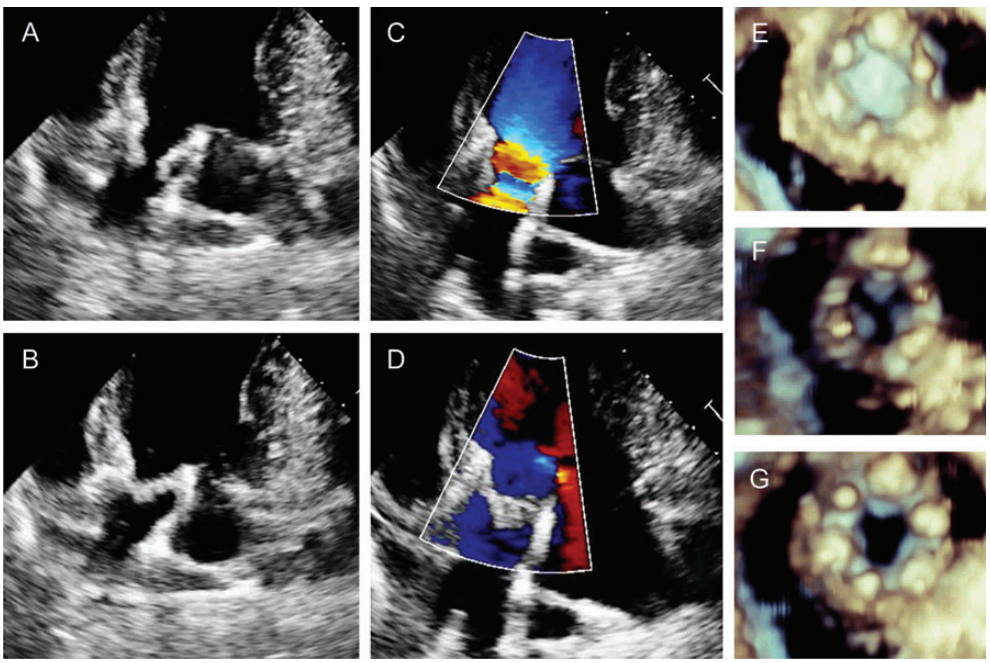

Figure 4: Echocardiographic assessment of TEHV functionality. Following implantation, TEHV tolerated the loading pressure of the systemic circulation adequately, and TEHV functionality was controlled via 2D (**A** and **B**), 2D color (**C** and **D**) and 3D echocardiography (**E** and **F**). TEHV displayed sufficient leaflet mobility and a sufficient opening and closing pattern along with an appropriate coaptation area. No stent dislocation, migration or affection of the mitral valve was observed.

