Transapical mitral valve repair procedures: primetime for microinvasive mitral valve surgery

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Abstract

Introduction: Nowadays micro-invasive procedures (off-pump, beating heart) for mitral valve repair (MVRe) are abruptly expanding with the potential to be adopted as a valuable alternative to surgery. In the present manuscript, the Authors review the available technologies intended to treat mitral regurgitation (MR) through transapical approach, including annuloplasty and chordal repair options. Annuloplasty: To date, Valcare Amend is the only transapical mitral valve (MV) ring to have been implanted in patients. The device allows for stabilization of the annulus through a complete semirigid D-shaped ring. The first-in-human successful procedure was performed in 2016 by our Group and subsequent clinical experience included a total of 14 implanted patients. Currently the technology is under clinical trial evaluation to validate the efficacy and safety profile of the device. Chordal Repair: Beating heart chordal implantation via trans-apical approach is a current feasible, safe and reproducible option. Neochord DS1000 is the most widely used technology in the field, with a solid procedural experience and good results in well-selected patients. Its clinical use has been validated in Europe since 2012, while it is still under clinical investigation in the United States. Harpoon TDS-5 system is a novel technology, recently CE mark approved for clinical use. Conclusions: Transapical micro-invasive technologies are current viable therapies to treat MR in selected patients. Embracing transcatheter MVRe therapies should guide the cardiac surgeon through the new revolution of micro-invasive MV tailored repair.

Transapical mitral valve repair procedures: primetime for microinvasive mitral valve surgery

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Abstract

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Annuloplasty: To date, Valcare Amend is the only transapical mitral valve (MV) ring to have been implanted in patients. The device allows for stabilization of the annulus through a complete semirigid D-shaped ring. The first-in-human successful procedure was performed in 2016 by our Group and subsequent clinical experience included a total of 14 implanted patients. Currently the technology is under clinical trial evaluation to validate the efficacy and safety profile of the device.

Chordal Repair: Beating heart chordal implantation via trans-apical approach is a current feasible, safe and reproducible option. Neochord DS1000 is the most widely used technology in the field, with a solid procedural experience and good results in well-selected patients. Its clinical use has been validated in Europe since 2012, while it is still under clinical investigation in the United States. Harpoon TDS-5 system is a novel technology, recently CE mark approved for clinical use.

Conclusions: Transapical micro-invasive technologies are current viable therapies to treat MR in selected patients. Embracing transcatheter MVRe therapies should guide the cardiac surgeon through the new revolution of micro-invasive MV tailored repair.

Introduction

Mitral valve regurgitation (MR) affects more than 4 million people in the United States (US) and Europe, with an incidence of 1-2% of the western population. Its prevalence increases with age, affecting up to 10% of the population above 75 years11Nkomo VT, Gardin JM, Skelton TN, et al. Burden of valvular heart diseases: a population-based study. Lancet 2006;368:1005-11. 10.1016/S0140-6736(06)69208-8.

According to current American and European guidelines, surgery is the gold standard therapy to treat MR in symptomatic patients, supporting surgical repair over replacement with extracorporeal circulation whenever possible 22Authors/Task Force Members:, et al. "2017 ESC/EACTS Guidelines for the management of valvular heart disease." European journal of cardio-thoracic surgery 52.4 (2017): 616-664.. Despite MR represents the most frequent valvular heart disease requiring surgery in the US and the second most common in Europe33Enriquez-Sarano, Maurice, Vuyisile T. Nkomo, and Hector I. Michelena. "Mitral regurgitation." Valvular Heart Disease. Humana Press, 2009. 221-246., up to one third of patients with severe MR are never referred and nearly half are denied for surgery because of prohibitive risk due to age and comorbidities44Vesely MR, Benitez RM, Robinson SW, et al. Surgical and Transcatheter Mitral Valve Repair for Severe Chronic Mitral Regurgitation: A Review of Clinical Indications and Patient Assessment. J Am Heart Assoc 2015;4. doi: .10.1161/JAHA.115.002424. Moreover, by 2030, the increase of the population age will translate in an estimated increase of 50% in heart failure prevalence, resulting in a significantly higher rate of MR, especially due to functional mechanisms55Udelson JE, Stevenson LW. The future of heart failure diagnosis, therapy, and management. Circulation. (2016) 133:2671–86. 10.1161/CIRCULATIONAHA.116.023518. Therefore, new less-invasive therapies are needed to further expand the slice of population to be treated.

