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THESIS TITLE

Mitral valve repair for Degenerative mitral regurgitation: towards the optimal therapeutic option in the «micro-invasive» scenario

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ABSTRACT

The application of "*microinvasive"* approach in cardiac surgery represents a challenge for surgeons and for the whole team. The ability to perform isolated (i.e.: aortic valve replacement; inter-atrial defect closure; mitral valve repair with different devices) or combined cardiac surgical interventions avoiding the use of cardiopulmonary bypass, on-beating heart and with an impressive field (a thorax wide-shut) means overcoming and resetting old *clichés*.

Mitral valve repair with the application of transapical, artificial chordae in a micro-invasive fashion (i.e. Neochord DS1000) enables the correction of DMR in case of leaflet prolapse/flail with no CPB nor aortic CC. This procedure has been recently introduced into clinical practice and has shown promising results.

No data about a mid- and long-term follow up of patients treated with this device nor a direct comparison between Neochord (NC) and conventional surgery (CS) in patients with mitral prolapse/flail have been collected and analyzed until now.

The main resulting conclusions of our studies are:

- NC can be considered a reasonable therapeutic option in patients suffering from severe DMR with favorable anatomy (type A-B) since it provides good early and long-term results up to 5-year in terms of: *freedom from severe MR*, favourable *LV remodeling*, relief of *symptoms*
- Patient selection plays a crucial role; patients with unfavorable anatomy should be probably treated by CS
- PCI before NeoChord mitral repair procedures is a safe and effective strategy and performing PCI before NeoChord does not affect outcomes in low-risk patients with critical CAD
- A combined micro-invasive strategy in selected patients suffering from degenerative MR and CAD should be considered a reasonable alternative to conventional surgery

The originality of this work is related not only to a mere data analysis about a "new device", but, above all, it was a "journey" aimed to the application of to a new concept of surgery, intended as a different state-of-mind in clinical practice.

ABSTRACT

L'applicazione dell'approccio "micro-invasivo" in cardiochirurgia rappresenta una sfida non solo per i chirurghi ma per l'intero team. Realizzare un intervento cardiochirurgico isolato (i.e.: sostituzione valvolare aortica, chiusura di difetto interatriale...) o combinato, evitando la circolazione extra-corporea (CEC) ed il clampaggio aortico (CA), a cuore battente significa risettare il modo di intendere l'approccio agli interventi cardiochirurgici, superando quindi retaggi consolidati. La riparazione valvolare mitralica con l'applicazione di corde artificiali per via transapicale in approccio "micro-invasivo" (i.e. mediante l'utilizzo del device Neochord DS1000) permette la correzione di DMR in caso di leaflet/prolasso senza l'utilizzo di CEC o CA. Questa procedura è stata recentemente introdotta in pratica clinica, mostrando risultati promettenti. Finora non sono mai stati analizzati e resi noti risultati relativi a follow up a medio e lungo termine riguardo pazienti sottoposti a questa procedura.
Le principali conclusioni cui siamo giunti sono le seguenti:

- NC può essere considerata un'opzione terapeutica ragionevole in pazienti affetti da DMR con insufficienza valvolare severa e con anatomia valvolare favorevole (sottotipo A-B) in quanto ha dimostrato risultati soddisfacenti (fino ad un follow up di 5 anni, il più lungo finora pubblicato a nostra conoscenza) in termini di: libertà da MR recidivante severa, rimodellamento inverso del ventricolo sinistro, miglioramento dei sintomi
- la corretta selezione del paziente gioca un ruolo cruciale: pazienti con anatomia valvolare non favorevole (sottotipo C-D) dovrebbero probabilmente essere trattati mediante interventi tradizionali
- PCI prima di una procedura NC è un 'opzione sicura ed efficace e non compromette l'outcome dei pazienti a basso rischio ed affetti da coronaropatia critica
- una strategia combinata micro-invasiva in pazienti selezionati, affetti da DMR e CAD può essere considerata una valida alternativa al trattamento chirurgico tradizionale

L'originalità di questo progetto di ricerca non risiede tanto nella mera analisi di dati relativi ad un nuovo device ma soprattutto è stato "un viaggio" diretto all'applicazione di un nuovo concetto di chirurgia inteso come "state-of-mind" applicato in pratica clinica.

Chapter 1

Introduction and Outline of the thesis

ANATOMY and DEFINITION

The AV valve of the left ventricle is the mitral valve.
It is composed of 2 leaflets: the anterior (or septal, or aortic) and the posterior (ventricular) one. The larger anterior leaflet is triangular in shape, with the base inserting on about one third of the annulus. The septal leaflet composes the larger portion of the annulus; it has a relatively smooth free margin with few indentations. A ridge separates the rough zone (region of closure) from the clear zone.
The resulting area of the two mitral leaflets is twice that of the mitral orifice creating a large area of coaptation. The malalignment of the leaflets causes the loss of this area generating a regurgitant valve.
The aortic leaflet is in fibrous continuity with the aortic valve through the aortic-mitral annulus and forms a boundary of the leaflet ventricular outflow tract.
The smaller posterior inserts in about two thirds of the annulus.
The mitral valve leaflets may be anatomically described using a segmental classification in 6 sections. A1 to A3 for the anterior, P1 to P3 for the posterior leaflet.
The great part of the *chordae tendineae* originates from the papillary muscles of the left ventricle, the anterolateral and the posteromedial. Each leaflet receives chordae from both the papillary muscles. Tissue between the two leaflets is called *commissural.*
The papillary muscles are often thought of as a fingerlike structure protruding into the left ventricular cavity. There are usually 4 to 12 chordae originating from each papillary muscle group. Chordal branching resulted in a number of chordae inserting to the mitral valve leaflet. Tandler defined three orders of chordae[1].
First order's chordae insert on the free margin of the leaflet; second order's chordae insert few millimeters back from the free edge; third order's chordae insert at the base of the leaflet. Lam and colleagues reclassified chordae into rough zone, cleft, basal, and commissural chordae. The annulus is a saddle-shaped, fibrous ring around the leaflets and provides strength and proper closure of the leaflets by changing shape during the heart cycle. (Figure 1-2)

Mitral regurgitation (MR) is the second most common valvular disorder requiring surgery in Europe; it is the most prevalent valvular heart disease in US[2]. Major causes of surgical mitral regurgitation in western countries are degenerative (primary myxomatous disease, primary flail leaflets, annular calcification), representing 60–70% of cases, followed by ischemic mitral regurgitation (20%), endocarditis (2–5%), rheumatic (2–5%), and miscellaneous causes (cardiomyopathies, inflammatory diseases, drug-induced, traumatic, congenital).

Degenerative mitral regurgitation is the most reparable form, warranting early and careful assessment.

Both degenerative and functional MR can lead to decompensation *cordis* and are often accompanied by symptoms as dyspnea and fatigue.

There are several options to treat MR, such as surgery, medical therapy, and percutaneous treatment.

Despite well-established results in the treatment of mitral valve regurgitation, outcomes of patients undergoing mitral valve repair are still burdened by several factors. Surgical strategy is one of them: it is never obvious since it plays an important role on early and late recurrence of MR and on patients' quality of life. The evolution of surgical strategy led to percutaneous treatments of this pathology. We present below a brief review of these devices.