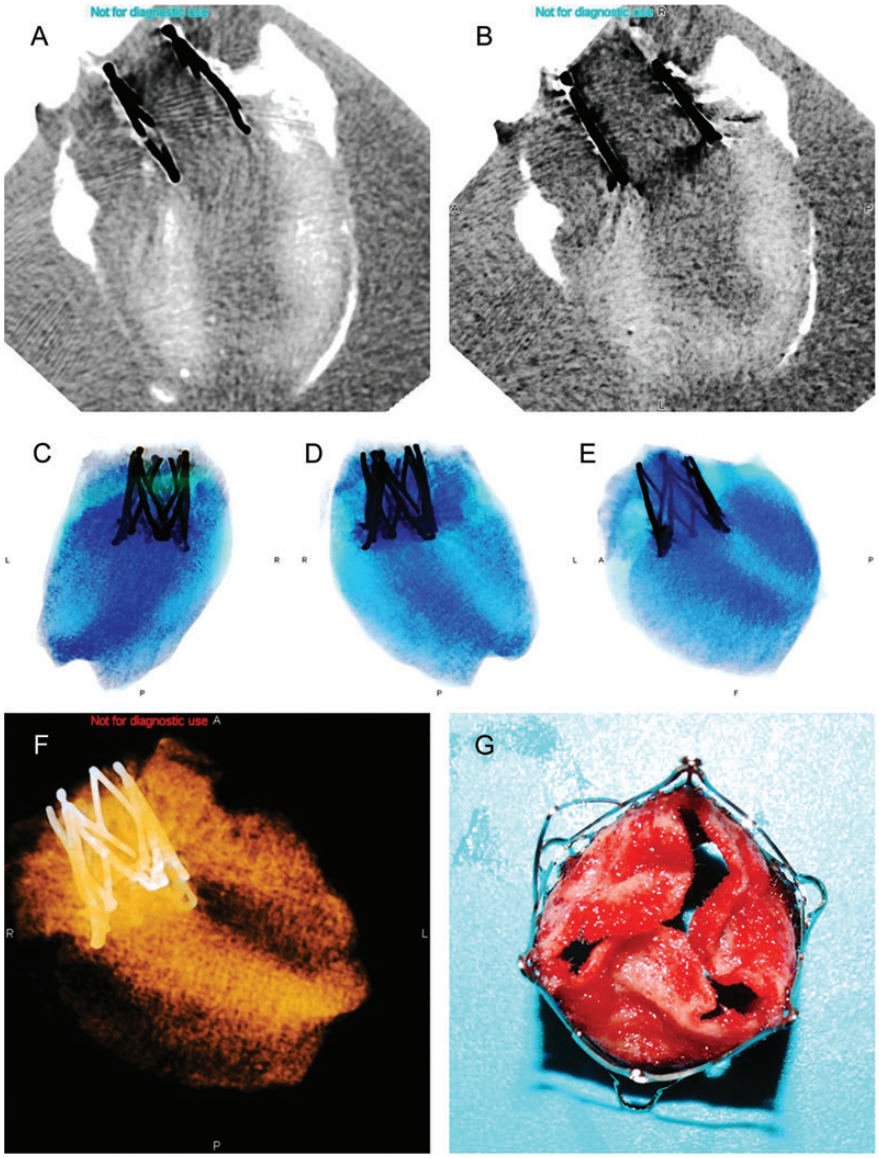

Figure 5: Computed tomography analysis and gross examination of TEHV. Post-mortem computed tomography (**A** and **B**) and 3D reconstruction analysis (**C**–**E**) displayed sufficient stent positioning after anatomically oriented transapical delivery of the TEHV. Gross examination of the TEHV displayed intact leaflet structures with well-identifiable cusps, while there were no signs of leaflet thickening, shrinking or thrombus formation (**F**).

central coaptation gaps due to excess of tissue in the coaptation area. Therefore, in the following TEHV constructs, the leaflet opening angle was changed to 15–30°, which resulted in reduction of central regurgitation and improved leaflet mobility.

DISCUSSION

This is the first report elucidating the principal technical feasibility of combining a clinically relevant HVTE approach with a clinically applied, anatomically oriented, latest-generation transapical stent delivery system. In the setting of an adult sheep model, we were able to demonstrate that BMMC-based TEHVs can be successfully implanted into the orthotopic aortic valve position with the JenaValve stent and delivery system. The implanted TEHV displayed sufficient *in vivo* functionality, and importantly, an optimal delivery and positioning without any coronary compromise was achieved when using an anatomically oriented stent and delivery system.

Transcatheter aortic valve implantation (TAVI) is a valid and accepted treatment option for the elderly, high-risk patient suffering from symptomatic aortic valve stenosis [1, 19–22]. Numerous reports indicate the efficacy of transcatheter approaches along with the established benefits comprising the avoidance of sternotomy and extracorporeal circulation. However, the utilized prosthesis of the current TAVI concepts are bioprosthetic and therefore prone to continuous and generalized degeneration. In addition, and despite considerable mid-term clinical data [19], nothing is known about potential crimping-associated structural damage and its impact on long-term clinical outcome and durability of these prostheses.