Recently a new concept of micro-invasive cardiac surgery has been introduced to identify a revolutionary group of techniques requiring neither cardiopulmonary bypass nor aortic cross-clamping66D'Onofrio A, Gerosa G. Shifting a paradigm of cardiac surgery: from minimally invasive to micro-invasive. J Heart Valve Dis. 2015. 24: 528-30.. This evolution in technologies allows for off-pump, beating heart procedures, with a very small skin incision or even totally percutaneously performed, often requiring limited anesthesiologic support, with the contribution of multimodality imaging77D'Onofrio A, Gerosa G. Technique versus technology and the (r) evolution of cardiac surgery: a professional journey from classical surgery to embracing intervention. European Journal of Cardio-Thoracic Surgery. 2017. 52.5: 835-837.. Transcatheter aortic valve replacement represents the clearest example of such micro-invasive procedures. In the very near future these emerging therapies will likey have a central role, especially in the high-risk patient population, in both degenerative and functional MR treatment, despite only weak recommendations are given for their use by current guidelines (COR IIb, LOE C)[2].

Nowadays the interest of the cardiac surgeon community towards new micro-invasive procedures is abruptly expanding with the potential to be adopted as a valuable alternative to conventional surgery, even if, as far as MVRe is concerned, there are still limitations that need to be overcame. Once the MV is reached by the use of transapical or transfemoral puncturing, these technologies can often perform just a single repair technique, acting on a specific component of the mitral apparatus (chordae OR leaflets OR annulus), in contrast to surgical repair, that allows for combined multi-target procedures (chordae AND leaflets AND annulus). Nevertheless, simultaneous implantation of different devices has already been reported in well-selected patients, even if more data are needed to validate the practice88Colli A, Raanani E, Cobiella J, Wrobel K, Nombela L, Maroto L, et al. Transapical and transfemoral combined mitral valve repair with annular and leaflet therapies. The Annals of Thoracic Surgery. 2020..

In the present manuscript, we aim to review currently available technologies intended to treat MR through a micro-invasive transapical approach, including annuloplasty and chordal repair options.

Annuloplasty

Transcatheter ring implantation technologies can be divided into direct and indirect annuloplasty, depending on the type of interaction with the native annulus11Colli A, Fiocco A, Nadali M, Besola L, Pradegan N, Folino G et al. Transcatheter mitral valve therapies for degenerative and functional mitral regurgitation. 2020. In Emerging Technologies for Heart Diseases (pp. 417-461).. Academic Press.. Indirect annuloplasty devices are typically implanted into the coronary sinus and potentially are simpler for deployment, but can perform a lower grade of reduction in terms of native annular dimensions, compared to direct annuloplasty. Direct approaches can mimic a surgical annuloplasty in a more effective fashion, thus allowing for better annular stabilization and leaflet coaptation restoring.

Currently, clinical experience on transapical technologies is very limited, being Valcare Amend the only successfully implanted device in humans[9].

Valcare Amend

The AMEND (Valcare Medical, Herzliya Pituach, Israel) is a transcatheter-implanting solution for direct mitral annuloplasty (Figure 1). The device is intended to deliver a complete semirigid D-shaped ring to the LA, to anchor it to the annulus and stabilize it, resulting in reduced antero-posterior dimensions and improved leaflet coaptation. Three ring sizes are available (34, 40 and 46 mm), allowing to treat a wide range of patients, by fitting a diseased annulus ranging from 29 to 50 mm. Currently the Company developed both transapical and transseptal delivery options, through a 24F and 28F catheter, respectively.22Mangieri A,

Laricchia A, Giannini F, Gallo F, Kargoli F, Ladanyi A et al ... & Latib, A. Emerging Technologies for Percutaneous Mitral Valve Repair. Frontiers in Cardiovascular Medicine. 2019; 6.