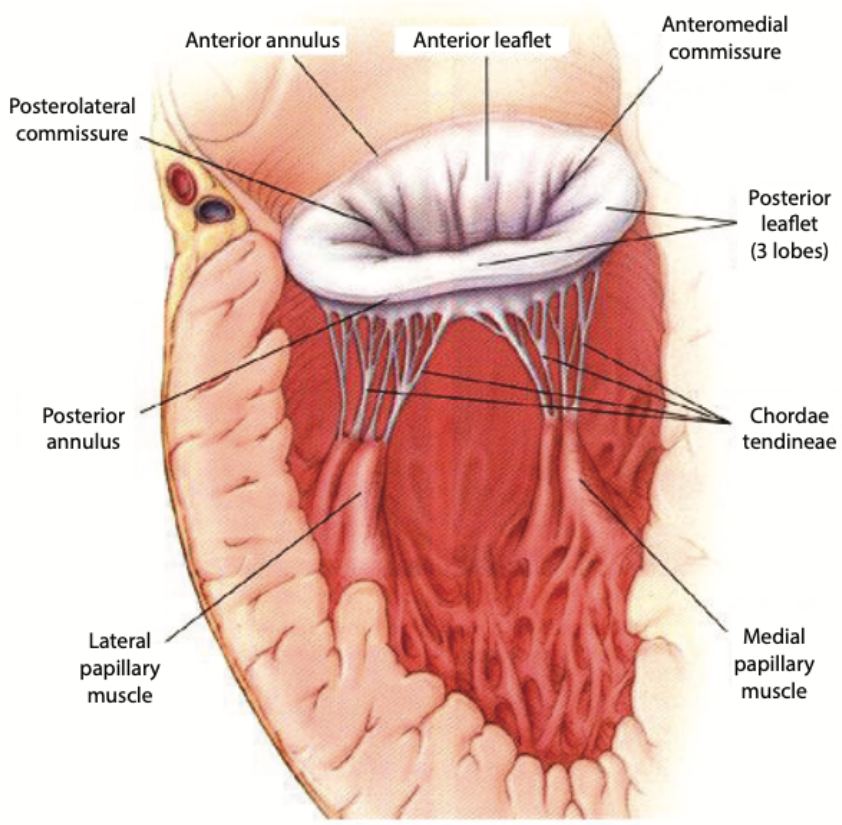

Figure 1 The anatomy of the mitral valve apparatus.

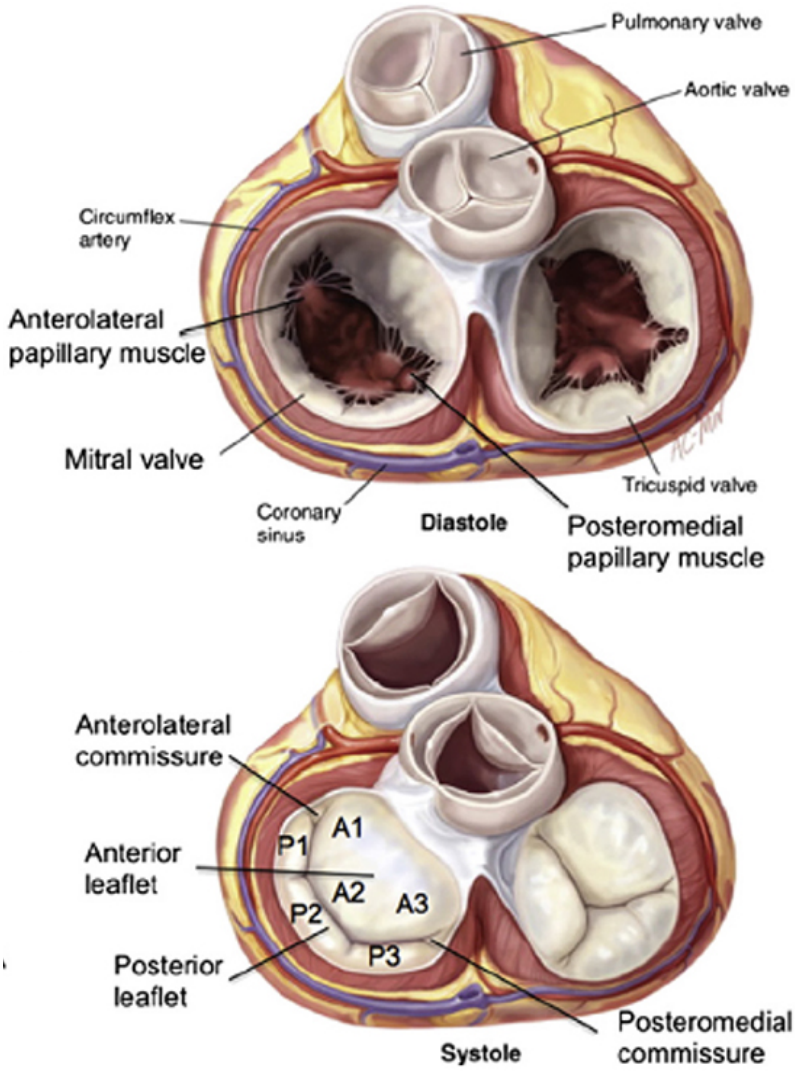

Figure 2: open mitral valve in diastole from the atrial view and surgical view of the closed mitral valve in systole showing the anterior sail-like leaflet and the posterior leaflet

TRANSCATHETER MITRAL VALVE THERAPIES

There are different types of devices, some have been abandoned, some are still under development. We intend to present few examples in order to describe the basic mechanism of action.
Percutaneous MV repair devices mirror the same principles of MV surgery: neochordae placement, leaflet plication, annuloplasty, papillary muscle modification, and LV remodeling. For majority of the percutaneous technologies used for MV repair, the surgical background of annuloplasty and leaflet repair has been adapted.
They can be grouped into those acting on the leaflets and sub-valvular apparatus, direct (DA) or indirect annuloplasty (IA), and chamber (LV) remodeling.

Percutaneous Leaflet Repair
These devices are based on the surgical edge-to-edge repair [3]:
The **MitraClip®** mechanism is based on suturing facing scallops of both leaflets with a mechanical clip using a TSP approach. The result is a double orifice valve. Under 2-dimensional and 3- TEE and fluoroscopic guidance, the clip is positioned above the MV. Once opened, it is advanced into the LV and subsequently, retracted, then, grippers and arms are closed to grasp leaflets permanently. This device was incorporated in international guidelines, it received CE mark approval in 2008.and FDA approval in 2013 for patients with severe DMR who are at high surgical risk[4].
The EVEREST-I and EVEREST-II randomized trials initially evaluated the system. EVEREST-I in 2005, a 6-month follow-up of 27 patients, reported no procedural complications. After 6 months, 13 of 14 patients had MR reduction to <2+[5]. The EVEREST-II trial randomized 279 patients to undergo either percutaneous repair (n = 184) or MV surgery (n = 95). At 5-years follow-up, recruiting 73% of patients with DMR, it demonstrated relatively low rates of surgery for MV dysfunction, endorsing the durability of MR reduction with the technique.
There are also registries and single-arm studies collecting data about outcome of patients affected by FMR. ACCESS-EU[6], TRAMI[8] and European Sentinel indicate that the edge-to-edge percutaneous technique with MitraClip is secure (3% mortality), feasible (94% procedure success) and effective (80% MR<2 and NYHA II after 1 year). There are three ongoing randomized trials (COAPT[9], RE-SHAPE-HF[10] and MITRA-FR[11]) comparing the efficacy of MitraClip with optimal medical therapy in FMR patients.

The novel Edwards **PASCAL** compared to MitraClip permits a simpler navigation in the LA (the system entails less dependency on TSP height).
23 compassionate patients with grade >3 MR have been included in the first report. With a 9% rate of periprocedural complications, after device implantation, a reduction of
MR to <2+ was achieved in 96% of cases. Technical success was achieved in 96% of patients, and three patients died during 30-days follow-up[12]. Today, the CLASP trial is enrolling patients to evaluate the safety and clinical outcomes of the PASCAL system [13].

Percutaneous chordal approach

The basic principle of this technique (supported by surgical long-term efficacy evidence) is to implant new synthetic chords or sutures fixing the leaflets to the LV, adjusting the length to achieve a better result under transesophageal echocardiogram (TEE) control. This approach is mainly for DMR.

NeoChord DS1000 (Neochord, Inc., Minnetonka, MN) is the most commonly used device receiving CE Mark approval in 2013 and FDA approval in 2016. It is used by transapical access (TA), in a beating-heart setting. It will be extensively explained below in this thesis.

The **MitraFlex** (TransCardiac Therapeutics, Atlanta, GA) is based on the same concept and access, but fixed to the LV through an anchor[14]. This device permits also to perform an edge-to-edge repair at the same time by deploying a clip.

The **Harpoon** Medical device (Harpoon Medical, Inc., Baltimore, MD) has a TA access for implantation of artificial chords anchored to the LV epicardium to fix the prolapsed leaflet. This system simplifies part of the process automating part of it. A preformed knot is deployed on the atrial surface of the prolapsing leaflet, improving coaptation. Considering the last study invloving 43 patients: after 30 days a technical success was achieved in 95% and 30 days procedural success in 93% with no stroke, myocardial infarction or death. There were only two surgical conversions[15]

Percutaneous mitral annuloplasty

These devices pursue to reduce MV annulus circumference causing consequently improvement in leaflet coaptation: they permit to achieve this result in Direct (DA) or Indirect annuloplasty (IA).