HVTE concepts generating living, autologous heart valve constructs have been repeatedly proposed as a potential solution due to their regeneration and growth capacity and may extend the indication for TAVI to younger patient populations. On the other hand, and in the light of clinical relevance, previous HVTE concepts have been criticized for their high logistical and financial demands limiting a broad clinical applicability. Ideally, a

translational, clinically relevant HVTE concept comprises minimally invasive techniques for both cell harvest and valve delivery [14]. Therefore, and based on previously reported technologies in the setting of tissue-engineered vascular grafts [16–18, 23, 24], we have recently introduced the novel concept of generating and implanting autologous BMMC-derived TEHV in a single-step intervention. In a preclinical setting, we were able to demonstrate the feasibility of this novel technology by replacing pulmonary and aortic valves of primates [14] and adult sheep [12, 13]. However, in these studies, only self-made or generic, non-clinical concept stent and delivery systems were used for transapical delivery, while a translational, clinically HVTE approach also requires the implementation of state-of-the-art stent and delivery systems, in particular when addressing the systemic circulation [12, 13].

Although numerous transcatheter devices have been established in the clinical setting [12–14, 25], major concerns associated with current TAVI systems include on the one hand, mal-positioning leading to central AR or PVL and on the other hand, the important risk of CO. In this regard, the utilization of next-generation, anatomically oriented devices has been suggested to be beneficial, thereby minimizing the risk of the occurrence of AR, PVL and CO [14].

Therefore, in this study, we successfully combined our one-step BMMC-based approach with a state-of-the-art, anatomically oriented transapical delivery system as a further step towards translational, clinically relevant HVTE concepts. Importantly, our results show that the occurrence of mal-positioning and importantly, stent dislocation as it was observed in our previous studies [13, 14], can be successfully minimized when using state-of-the-art, anatomically oriented transapical systems with feeler-guided positioning and an active clipping mechanism. Moreover, the safe and effective JenaValve delivery technology further simplified our procedural steps significantly when compared with the devices used for valve delivery in our previous studies [12–14, 25].

In general, the transapical delivery system used in this study has proven its safety in clinical pilot studies [5, 6] and in particular, its effectiveness with regard to the minimization of the occurrence of PVL [5, 6] and although the occurrence of PVL and AR was encountered in this study, it was primarily related to the scaffold design and integration within the stent, but not to the Jena Valve stent or the delivery system itself. After delivery in the first two animals, the TEHV systems revealed moderate central AR, which was most likely related to the steep belly-wall angle of the constructs. Therefore, in the following animals, the radial leaflet extension was decreased before implantation to ensure optimal leaflet coaptation *in situ* and to prevent central AR. After the delivery of these two constructs, less regurgitation and higher improved leaflet mobility were observed, suggesting that (i) TEHV native analogous leaflet geometry is indispensable for the optimal functionality of anatomically oriented TEHV systems and (ii) that too-steep belly-wall angles of TEHV leaflets lead to central AR due to the lack of sufficient leaflet coaptation.

Limitations

There are several limitations that need to be mentioned: first, the animal numbers are low, and consecutive studies will need larger cohorts, particularly when assessing the issue of optimized scaffold designs. In addition, this was an acute study with the primary aim of assessing the principal technical feasibility of combining our BMMC-based one-step approach with a state-of-the-art, anatomically oriented transapical stent and delivery system. Further data are necessary to evaluate the long-term safety and efficacy of the presented technology.

CONCLUSION

For the first time, we demonstrate the technical feasibility of a transapical marrow stromal cell-based TEHV delivery into the aortic valve position using an anatomically oriented, clinically applied transapical implantation system. Our data indicate that the combination of TEHV and a state-of-the-art transapical delivery system is feasible, representing an important step towards translational, transcatheter-based TEHV concepts that may broaden the indication for TAVI to younger patients. To minimize central regurgitation and the occurrence of PVL, further scaffold design and valve geometry optimization are necessary.

SUPPLEMENTARY MATERIAL

Supplementary material (Video 1 and 2) is available at *EJCTS* online.

Video 1: Fluoroscopy shows functionality of the tissue-engineered heart valve after anatomically oriented, transapical delivery.

Video 2: Two-dimensional echocardiography after anatomically oriented, transapical delivery of the tissue-engineered heart valve.

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Conflict of interest: Luc Behr and Sebastien Sammut are employees of IMM Recherche, Paris, France.

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