The first-in-human successful implantation was performed and described in 2016 by our Group 33Gerosa G, Besola L, Manzan E et al. First-in-Human of Catheter-Delivered Annuloplasty Ring to Treat Functional Mitral Regurgitation. JACC Cardiovasc Interv. 2016 Nov 14;9(21):e211-e213.. Transapical implantation is performed in a hybrid operating room, under general anesthesia, using a conventional left anterior mini-thoracotomy. The entire procedure is guided by transesophageal echocardiography (2D and 3D TEE) and fluoroscopy. After introduction into the LV, the 28-F AMEND system is navigated over a wire through the mitral valve into the LA. Once unsheated, the ring adoptes its closed D shape and can be appropriately oriented by the use of multiple adjustment tools of the delivery system. Once the desired position is confirmed by fluoroscopic guidance, a two-step anchoring procedure is performed. First, multiple anchors are deployed on the posterior segment of the ring, allowing for a secure fixation of the device to the posterior annulus. During the second step, the sheath is steered anteriorly toward the aortomitral continuity and once good contact is achieved, the anterior anchors are deployed, resulting in both complete fixation and antero-posterior diameter reduction. The device is finally released and the delivery system is retracted from the heart.

Current clinical experience includes a total of 14 implanted patients[10]. Eight of them were treated for FMR as a single annuloplasty therapy, while 2 patients were implanted to treat DMR as a single therapy. In 4 other patients, AMEND ring implantation was performed in a combination procedure, with MitraClip (3 patients) and NeoChord (1 patient), thus representing a solid foundation for stand-alone or combined repair, to improve both leaflet and chordal repair procedures[10,44]Meerkin D. The AMEND Mitral Repair System: Technology and Clinical Updates. Presentation CRT 2019. Chicago, IL 2019.. Post-procedural MR was [?] 2+ in all performed implantations. In treated patients (n=14), 20% mean reduction of AP diameter was achieved, no residual pulmonary flow reversal in all cases was reported, mean reduction of the jet area was 74%[10,12].

The AMENDTM trial (NCT02602613, Annuloplasty Ring Applied in a Transcatheter Method) is currently recruiting to evaluate the efficacy and safety of the device, with a target sample size of 40 patients[10].

Chordal Repair

Transcatheter chordal repair technologies are primarily intended to treat DMR. Although the disease can involve multiple components of the MV apparatus, rupture of native chordae represents one of the leading mechanisms.

In the past decades, surgical practice introduced chordal replacement by polytetrafluorethylene (PTFE) sutures implantation55Zussa C, Frater RW, Polesel E, et al. Artificial mitral valve chordae: experimental and clinical experience. Ann Thorac Surg 1990;50:367-73., alone or together with the positioning of a ring, demonstrating excellent results in terms of long-term clinical outcomes. Further validation of the chordal therapy was later achieved, after the introduction of the "respect rather than resect" principle66Carpentier A. Cardiac valve surgery–the "French correction". J Thorac Cardiovasc Surg. 1983 Sep;86(3):323-37.,77Frater RW1, Vetter HO, Zussa C, Dahm M. Chordal replacement in mitral valve repair. Circulation. 1990 Nov;82(5 Suppl):IV125-30.,88Adams DH1, Rosenhek R, Falk V. Degenerative mitral valve regurgitation: best practice revolution.*Eur Heart J.* 2010 Aug;31(16):1958-66., becoming a mainstay in open heart MVRe techniques.

Several years later, the expanding field of Transcatheter Mitral Valve Repair (TMVRe) technologies has embraced the chordal repair philosophy.

Mostly by beating-heart transapical approach99Noack T, Borger MA. Chordal replacement: future surgical gold standard or first-line option as bridge to definitive therapy in primary mitral regurgitation? Ann Cardiothorac Surg 2020. doi: 10.21037/acs-2020-mv-22, this technique stresses the concept of micro-invasiveness and is currently the only one in clinical practice to allow a real-time heart-beating assessment of residual MR during the chordal tensioning phase, with a filled left ventricle through live three-dimensional intraoperative

trasesophageal echocardiography . It has become a feasible, safe and reproducible option in selected patients with non-complex primary MR and can be potentially adopted in combined procedure, together with other-targeting transcatheter technologies, covering in that way the wide spectrum of MV lesions. In the scenario of transapical chordal repair systems, we focus on currently available devices in clinical practice: Neochord DS 1000 and Harpoon Mitral Valve Repair System (MVRS).