Direct annuloplasty devices: try to reduce MR from the annulus.

The **Cardioband** (Edwards Lifesciences; Irvine, USA) uses a TSP approach mimicking the surgical approach[16]. This off-pump, on beating heart technique permits, under TEE, to reach the anterolateral commissural area (atrial side). During implantation, sequential anchors fixate the Cardioband from trigon to trigon allowing approximately 30% reduction of the mitral annular diameter[17]. The device received the CE mark for MR in 2015. A one-year follow-up involving 38 patients was recently presented, with a high rate of technical success and no procedural deaths. It also shows promising results in terms of anatomical and clinical data (functional improvement measured by the 6-min walk test) [18].

The **Mitralign** (Mitralign, Tewksbury, MA, USA) follows the surgical principles of Kay annuloplasty; it uses a transfemoral access to approach the posterior MA through the LV; once reached the peri-annular space with two catheters, intra-annular pairs of pledgets are connected with a suture directly on the posterior MA and cinched together to reduce the MA.

The device received the CE Mail approval in 2016. An implant success of 70,4% was reached in the first study regarding this device. MR reduction occurred in only 50% of patients obtaining LV positive remodeling and symptom improvement[19]

The **Accucinch** (Guided Delivery Systems, Inc., Santa Clara, CA) causes a remodeling of the basal portion of the LV. The mechanism is based on anchors, connected by a nitinol wire to the sub-annular space, that are cinched circumferentially from trigone to trigone to improve MR. The report by Kleber, in 2013 showed data of 18 patients in whom this device achieved about 40% reduction of MR, 5 were converted to surgery and no 30-day deaths occurred[20].
Millipede (Millipede Inc., Santa Rosa, CA) is a full semi-rigid nitinol ring to be implanted by TSP in MA. It is implanted and driven on the atrial side and it is repositionable thank to its design.
The **Amend** device (Valcare Medical) is a semirigid, D- shaped ring implanted by TA route: it is fixed to posterior MA via a series of stabilizers and, pulling the posterior MA anteriorly, is fixed in the anterior MA. In this way the anterior-posterior MA dimension is reduced, improving the leaflet coaptation[21](first implanted in human in 2016).
Indirect annuloplasty: some technologies for TMVr are designed to be placed in the coronary sinus (CS) which surrounds the postero-lateral MA. This strategy may allow devices, going through, to indirectly modify the MA geometry by transmitting tension from outside. There are some obstacles using this approach to consider (e.g. anatomical variability of the CS and the MA, or compression of the circumflex coronary artery) leading to higher rates of complications.
The **Carillon Mitral Contour System** (Cardiac Dimension, Inc., Kirkland, WA, USA) remodels the posterior MA using a curve self-expandable nitinol arch. The trans-jugular access permits to reach the CS with delivery catheter. 36 patients have been enrolled in the TITAN II trial, showing improvements in clinical and echocardiographic parameters[22].
The **Arto System** (MVRx, Inc., Belmont, CA, USA) consists of 2 magnetically linked catheters introduced through the right internal jugular vein and right common FV, which are placed in the great cardiac vein. The MAVERIC trial involved 11 patients and showed improvements in clinical and echocardiographic data at 30-day follow-up.[23]
There are other systems for IA at different stages of development.

TRANSCATHETER MITRAL VALVE IMPLANTATION

Patients at high surgical risk, not amenable to CS are potential candidate for Transcatheter MV implantation (TMVI). Several devices are currently under development.
The **Tendyne system** is designed for TA approach and has a ventricular apical fixation system: this device consists of a trileaflet porcine pericardial valve in a nitinol frame that is fully retrievable and repositionable. The valve is designed for TA approach, intra-annular positioning and has a. The Global Feasibility Study, involving 30 patients, demonstrated 93.3% of successful implantation, no deaths, strokes or myocardial infarctions. At 30 days, 86.6% were free of cardiovascular mortality, stroke, and device malfunction[24].
The **Twelve Intrepid system** (Medtronic, Minneapolis, MN, USA) is a TA self-expanding bovine pericardial bioprosthesis in a nitinol frame (symmetrical). It was designed to fit the variability of the MA, facilitating anchoring through a 'champagne cork' like effect.
Cardiovalve is a transfemoral TSP device. It is a self-expandable trileaflet bovine pericardial valve that has a robust anchoring and migration forces distribute over 24 focal points. It also has a robust sealing to prevent paravalvular leak.

AIM AND OUTLINE OF THE THESIS

The concept of *"micro-invasive"* was firstly introduced by Gerosa. Application of "*microinvasive"* approach in cardiac surgery represents a challenge for surgeons and for the whole team[25]. Performing isolated (i.e.: aortic valve replacement; inter-atrial defect closure; mitral valve repair with different devices) or combined cardiac surgical interventions avoiding the use of cardiopulmonary bypass, on-beating heart and with an impressive field (a thorax wide-shut) means overcoming and resetting old *clichés*.

The focal point of this project was reaching the same effective results of "classical" surgery as conventionally deemed and widely accepted. Lesson already learnt from transcatheter aortic valve replacement: technological evolution is always coupled with improvement of clinical results.

Mitral valve repair through the application of transapical, artificial chordae in a micro-invasive scenario enables the correction of DMR in case of leaflet prolapse/flail with no CPB nor aortic CC. This procedure has been recently introduced into clinical practice and has shown initial promising results.

No data about mid- and long-term follow up of patients treated with this device nor a direct comparison between Neochord (NC) and Conventional Surgery (CS) in patients with mitral prolapse/flail have been collected and analyzed until now.

This thesis is the result of a "journey" through years of evolution in the field of surgical mitral valve repair in order to study and analyze the change of surgeon's perspective pursuing innovative, even if more challenging, techniques and technologies.

The originality of this work is related not only to a mere data analysis about a "new device", but, above all, to the application of to a new concept of surgery, intended as a different state-of-mind in clinical practice.

Aims of our project were:
- to describe the journey of surgical mitral valve repair: as conventionally deemed, to the most advanced approach;
- to analyze outcomes of patients who underwent mitral repair through the micro-invasive device Neochord 2000 (NC) at the longest of follow up to our knowledge (5 years);
- to compare clinical outcomes of patients who underwent mitral repair through different approaches: NC and conventional surgery (CS);
- to assess early outcomes of a totally micro-invasive strategy (percutaneous coronary intervention-PCI-followed by transapical off-pump NeoChord mitral repair) in patients with concomitant coronary artery disease (CAD) and degenerative mitral regurgitation (MR)

We present our studies in 4 chapters:

- Chapter 2 presents the journey of cardiac surgery applied to mitral valve repair: from the first technique to the most advanced therapy, from 'resect', to 'respect', to 'restore';
- Chapter 3, 4 and 5 examine the results of NC procedure in different studies: outcomes of patients at the longest follow-up to our knowledge; the comparison of NC vs. CS; the combined strategy "PCI and NC".

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CHAPTER 2

A journey from resect to respect to restore. Aiming at optimal physiological surgical mitral valve repair. Review

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ABSTRACT

The concept of 'repairing' a degenerated mitral valve in order to restore the native competence means achieving the more physiological result coupled with the least invasiveness approach: this represents an interesting challenge for cardiac surgeons. The evolution of cardiac surgery through the years involved techniques and technologies in every field of interest.

From 'resect', to 'respect', to 'restore': the micro-invasive approach based on Neochord implant implies a transapical beating heart surgery which is based on the concept of implanting artificial chordae, preserving the physiological dynamics of the mitral annulus and avoiding the disadvantages of cardiopulmonary-bypass and cardioplegic arrest of the heart.

INTRODUCTION

Mitral valve repair (MVR) is the treatment of choice for Degenerative Mitral Regurgitation (DMR) providing excellent long-term outcomes.

The technique and technological revolution applied to all fields of cardiac surgery has the ultimate goal of coupling the least invasiveness and the most effective results for patients in terms of survival and quality of life. This concept is even more true for mitral valve repair.

Aim of this review is to analyze the current therapeutic options when dealing with DMR looking at advantages and limits of each technique and approach.

MITRAL VALVE ANATOMY AND PATHOPHYSIOLOGY

The essential principle for every surgeon approaching MVR is a meticulous knowledge of mitral anatomy and pathophysiology in order to identify the ideal therapeutic strategy.

In fact, the complex interplay between valvular and ventricular structures involved confers to the mitral valve the dignity of an 'apparatus'.