Neochord DS 1000:

The Neochord DS 1000 device (Neochord Inc, St. Louis Park, MN) is a transapical off-pump MVRe system based on expanded polytetrafluorethylene (ePTFE) chordal implantation. Currently more than 1,200 patients have been already treated with Neochord in the world1010Fiocco A, Nadali M, Speziali G, Colli A. Transcatheter mitral valve chordal repair: current indications and future perspectives. Front Cardiovasc Med. 2019;6:128. https://doi.org/10.3389/fcvm.2019.00128..

In December 2012, the results reported by the TACT Trial (Transapical Artificial Chordae Tendinae - NCT01777815) allowed this technology to gain CE mark approval1111Seeburger, J., Rinaldi, M., Nielsen, S. L., Salizzoni, S., Lange, R., Schoenburg, M., ... & Aidietis, A. (2014). Off-pump transapical implantation of artificial neo-chordae to correct mitral regurgitation: the TACT Trial (Transapical Artificial Chordae Tendinae) proof of concept. Journal of the American College of Cardiology, 63(9), 914-919. 1212*https://www.clinicaltrials.gov/ct2/show/NCT01777815*, being the first transcatheter chordal repair device available on the market. In the US it received the investigational device exemption (IDE) approval from the United States Food and Drug Administration (FDA), and early clinical experience has been recently reported in Asian countries, mainly represented by China.1313Wang, L. H., Pu, Z. X., Kong, M. J., Jiang, J. B., Ren, K. D., Gao, F., ... & Liu, X. B. (2019). The first four cases of successful NeoChord procedure in mainland China. World journal of emergency medicine, 10(3), 133. Preoperative anatomic and echocardiographic selection criteria as well as progressive technique refinement, contributed to create a solid procedural framework, thus the procedure evolved into a reproducible and safe technique, with good results in selected patients.

The procedure is performed, under general anesthesia, selective lung intubation and real-time 2D/3D TEE guidance. Through an antero-lateral left mini-thoracotomy in the fifth-intercostal space, the pericardium is opened and suspended, and the left lung is selectively excluded, exposing the left ventricle (LV) apex. The ideal entry side is identified about 2 cm–4 cm postero-lateral from the real apex 1414Colli, A., Bizzotto, E., Manzan, E., Besola, L., Pradegan, N., Bellu, R., ... & Gerosa, G. (2017). Patient-specific ventricular access site selection for the NeoChord mitral valve repair procedure. The Annals of Thoracic Surgery, 104(2), e199-e202.and confirmed with a gentle digital palpation under 2D-TEE imaging. Two pledgeted round purse-string are sutured around the identified entry-site which is then scalpeled with an 11 inch blade, performing a trans-wall ventriculotomy. The device is first gently introduced inside the LV and then carefully navigated trough the LV avoiding papillary muscles damage and interference with subvalvular apparatus of anterior mitral leaflet (AML). Ventricular navigation is real-time guided through TEE X-plane view. Once the valve is crossed, a 3D imaging assessment allows for a precise positioning of the tip on the targeted scallop which is grasped by closing the jaws of the device. A fiberoptic display gives a feedback on the secured leaflet capture, before grasping. The grasped leaflet is then pierced at its edge, allowing for the deployment of a single pair of chords (Figure 2). The device is subsequently opened and gently retrieved from the ventricle, leading outside the chordal loop. The two ends of the suture are then passed in the loop, forming a girth hitch knot that is advanced till the free edge of the scallop. The procedure is repeated for each pair of chords deployed. Finally under 2D and 3D TEE control, the chords are tensioned, until adequate leaflet coaptation is achieved and all the chordal free ends are then secured to the LV wall 1515Colli, A., Adams, D., Fiocco, A., Pradegan, N., Longinotti, L., Nadali, M., ... & Gerosa, G. (2018). Transapical NeoChord mitral valve repair. Annals of cardiothoracic surgery, 7(6), 812. on a Teflon felt.

The learning curve needed to perform optimally NC procedure, combining procedure standardization, technical refinements and adequate patient-selection, has been analyzed in a single center study.1616Colli A,

Bagozzi L, Banchelli F, Besola L, Bizzotto E, Pradegan N, et al. Learning curve analysis of transapical NeoChord mitral valve repair. Eur J Cardiothorac Surg. (2018) 54:273–80. doi: 10.1093/ejcts/ezy046 In the CUSUM analysis performed by Colli et.al, the procedure demonstrates to be safe and effective. Threshold, beyond which the number of deaths or ineffective procedures would be unacceptable, was never reached, showing a good surgical performance even at the beginning of the experience. The study estimates a need for 50 cases per surgeon to standardize the technique and reach the "good performance period". The Authors underline that most of the early failures were linked to technical errors during MV crossing phase, which were subsequently avoided with the improvement of the intraventricular navigation technique and adoption of different imaging views to cross the MV. To reduce the learning curve effect, acting on the technical refinement and procedure standardization, a dedicated preclinical training program was introduced, by the use of proctored highly realistic simulation on ex-vivo pulsatile models.1717Leopaldi AM, Wrobel K, Speziali G, van Tuijl S, Drasutiene A, Chitwood WR Jr. The dynamic cardiac biosimulator: a method for training physicians in beating-heart mitral valve repair procedures. J Thorac Cardiovasc Surg. (2018) 155:147–55. doi: 10.1016/j.jtcvs.2017.09.011

Concerning echocardiographic selection criteria, both the extension of prolapsing segments and the annular dimension demonstrated to have an impact in term of outcomes on Neochord repair procedure. The prolapse/flail anatomical aspects were classified based on growing complexity as "Type A" isolated central posterior leaflet prolapse/flail, "Type B" posterior multi-segment prolapse/flail, "Type C" anterior or bi-leaflet prolapse/flail, "Type D" para-commissural prolapse/flail or presence of significant leaflet/annular calcifications. Several studies underlined differences between these groups, reporting better results in terms of outcomes when posterior leaflet disease (A and B type) was treated, compared to more complex leaflet lesions (Type C-D). 1818Colli, A., Manzan, E., Rucinskas, K., Janusauskas, V., Zucchetta, F., Zakarkaitė, D., ... & Gerosa, G. (2015). Acute safety and efficacy of the NeoChord procedure. Interactive cardiovascular and thoracic surgery, 20(5), 575-581 1919 Colli A, Manzan E, Besola L, et al. One-Year Outcomes After Transapical Echocardiography-Guided Mitral Valve Repair. Circulation 2018;138:843-5. 10.1161/CIRCULATIONAHA.118.033509 The leaflet-to-annulus index (LAI) was further introduced to improve the patient-selection process. LAI was calculated by the ratio between the sum of anterior and posterior leaflet length and the antero-posterior diameter. It represents the amount of overriding tissue that is potentially responsible of coaptation, considering annular dilatation in relation to the extension of the leaflets and not as an absolute concept. An excess of leaflet tissue of at least 20% (corresponding to LAI >1.2) has shown to be a positive predictor of MR [?] mild at 1 year follow-up2020Colli A, Besola L, Montagner M, Azzolina D, Soriani N, Manzan E, et al. Prognostic impact of leaflet-to-annulus index in patients treated with transapical off-pump echo-guided mitral valve repair with NeoChord implantation. Int J Cardiol 2018;257:235–7.. Thus, LAI can be used to identify patients without leaflet-to-annulus mismatch, who could benefit from a ringless repair procedure such as Neochord.