Moreover, the ability to gain high percentage of repair represents a crucial parameter when judging quality of heart valve clinics.
DMR is the most frequent cause of mitral regurgitation in Western countries [1-2] and represents the most reparable form, warranting an early referral.
DMR recognizes 2 different phenotypes: FibroElastic Deficiency (FED) and Degenerative Myxomatous Disease (DMD), the latter is characterized by a more extensive pathology involving both leaflets.

Leaflets affected by DMR pathology are very often characterized by prolapsing segments, cleft-like lesions or sub-commissural indentations (i.e. extending >50% into the leaflets from the free edge to the annulus) which are frequent cause of post repair residual regurgitation.[3]

The complex equipoise within ventricular apparatus exerted by tethering and closing tension explains the pathophysiology of functional regurgitation of the MV (FMR) secondary to unfavorable remodeling of the LV due to MI or HF [4]

Ischemic left ventricle dilatation and dysfunction lead to papillary muscles displacement with consequent increased tethering forces; the impaired LV contractility causes inadequate closure of mitral leaflets; while mitral annular dilatation should be the direct consequence of either atrial or ventricular dilatation. Prognosis is related to FMR severity which, indeed, follows LV dilatation and dysfunction.[5]

Several techniques have been adopted to correct FMR, the most used is the restrictive annuloplasty. An undersized rigid ring is implanted in order to reduce the annular diameter and favor leaflets coaptations. This a relatively simple and reproducible method, even though does not provide durable results due to high recurrence of post-operative MR. This is due to the unsolved underlying mechanism of MR: LV dilatation and dyssynchrony. A very recent experience would suggest that mitral valve replacement with sparing of the mitral valve apparatus might provide more favorable outcomes [6-7-8]

However, mitral annular (MA) dilatation is not the only culprit: left atrial enlargement and alteration of annular dynamics play an important role in specific cases.[9]

Patients affected by atrial fibrillation, with anatomical integrity of MV apparatus, nor dilated LV, may present with the so-called atrial functional mitral regurgitation (4-8% of cases)[10], which is characterized by atrial enlargement (Carpentier type I) with a prevalence of 28% in patients presenting long-standing lone AF.[11]

Even though the precise mechanism of atrial functional MR is not defined,-significant atrial functional MR may be detected in patients with recurrence of AF after catheter ablation. [10]

On the other hand, patients successfully treated with catheter ablation, once in sinus rhythm showed significant reduction in terms of MA dilatation and atrial dimension[9].

Furthermore, early referral of symptomatic patients (NYHA II-III) presenting with atrial functional MR treated with annuloplasty reduces MR severity, induces a reduction in LA dimension leading to improvement of NYHA functional class and lower incidence of rehospitalizations due to HF. [11-12]

According to the Mitral Regurgitation International Database (MIDA) registry which includes more than 3000 patients affected by isolated DMR due to flail leaflet, MV repair is associated with lower operative mortality and better long-term survival compared to replacement. [13] The high potential advantages deriving from early MR compared to conservative medical therapy have been widely proven[14] highlighting the higher probability of repair success in patients without experience of heart failure nor affected by LV dysfunction.

The most challenging conditions which may hinder feasibility of mitral surgical repair are as follows: anterior or bileaflet prolapse, presence of calcification involving leaflets or annulus; diffuse thickening of subvalvular apparatus with leaflets retraction.[15]

SURGICAL INDICATIONS for DMR

According to the recently updated European guidelines [16], surgery is recommended for symptomatic patients affected by severe mitral regurgitation who are operable and not high risk and for asymptomatic patients with LV dysfunction (LVESD ≥ 40 mm; and /or LVEF ≤ 60%). (Class I; Level B)

Considering asymptomatic patients, with preserved LVEF (> 60%), surgery should be considered if at least one of the following conditions are present: atrial fibrillation secondary to mitral regurgitation or pulmonary hypertension (SPAP at rest >50 mmHg) and in low-risk asymptomatic patients with left atrial enlargement (≥60 mL/m^2) (Class IIa; Level B).

According to the complex morphology of mitral apparatus, surgical techniques have to be supported by extensive surgical skills.

A rough estimate of the "comfort zone" indicates satisfactory results for volume of 25 repairs per year per surgeon and 50 repairs per year per Center. [17]

A heart valve center in order to be competitive, should guarantee hospital mortality lower than 1% and the highest repair rate. [18-19]

SURGERY FOR DMR

The **strategy** conceived throughout the years, in order to satisfactorily correct a DMR is based on:

- reaching adequate leaflet coaptation (specifically a leaflet coaptation line of 5-8 mm [20])
- correcting mitral annular dilatation [20]

Two techniques have been widely adopted to repair DMR,

- *'resect'*
- *'respect'*

This terminology practically reflects a completely different "state-of-mind" to face the problem. *'Resect'* (standardized by Carpentier; i.e. "French technique") implies resection of leaflet tissue leading to a rearrangement of valve morphology in order to gain its competence; conversely, *'respect'* focuses on reducing the leaflets height, anchoring the free edge to the papillary muscles, without undermining leaflets integrity therefore respecting the native valve tissue.
Minimally invasive approaches are nowadays gaining wider consensus: the above-described surgical techniques are therefore reproduced in a minimally invasive fashion in order to reach the least invasiveness.
In this paper we provide an overview of the tenets underlying both methods and we compare them with the innovative concept of *'restore'*. Such approach is allowed by using the novel *"micro-invasive"* cardiac surgery definition applied to MVR [64]. Table 1 summarizes the most critical concepts explained in this review.

TABLE1

	RESECT	RESPECT	RESTORE
Aim	Readapt the native shape of leaflet creating de facto a new valve	A non-demolitive approach which reinstates an adequate equipoise to native valvular and sub-valvular apparatus	The off-pump mitral valve repair which restores valve competence preserving native structures without interfering with native mitral annulus physiology
Modality	**INCISION**: FULL STERNOTOMY / RIGHT MINITHORACTOMY **CPB / CC** : ON	**INCISION**: FULL STERNOTOMY / RIGHT MINITHORACTOMY **CPB / CC** : ON	**INCISION**: LEFT MINITHORACOTOMY **CPB / CC** : OFF
Technique	Quadrangular /triangular resection + annuloplasty (± sliding plasty)	Implant of artificial chordae anchoring papillary muscles to the free edge of leaflet and ring implantation	Transapical Implant of artificial chordae anchoring the free edges of mitral valve to left ventricle

' RESECT'

Back to 1983, Carpentier was the first to standardize the surgical techniques for repairing the mitral valve[21]. This technique, as conventionally deemed, involves extensive leaflet resection and was originally intended as quadrangular resection of the prolapsed segment, then modified by

other authors,[22] in order to achieve maximum results even in more complex cases. The triangular resection is an evolution of the previous one thought to correct specifically posterior leaflet prolapse avoiding extensive tissue excision. [23] Less aggressive excision of the leaflet, limiting to a triangular segment of the prolapsed region has been associated with good long-term outcomes in terms of survival and freedom from reoperation.[24] Extensive resection in a quadrangular shape requires annular plication, reducing in this way considerably annular length and consequently the orifice area. However, stabilization of the annulus by ring implantation showed to improve long term outcomes and was therefore considered essential (figure 1). [25-26-27-28] Ring implantation carries the potential risk of systolic anterior motion (SAM); but it has been proved that annular stabilization avoiding annulus over-reduction proved to be an efficacious solution.[29] Braunberger analyzed 20 years outcomes of 164 patients who underwent mitral valve repair according to Carpentier's technique. He demonstrated excellent long term patients' survival which was similar to the general population with a freedom from reoperation of 82.2% at 20 years in case of isolated anterior prolapse and 96.95% in case of posterior isolated prolapse. In case of bileaflets prolapse freedom from reoperation at 20 years was 82.6%. [30] Both techniques (particularly quadrangular resection) may lead to a negative remodeling of the MV morphology due to the excessive stress posed to the posterior leaflet limiting its mobility. The demolitive approach induced by the resection implies the rearrangement of the MV morphology and even of the sub-valvular apparatus.