Since its first in human application in 20102121Seeburger, J., Borger, M. A., Tschernich, H., Leontjev, S., Holzhey, D., Noack, T., ... & Mohr, F. W. (2010). Transapical beating heart mitral valve repair. Circulation: Cardiovascular Interventions, 3(6), 611-612., the device demonstrated good outcomes in reducing mitral regurgitation along with safety feasibility in patients with DMR2222Rucinskas K, Janusauskas V, Zakarkaite D, et al. Off-pump transapical implantation of artificial chordae to correct mitral regurgitation: early results of a single-center experience. J Thorac Cardiovasc Surg 2014;147:95-9. 10.1016/j.jtcvs.2013.08.012. The TACT trial (Transapical Chordae Tendinae, NCT01777815) was the first prospective, multicenter, single arm study designed to evaluate the safety profile and efficacy of NeoChord DS 10002323Seeburger, J., Rinaldi, M., Nielsen, S. L., Salizzoni, S., Lange, R., Schoenburg, M., ... & Aidietis, A. (2014). Off-pump transapical implantation of artificial neo-chordae to correct mitral regurgitation: the TACT Trial (Transapical Artificial Chordae Tendinae) proof of concept. Journal of the American College of Cardiology, 63(9), 914-919.. Thirty patients with severe MR due to isolated posterior prolapse scheduled for off-pump transapical implantation of neo-chordae were included between 2009 and 2014. Acute procedural success, defined as the placement of at least 1 neochord and reduction of MR from 3+ or 4+ to at least 2 grades was achieved in 86.7% of patients (26). The trial highlighted the link between improvement of results and increased experience, since durable

reduction in MR to [?]2+ at 30 days was achieved in 5 of the first 15 patients and 12 of the last 14 patients. The procedure was technically safe and feasible and yields further potential for improvement of efficacy and durability[31,]2424*https://www.clinicaltrials.gov/ct2/show/NCT01777815.* Of 6 patients initially enrolled in the early experience of the TACT trial at Leipzig-Heart Center, 3 of them reach a 5 year follow up showing up to mild-to moderate MR and good clinical condition. In these patients a trend toward reverse remodeling of the left ventricle and no increase in mitral annular dilatation was observed2525Kiefer, P., Meier, S., Noack, T., Borger, M. A., Ender, J., Hoyer, A., ... & Seeburger, J. (2018). Good 5-year durability of transapical beating heart off-pump mitral valve repair with neochordae. The Annals of thoracic surgery, 106(2), 440-445..

A single-center experience (144 patients) reports early procedural success of 98.6% (142), early mortality of 1.4% (2) and patient success (endpoint composite by MR [?] 2 and freedom from reoperation) of 89% at 1 year[27]. A multicenter European study published in 2018 enrolling 213 patients reported an excellent procedural success rate. Procedural success was achieved in 206 (96.7%) patients, at 1-year follow-up, overall survival was 98 ± 1% and composite end point was achieved in 84 +- 2.5% for the overall population.2626Colli, A., Manzan, E., Aidietis, A., Rucinskas, K., Bizzotto, E., Besola, L., ... & Drasutiene, A. (2018). An early European experience with transapical off-pump mitral valve repair with NeoChord implantation. European Journal of Cardio-Thoracic Surgery, 54(3), 460-466.

As above mentioned, in the United States the NeoChord technology has received investigational device exemption (IDE) approval from FDA. Patients are being enrolled in a prospective, multicenter, randomized controlled clinical trial (ReChord trial NCT02803957) comparing traditional surgical repair with NeoChord repair with a 1:1 randomization2727https://clinicaltrials.gov/ct2/show/NCT02803957. Neochord technology was already employed in combined transcatheter MVRe procedures with a simultaneous two-step annuloplasty and chordal repair session2828Colli, A., Raanani, E., Cobiella, J., Wrobel, K., Nombela, L., Maroto, L., ... & Meerkin, D. (2020). Transapical and transfemoral combined mitral valve repair with annular and leaflet therapies. The Annals of Thoracic Surgery. 2929Von Bardeleben, R. S., Colli, A., Schulz, E., Ruf, T., Wrobel, K., Vahl, C. F., ... & Beiras-Fernandez, A. (2018). First in human transcatheter COMBO mitral valve repair with direct ring annuloplasty and neochord leaflet implantation to treat degenerative mitral regurgitation: feasibility of the simultaneous toolbox concept guided by 3D echo and computed tomography fusion imaging. European heart journal, 39(15), 1314-1315.. During the first step AMEND ring was implanted, obtaining annular stabilization, A-P dimension reduction and thus increasing the overriding of the flailing leaflets. In a second phase, deployment of artificial chords with Neochord procedure allowed for flail treatment and restored leaflet coaptation.