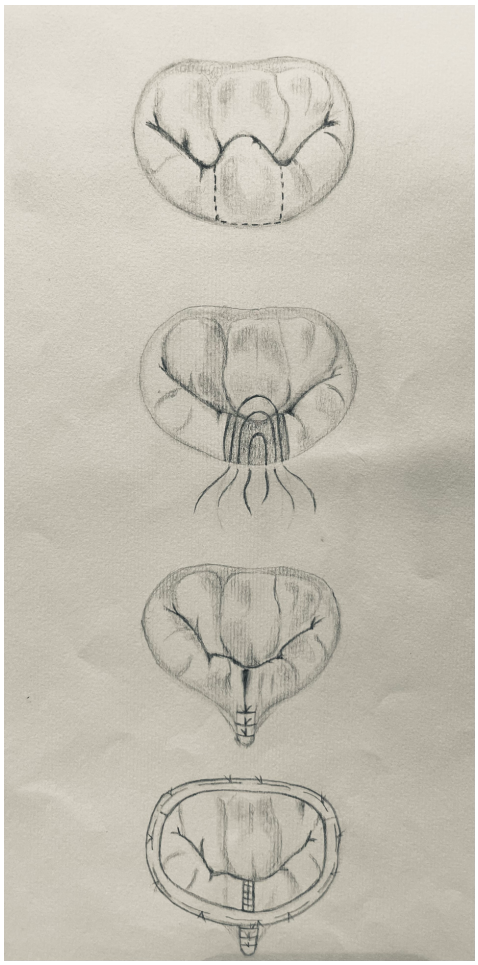

Figure 1: French technique. Quadrangular resection, sliding plasty and implant of ring.

'RESPECT'

The introduction of artificial chordae (AR) represented a further improvement in order to gain a more physiological mitral valve repair since the rationale is to achieve optimal coaptation applying adjunctive chordae normalizing the prolapsing segments. Various materials have been used for chordal replacement such as silk, teflon, nylon, and pericardium either autologous or heterologous glutaraldehyde-treated. Frater firstly proposed the implant of AR using pericardium. Vetter in 1985 presented excellent results using artificial PTFE chordae [31]

The growing experience has confirmed the efficacy of AR use. From a surgical standpoint of view the most challenging step is to optimize the chordal length. A review published by Ibrahim et coll. reported over 40 techniques for chordal application[32].

Technically, a single double-arm suture is passed through the free edge of the prolapsing region of the leaflet, and then anchored to the fibrous region of the correspondent papillary muscle. When necessary multiple chords can be created with a single suture passing twice through the interested leaflets (every AR should be 2-3 mm distanced each other) (figure 2A) Von Oppell and Mohr described the “loop technique” that consists of multiple chordal loops originating from a single suture. Callipers are used to define the optimal length of the ePTFE chordae, and to construct the loop. (figure 2B) Chordae are fixed with pledgets to the papillary muscle and then anchored to the atrial side of the prolapsing cusp, tying knots on the ventricular side. This technique represented a milestone on which subsequent methods have been derived.[33]

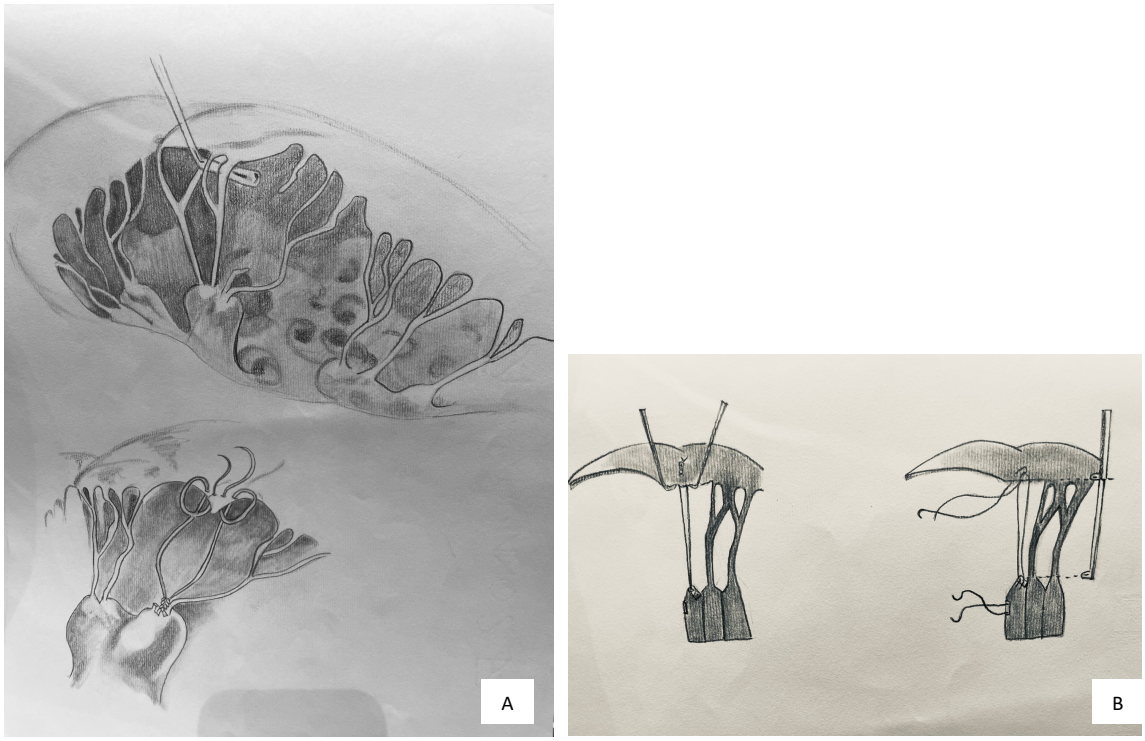

Figure 1A: American technique: artificial chordae placement with simple knot on the atrial side; 2B: Comparison of technique: a) single artificial chordae placed on the papillary muscle; b) Loop technique: the caliper measures the distance between the reference point of the leaflet and the tip of the papillary muscle

The 'David technique' is based on creating interconnected self-adjustable multiple-loops that provide a more physiological force distribution among the structures.[31] A simple method described by Kasegawa is based on readjusting chordal length by placing tourniquets and optimizing the length after competence testing. [34] Alternatively, the plane of the annuloplasty ring's suture proved to be an effective point to adjust the optimal length; even just considering the anterior annulus and a dedicated prosthetic ring has been developed accordingly.[35-36-37]

Last but not least, a fundamental technique based on the non-resectional statement is the 'double orifice' originally described by Pomerantzeff and later identified as 'edge-to-edge' which aims to reduce the valve incompetence suturing the A2-P2 zone in order to create a double-orifice area.[38] This technique "respects" native structures, although it does not reproduce a physiological competence. (figure 3)

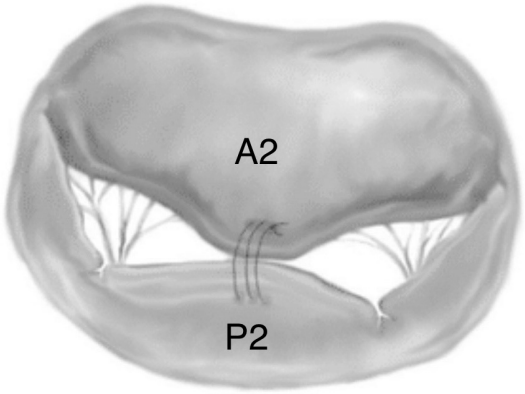

Figure 3: Double-orifice technique

Several studies demonstrated very satisfying long-term results combined with ring annuloplasty.[39-40] This approach gained wide success thanks to its simplicity and reproducibility and paved the base for a novel transcatheter procedure (MitraClip) now followed also by the PASCAL systems.