Anecdotal cases of non-conventional use of Neochord device have been recently reported.

In 2018 the first in human edge-to-edge MVRe with neochord technology was applied on a high-risk surgical patient rejected for MitraClip due to unfavorable anatomy3030Colli, A., Besola, L., Bizzotto, E., Peruzzo, P., Pittarello, D., & Gerosa, G. (2018). Edge-to-edge mitral valve repair with transapical neochord implantation.. Furthermore, a transcatheter mitral valve replacement (MVR) case, combined with neochord implantation was reported. In the presence of a long AML, the risk of neo left ventricular outflow tract obstruction was reduced by previous neochord deployment on the AML and subsequent artificial tethering of the leaflet3131Beiras-Fernandez A, Ruf, T. F, Obadia J. F. I., Munzel T, Kreidel F, & von Bardeleben R. S. Neochord anterior leaflet treatment to facilitate transcatheter mitral valve replacement with 3D real-time echocardiography. European Heart Journal. 2020.

An interesting case of MVRe through neochord implantation in a patient affected by dextrocardia and situs-inversus, reporting no significant issues during the procedure was also described 3232Bhatia, I., Chan, D. T. L., Lam, S. C. C., & Au, T. W. K. (2020). Feasibility of novel transapical off pump beating heart mitral valve repair in a patient with dextrocardia and situs inversus. European Journal of Cardio-Thoracic Surgery..

Harpoon TDS-5

Harpoon Mitral Valve Repair System (Edwards Lifesciences, Irvine, CA) is a novel transapical off-pump mitral valve repair (MVr) system based on ePTFE chordal implantation. Differently from Neochord DS 1000 it was developed and tested to target severe DMR with isolated prolapsing Posterior Mitral Leaflet (PML). At present indeed, the device has not been evaluated for the treatment of Anterior Mitral Valve Leaflet (AML) disease, bileaflet prolapse and flail forms. Currently available for clinical use in Europe, it gained the CE mark in 2020[9].

The procedure is performed under transesophageal 2D /3D echocardiography guidance, general anesthesia, single lumen intubation. Trough anterior left mini-thoracotomy in the fifth intercostal space, the optimal entry site on LV apex is identified slightly more anterior than in Neochord procedure, and confirmed by finger testing under 2D TEE. Two small purse strings sutures are placed on-site and the ventricle is punctured, allowing for the positioning of a 14 Fr introducer. This is equipped with an inner hemostatic valve that allows for LV navigation without significant blood loss. The TEE X-plane view and 3D imaging assessment lead the positioning of the delivery system tip under the dome of the targeted scallop 11Gerosa, G., D'Onofrio, A., Besola, L., & Colli, A. (2018). Transoesophageal echo-guided mitral valve repair using the Harpoon system. European Journal of Cardio-Thoracic Surgery, 53(4), 871-873.. The needle passes through the leaflet tissue, far from the edge, releasing the suture. Then it's automatically withdrawn, tightening the ePTFE coil and forming a double-helix knot on the atrial surface of the leaflet22Gammie, J. S., Bartus, K., Gackowski, A., D'Ambra, M. N., Szymanski, P., Bilewska, A., ... & Duncan, A. (2018). Beating-heart mitral valve repair using a novel ePTFE cordal implantation device: a prospective trial. Journal of the American College of Cardiology, 71(1), 25-36. (Figure 3). The device is subsequently retrieved, carrying outside the neochordal free-end through the introducer. The procedure is repeated until the desired number of chords is implanted, using a different delivery system for each chord. Since the needle throw during device deployment is approximately 22 mm, Valsalva maneuver may be essential to promote an increase in left atrial volume and so increase the distance between the leaflet and the posterior LA wall to >25 mm during the leaflet piercing33Diprose, P., Fogg, K. J., Pittarello, D., Gammie, J. S., & D'Ambra, M. N. (2020). Intensive care and anesthesia management for HARPOON beating heart mitral valve repair. Annals of Cardiac Anaesthesia, 23(3), 321.. Under 2D/3D TEE guidance the chords are finally tightened to reach the best MR reduction, and then secured to the LV wall44Colli, A., Adams, D., Fiocco, A., Pradegan, N., Longinotti, L., Nadali, M., ... & Gerosa, G. (2018). Transapical NeoChord mitral valve repair. Annals of cardiothoracic surgery, 7(6), 812..

To identify patients potentially suitable for the Harpoon MVRS, a careful preoperative screening is required, including detailed preoperative three-dimensional TEE. This allows to calculate the ratio of prolapsing PML length compared to the anteroposterior distance from the base of PML to the free edge of the AML, which is a predictor of adequate coaptation when the value is 1.5/155Gammie, J. S., Bartus, K., Gackowski, A., D'Ambra, M. N., Szymanski, P., Bilewska, A., ... & Duncan, A. (2018). Beating-heart mitral valve repair using a novel ePTFE cordal implantation device: a prospective trial. Journal of the American College of Cardiology, 71(1), 25-36..

Since its first in human application in 201566Gammie, J. S., Wilson, P., Bartus, K., Gackowski, A., Hung, J., D'Ambra, M. N., ... & Kapelak, B. (2016). Transapical beating-heart mitral valve repair with an expanded polytetrafluoroethylene cordal implantation device: initial clinical experience. Circulation, 134(3), 189-197., the device demonstrated to be safe and effective in reducing mitral regurgitation in patients with DMR. The TRACER trial (Mitral TransApical NeoChordal Echo-Guided Repair; NCT02768870) a prospective non-randomized multicenter clinical study[45], enrolled 30 patients from April 2016 to November 2017, including subjects from 6 different European Centers with isolated severe degenerative MR due to P2 prolapse. Data published by Gammie et al. show how primary endpoint (30-day successful implantation of cords with MR reduction to moderate or less) was met in 27 out of 30 patients (90%). There were no deaths, strokes, or permanent pacemaker implantations. At 6 months, MR was mild or less in 85 % (22 of 26) and severe in 8% (2 of 26). A favorable cardiac reverse remodeling was demonstrated at 30 days.[45] More recent clinical data from the TRACER CE trial were presented in June 2019 at TVT Structural Heart Summit (data lock on 17th December 2018).77https://www.tctmd.com/slide/harpoon-transapical-technology-and-clinical-

updates The enrollment reached 65 patients; among them 62 had been successfully treated with Harpoon, 2 were converted to open surgery and 1 procedure had been aborted. No perioperative death or stroke were reported. Ten patients were later lost at follow up (2 of them died and 8 exit from the study for secondary intervention). Fifty-two patients reached 1 year of follow up, MR was mild or less in 75% (39 of 52) and severe in 2% (2 of 26). Positive reverse remodeling (in term of annular diameter and LEDV reduction) was confirmed at one year. The Harpoon program was also paused because of 4 additional cases of severe MR recurrence due to ePTFE chords rupture,[9] then restarted and finally gained the CE mark in May 2020.

Conclusion

Transapical micro-invasive technologies are safe and effective options to treat MR in selected patients. Limitations are still present, first of all the lack of knowledge on durability. Moreover, the ability to treat a single component of the MV apparatus needs to face against the complexity of the mechanisms involving the disease.

Therefore, the cardiac mitral surgeon will have to fill these gaps by acting on a double front: on one hand he must extensively embrace micro-invasive solutions and apply them on well-selected patients; on the other hand he must gain a complete tool-box which allows for a tailored valve repair, based on combined multi-targeting procedures.

This evolution can guide the surgeon through the new revolution of MV micro-invasive tailored repair.

Figure Legend

Figure 1. *The AMEND ring and procedure*

Figure 2. *The Neochord DS 1000 device and procedure*

Figure 3. *The Harpoon Mitral Valve Repair System and procedure*