DISCUSSION: LITERATURE ANALYSIS

Surgical techniques further evolved according to the following concepts:

- respect the native tissue,
- correct the pathologies in the simplest and easiest way
- reduce the invasiveness of the procedures (minimally invasive MVR)

The results achieved by these techniques are extremely satisfactory providing long term freedom from reoperation and recurrent MR. [41]

The concept of "respect rather than resect", firstly described by Perier, underlines the importance of preserving native tissue by using AR which grants better long term results [42]

Recently Cetinkaya and coll compared, by using a propensity matched analysis, long term outcomes of triangular and quadrangular resection vs loop implantation for treatment of posterior leaflet prolapse. The authors reported similar long-term survival among groups; however, loop implantation showed better outcomes in terms of freedom from reoperation and operative complications. [43]

Results derived from two recent meta-analyses comparing chordal replacement to leaflet resection for the treatment of posterior leaflet prolapse prove that implant of neochordae is associated with excellent long-term outcomes in terms of freedom from reoperation and recurrence of MR [44-45]

By using virtual MV repair simulation both approaches have been extensively studied and compared for better understanding of MV function and dynamics. The application of AR granted a lower stress concentration when compared to resection techniques with improved coaptation and a more physiological tension distribution. [46]

These results were confirmed by Zekry who identified a more physiological valvular motion by using a non-resectional approach compared with resection. Even though both techniques induce a reduction of leaflets mobility, the application of AR ensures a more balanced mobility of the leaflets, conversely resection of leaflets leads to an unbalanced stress reducing leaflet mobility. [47]

Similar results have been confirmed by Pompeu Sà et al.: in a meta-analysis including 17 studies (accounting more than 6000 patients) despite longer CPB and CC time 'respect' technique showed lower mean gradients and less need of permanent pacemaker.[48]

Finally, according to the literature, the "*no-touch-leaflets*" approach seems to be the preferred technique being able to provide optimal long-term results and lower postoperative complications.

Even though, surgeon's expertise and experience play a major role in the decision flowchart: a retrospective study conducted by Dreyfus on 700 patients showed that respect technique was appliable in 20% of cases, whereas the remnants 80% necessitated adjunctive maneuvers. Prolapse of posterior leaflet, in the authors opinion, does not overlook the resectional technique, that is the reason why they "respect whenever possible and resect whenever needed" [49].

THE MINIMALLY INVASIVE APPROACH: RESULTS AND RESPONSABILITIES

The minimally invasive mitral valve surgery approach (MIMVS) is gaining increasing interest in order to obtain optimal results with the least invasiveness. The classical concept of minimally invasive surgery as generally intended is based on the minimal access through a small lateral incision, overlooking the potential invasiveness related to cardiopulmonary by-pass (CPB) and

aortic cross-clamping (CC). The concept of surgical success has to include not only minimal residual valve regurgitation, but, even more importantly, a faster recovery to a normal quality of life with, eventually, cost savings [50] A minimally invasive approache allows cardiac operations through a small incision, thus reducing blood loss, wound dehiscence and providing better cosmetic results, faster postoperative recovery but granting clinical outcomes comparable to conventional surgery[51-52-53-54]. Furthermore, all these-plus might be extended also to high-risk patients. MIMVS still implies CPB and CC which have a potential harmful impact on patient's body. CPB generates a systemic inflammatory response with the production of cytokines [55] while the aortic CC has been independently associated with mortality as extensively demonstrated in standard open-heart surgery operations. [56]

As minimally invasive approaches are generally intended, a recent meta-analysis of studies reporting on small left thoracotomy incision compared to conventional median sternotomy for repair of complex mitral valve insufficiency showed similar early and long-term results for both approaches. Minimally invasive procedures were associated with prolonged CC and CPB times, but no worsening of clinical outcomes.[57]

SHIFTING THE PARADYGM, FROM CONVENTIONAL TO MICROINVASIVE CARDIAC SURGERY: THE RESTORE TECHNIQUE.'

Technical aspects

More recently, structural heart defects, typically treated by using CPB and CC may now be correct by using the so called micro-invasive approach .[58] This term is justified by the least invasiveness of these procedures avoiding both CPB and CC, which have been considered for several years the "conditio-sine qua-non" for performing cardiac surgery interventions. The current challenge consists in reproducing the same results obtained by using the conventional way, working on a beating heart. This concept radically changes the way to think cardiac surgery.

Transcatheter aortic valve implantation (TAVI); MitraClip and transventricular mitral chordae implantation are few examples derived from such concept.

These procedures require small skin incision (or no incision at all) and a very skilled coordination eyes -hands because of the change in perspective of visualization; in fact, multimodality imaging and no more the surgeon’s eyes, are the new techniques of visualization. As far as mitral valve repair is concerned, micro invasive approaches have already been practiced reproducing standardized techniques (i.e.: the edge-to edge or Alfieri stitch, the implant of ePTFE neochordae or ring annuloplasty). Percutaneous edge-to-edge repair (PE2E) aims to correct primary and secondary mitral regurgitation in high-risk patients. The EVEREST-2Endovascular Valve Edge-to-Edge Repair Study II trial analyzed PE2E outcomes in patients with degenerative primary MR and found that, at 1-year, conventional surgery proved better results in terms of resolution of mitral regurgitation (freedom from reoperation or moderate-severe mitral regurgitation) [59]

The registry of transcatheter treatment of mitral valve regurgitation (GIOTTO) collected data from near 1700 patients (19 Italian centers were included) who underwent MitraClip procedure to repair DMR or FMR. Technical success (according to MVARC definition) was achieved in 97.2%; cardiovascular death was the most frequent cause of death. FMR was related to a worse prognosis than DMR.[60]

Devices intended for percutaneous mitral annuloplasty imply different approaches to reduce valve incompetence.
These can be:
1) Direct (D): from the annulus
2) Indirect (I): from near structures.
Direct: Cardioband (Edwards Lifesciences; Irvine; USA) and MitraLign (Tewksbury, MA, USA) gained CE mark in 2015 and 2016 respectively; Indirect: Carillon Mitral Contour System (Cardiac Dimension, Inc., Kirkland, WA, USA) which received CE mark in 2009, is designed to be placed in the coronary sinus remodeling the annular geometry from outside. All these devices have been intended and developed specifically for functional MR.
'RESTORE': Devices and applications
The already mentioned excellent long-term results accomplished with the implant of expanded PTFE sutures in conventional surgery gives reason to the ~~subsequent~~ introduction of transventricular beating heart mitral valve repair. A further advantage deriving from these technologies is the real time assessment of the optimal chordal length and of the final surgical result. In fact, this procedure requires continuous live 3D TEE that provides the only operative visualization for the surgeon. Two devices are currently commercially available.

Neochord DS 1000
The first device used was the Neochord DS 1000 (NC) which enables off-pump, beating-heart correction of mitral valve regurgitation. (figure 4) Technical aspects of NC procedure have been widely described (figure 5) [61].

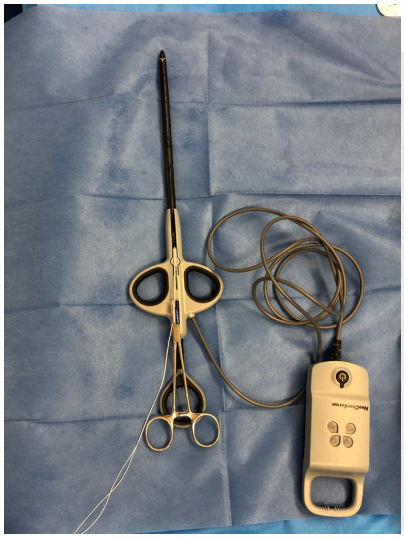

Figure 4: Neochord instument DS 2000

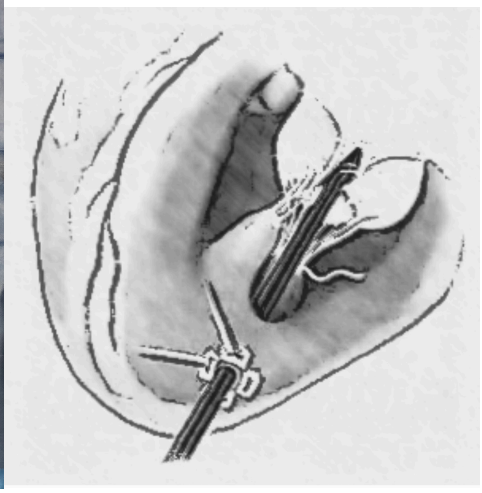

Figure 5: transapical beating heart implant of Neochordae

Briefly, under general anesthesia a left anterior minithoracotomy is performed in the 5th intercostal space and the pericardium is opened. Two concentric 2-0 polypropylene purse-string sutures with pledgets are placed on the left ventricular apex. Heparin is given and the apex is incised. After insertion of the device into the left ventricle, the tip of the instrument, under 2D echo guidance, is advanced into the atrium crossing the mitral valve. The jaws of the instrument are then opened and gently retracted in order to catch the prolapsing segment under 3D echo vision.
When an appropriate leaflet grasping is confirmed by the four device lights turning white the jaws are closed and the EPTFE suture is passed through the free edge of the leaflet. The EPTFE suture is then pulled out from the ventricle and, after performing an half-notch, secured on a mosquito. This sequence is repeated according to the total number of required chordae. The implanted chordae are then tensioned until the appropriate leaflet coaptation is achieved and fixed with a knot to the apex of the left ventricle.-The entire procedure is performed under live 2D and 3D TEE guidance.
In the USA, the NC technology has received investigational device exemption (IDE) endorsement from the Food and Drug Administration (FDA) and patients are being enrolled in a prospective, multicenter, randomized controlled clinical trial comparing the Neochord procedure with conventional surgical MV repair (clinicaltrials.gov NCT02803957).
A critical analysis of the procedure-operator performance during the learning curve period highlighted a decrease in the actual probability of failure to <10% after 49 cases performed and to 5% after >81 cases, with an acceptable adverse event rate threshold of 5%, below the 10-15% rate used in literature.[62]

Harpoon

The basic concept of the Harpoon device is similar to the previous one. It allows the insertion of ePTFE cordae on the posterior leaflet of the mitral valve puncturing the belly of the leaflet and securing the chordae by releasing an anchor made by multiple knots. This device has a thinner introducer (12 Fr), which allows to enter the LV multiple times without opening and closing the ventricular purse-string sutures as for the NC device thus minimizing blood loss.
Gammie recently published the first worldwide results of the Harpoon system: 65 patients have been treated with Harpoon device as part of the CE Mark clinical trial. At 1-year residual mitral regurgitation was trace or mild in 75% of patients. 98% of patients were asymptomatic or paucisymptomatic (NYHA I-II). Indeed, the author showed a 1-year favorable left ventricle remodeling. [63]

PATIENT SELECTION
Mitral valve repair requires a very careful pre-operative patient's selection in order to evaluate its feasibility and to gain the optimal post-operative results. This is even more true for micro invasive mitral valve repair, particularly by using the chordal repair strategy.
Identifying the ideal candidate for micro-invasive procedures is still an ongoing process.

NC is a feasible alternative to CS for patients with severe mitral regurgitation due to leaflets flail or prolapse. The presence of clefts is an absolute contraindication whereas annular dilatation may be counteracted by an adequate leaflets' length.
MV repair with NC ensures incremental benefit for the acute volumetric reduction of the left ventricle and atrium in this subset of patients. Mitral valve geometry also improves rapidly after chordae implantation. These observations have been confirmed in late-follow up periods. Patients selection criteria were developed thanks to the morphological/ anatomical description of the valve defect and echocardiographic measurements. According to mitral valve anatomy, four progressively more challenging groups have been identified:
- Type A: isolated P2 prolapse
-Type B posterior multisegment prolapse/ flail
- Type C anterior, bileaflet or paracommissural disease without leaflet and annular calcifications.
-Type D: prolapse/flail near the commissures or any conditions associated with significant annular or leaflet calcification.
Outcomes are strictly connected with the morphological classification and like traditional surgery, MV morphology is a crucial criterion for patient selection. Type A and Type B patients have better outcomes than those with more complex lesions.
Furthermore, with increased experience, some echocardiographic parameters have been derived:
1) Leaflet-to Annulus index (LAI): this parameter identifies the leaflet-to-annulus mismatch.
LAI is a ratio indicating the amount of valve tissue which grants leaflet coaptation highlighting the concept that annulus dilatation has to be considered in relation to the extension of leaflets.[64]
This index approximates the quantity of overlapping leaflet tissue and therefore predicts whether an appropriate level of coaptation will result from the Neochord procedure. Patients whose LAI is less than 1.25 threshold will nevertheless benefit from the Neochord procedure just varying the ventricular access site.
The entry site is progressively moved more anteriorly according to the specific leaflet to annulus index of less than 1.25. [65]
The ventricular access permits to modify the working angle of the posterior leaflet, stretches it below the anterior leaflet and could increase the leaflet coaptation.
According to our experience LAI > 1.25 is a strong predictor of less than mild MR at 1 year of follow-up [66]
The established value of 1.25 indicates the presence of 25% of excess tissue, as demonstrated by our group. In the same study the authors proved that a concomitant annuloplasty is not always mandatory during MVR.
2) tissue to gap ratio: Gammie defines "....the tissue/gap ratio as the ratio of the height/length of the prolapsing segment of the posterior leaflet to the gap between the coaptation surface of the anterior leaflet and the hinge point of the base of the posterior leaflet..." This is a parameter of paramount importance to judge the feasibility of mitral repair by using the Harpoon device [63].
One of the major concerns of NC is the lack of ring implantation. Annuloplasty has been introduced by Carpentier as a concomitant procedure in conventional surgery in order to gain annular stabilization.

It has been demonstrated that the prosthetic ring may lead to change within the ventriculo-annular dynamics leading to a discontinuity induced by the prosthetic ring itself. [67-68]
Furthermore, from our one-year results a significant annular remodeling (reduction of MV area, annulus circumference, aorto-mitral angle) has been demonstrated which is fundamental to reduce MR recurrence. [69]
Having said that the paramount importance of an earlier patient's referral is explained.

SHIFTING THE SURGICAL PERSPECTIVES: TEE

An efficient intracardiac imaging tool is of paramount importance for microinvasive cardiac surgery. Real-time 3D TEE is undoubtedly one of the key factors that has allowed the feasibility and reproducibility of the new micro-surgical procedures.
The TEE guidance is fundamental during every step of the procedure: evaluation of prolapse, insertion of the device, leaflet capture and evaluation of the final result.
For the insertion of the device should be used a multi-plane imaging (X-plane), unique to the matrix array transducer, that allows to view two real-time images simultaneously. In order to identify the correct ventricular puncture site is important to evaluate the ventricular apex.
Then, the probe is rotated in order to permit a double MV vision, in real time in two different planes. This procedure of double real-time images acquisition first guarantees the correct ventricular incision and then the insertion of the catheter in the left ventricle, being careful not to impact the native chordae.
When the microinvasive device reaches the ventricular chamber, the TEE guidance is essential to guarantee the surgeon a slow progress towards the left atrium, avoiding damage of the subvalvular apparatus.
Once reaching the left atrium 3D-TEE is necessary to have an optimal view of the device tip and to ensure correct grasping of the target point (flailing segment). Leaflet capture is confirmed by the four fiber-optic monitor lights changing from red to white. Then the artificial chord can be implanted in the prolapsing segment of the leaflet and then fixed to the ventricular wall. Once the appropriate number of neochordae has been placed, tensioning is performed. Fine tuning requires TEE guidance in order to achieve optimal coaptation.
In addition, real-time 3D-TEE improves visualization of the MV through the display of the whole valve from a single image. (figure 6)

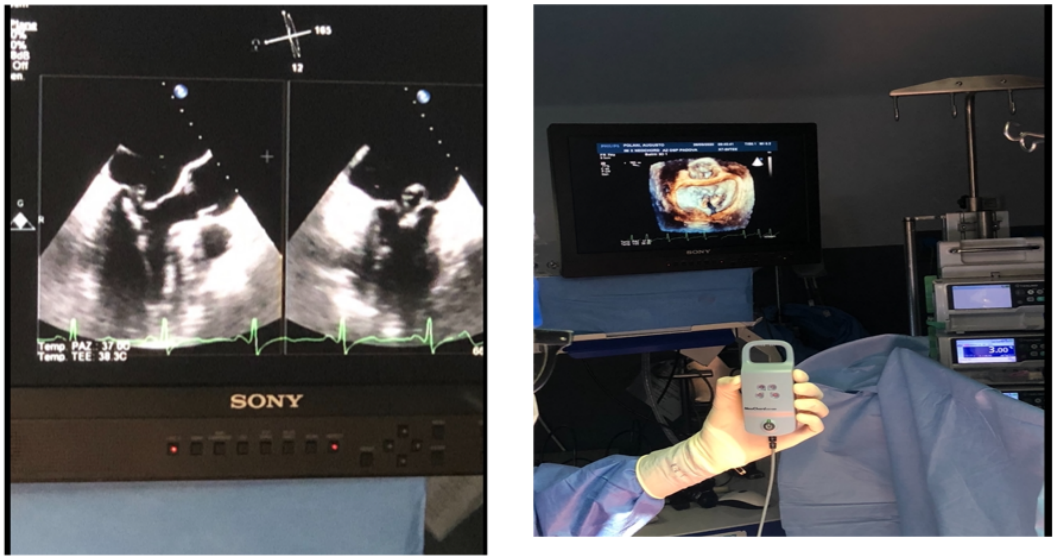

Figure 6: a direct view by TEE of the attempt to catch the prolapsing segment of the leaflet.

DATA FROM THE LITERATURE: LEARNING CURVE ANALYSIS AND FIRST EXPERIENCES

Surgeons, from the very beginning accustomed to open-heart surgery, face the operative field in a sort of wide-screen fashion. The micro-invasive approach changes these habits; a quick and sophisticated coordination eye-hand is required, visually guided reaching, grasping and object manipulation, together with the ability to visually decipher 2D and 3D TEE details moving in the beating heart.

These skills need a learning curve period. The threshold of acceptable events rate has been set at more restrictive 5% and the unacceptable at 15% in the early post-operative: these red lines were never crossed not even with the first patients [62], in fact, considering the first 20 patients the standardization of technical features (selection of ventricular access, correct tensioning of the chordae) revealed to be essential for the refinement of subsequent outcomes.

The first-year results showed promising and satisfying results; overall survival was 98%; 84 ± 2.5% achieved significant clinical benefits with improvements in the NYHA class and reduction of MR severity. Micro-invasive approaches, when compared to open heart, (either conventional or minimally invasive) can be defined as 'eyes wide open towards thorax wide shut'. [70-71-72-73]

A multi-center European study including 213 patients confirmed these data highlighting a procedural success of 97.6% and good mid-term results: overall survival 98±1%, patient's success 85± 2.5% at 1 year follow up [70].

MR was absent or mild in 75.4% of patients, moderate in 16.7% patients and severe in 15 7.9%patients. According to the aforementioned anatomical classification of MR, patients were stratified in 3 groups, considering type A (isolated P2 prolapse/flail) significant difference was observed in the primary end point at 6 months and at 1 year 'Type A', 94 ± 2.6%; 'Type B', 82.6 ± 3.8% and 'Type C' 63.6 ± 8.4% ($P < 0.001$).

The primary endpoint was composed of (i) procedural success (defined as the placement of at least 2 neochordae and mild or less MR at the end of the procedure) and (ii) freedom from death, stroke, structural or functional failure of the MVr (MR more than moderate), unplanned interventions related to the procedure or device, cardiac-related rehospitalization or worsening New York Heart Association (NYHA) functional class at 1 year and at each follow- up time.[70]

Notwithstanding the previously mentioned on-going learning curve analysis, in a more recent work Gerosa et al. recruited 312 patients in a multi-center study, verifying the wider adoption of Neochord procedure even to successfully treat failed conventional surgical mitral valve repair.[73]

One of the major concerns related to NC procedure is the absence of annular stabilization with prosthetic ring. However, it has been demonstrated that although annuloplasty is not applied, annular remodeling is observed and to date there is no evidence of annular dilatation over time in patients treated with NC procedure. [63]
The most recent updated analysis from Padua Center considered 100 patients affected by severe DMR due to PML prolapse/flail who underwent NC procedure from November 2013 to March 2016 showing results at 5 years, the longest follow up to our knowledge.

Two in-hospital deaths were reported: 87-years-old man, excluded from conventional surgical repair (CS) due to the extensive mitral calcification and a 78-years-old man with severe comorbidities.

A full completeness of follow up (median time 61 months) showed 72 patients alive, free from reoperation and asymptomatic for dyspnea (NYHA I-II).

Considering specifical anatomical types (favorable: TYPE A-B and unfavorable TYPE C – D) no differences in terms of survival were reported. Overall cumulative incidence of recurrence of severe MR was 23.7% at 5 years (CI 95%); a significantly lower incidence ($p<0.001$) of severe-MR recurrence and a lower incidence of reintervention ($p<0,001$) were reported, with the same period of follow up, in favor of patients with favorable anatomy when compared to unfavorable anatomy.[74]

Furthermore, our group performed a comparison between conventional surgery (CS) and transapical beating heart (NC) repair.
The overall population included 372 patients affected by isolated MR who underwent mitral repair by conventional surgery or NC procedure from 2010 to 2018.
Patients with complex valve anatomy (type D), combined procedures and history of previous cardiac surgery were excluded from the analysis.
Propensity match analysis selected 88 pairs of patients: no 30-days mortality and similar 5-year survival were detected in the two groups; patients undergoing NC showed worse freedom from moderate and severe MR but analyzing specifically type A anatomy this was similar for both groups at 5 years.[75]

Freedom from reoperation was lower in the NC group, but it was similar for patients with anatomical type A.
NC group had a significantly faster surgery duration with shorter ICU and in-hospital length of stay; this group also showed a lower incidence of post operative atrial fibrillation.
Patients in both groups showed a significant improvement of NYHA class.
Cardiac surgeons have now knowledge and skills, technique and technologies extremely effective to tailor procedures for the specific patients realizing the least invasive and the most effective results.

CONCLUSIONS

Even though different techniques have been standardized and optimized throughout the years, mitral valve repair still represents a challenge for today's cardiac surgeon.
We should, therefore, identify the optimal therapeutic option for each patient, applying the concept of precision medicine. The ultimate target is the following must: no hospital mortality, reduced recovery time and faster return to the highest quality of life.
Additionally, we have to tend to the best long-term results in terms of survival and freedom from major complications, avoiding further rehospitalization or reoperation due to repair failure.
The new emerging microinvasive procedures seem to be the correct answer to these issues, echoing Karl Popper in his famous book **The Open Society and its enemies**: "....Closed societies resist novelty and therefore pass up the chance to learn from experience", we should constantly reengineer our surgical practice.
These techniques already grant the least invasive approach with promising results in anatomically selected patients and the technological evolution will further expand these boundaries.

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Chapter 3

Outcomes of transapical mitral valve repair with neochordae implantation

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ABSTRACT

Objective: Transapical off-pump beating-heart neochord implantation (NC) has shown encouraging early results in patients with degenerative mitral regurgitation. The aim of this study was to evaluate clinical and echocardiographic 5-year outcomes of patients who underwent NC.

Methods: All patients who underwent NC at our institution from November 2013 to March 2016 were included. Indications were severe symptomatic degenerative mitral regurgitation due to leaflet prolapse/flail. Patients were classified as having favorable anatomy (FA) and unfavorable anatomy (UA) on the basis of the extent and severity of mitral valve disease. All patients underwent clinical and echocardiographic follow-up at 1, 3, 6, and 12 months, and annually thereafter. Data were prospectively collected and retrospectively analyzed. Outcomes were on the basis of the Mitral Valve Academic Research Consortium guidelines.

Results: One hundred consecutive patients were included in the analysis (FA: 81%; UA: 19%). Median age was 66 years (interquartile range, 58-76) and median European System for Cardiac Operative Risk Evaluation (EuroSCORE) II was 1.4% (inter- quartile range, 0.7-2.3). Technical and procedural success were 98% and 94%, respectively. Thirty-day mortality was 2%. Device success was 94%, 92%, and 78%, at 30 days, 1-year, and 5 years, respectively. Patient success at 1 year was 92%. Median follow-up was 5.1 years. At 5 years, overall survival was 83% with no difference between FA and UA patients. Cumulative incidence of severe mitral regurgitation recurrence at 5 years was 14% (95% CI, 6.5%-22.8%) in FA patients and 63% (95% CI, 39.7%-86.2%) in UA patients, respectively (P<.001). Patients with FA compared with UA had a lower incidence of reintervention (14.7% vs 43.4%; P<.001).

Conclusions: Transapical off-pump beating heart NC might represent an accept- able option in patients with degenerative mitral valve disease and FA. (J Thorac Cardiovasc Surg 2022;-:1-11)

INTRODUCTION

The standard therapy for patients with degenerative mitral regurgitation (DMR) is open-heart mitral valve (MV) repair (MVRe), which can be performed through a conventional sternotomy or through a minimally invasive access. Recently, the concept of microinvasive cardiac surgery has

been introduced. This includes procedures that mimic conventional surgery but are per- formed off-pump, on a beating heart, with minimal or no skin incision, and require advanced imaging techniques.[1]

In this context, neochord implantation (NC) represents a microinvasive cardiac surgery option for the treatment of DMR, with the NeoChord DS 1000 (NeoChord, Inc) device granted the CE mark since 2012 and marketed since quarter 1 2013, and currently under investigation to obtain US Food and Drug Administration approval. There are currently 2 commercially available devices: NeoChord DS 1000 and Harpoon (Edwards Lifesciences). Both have shown initial promising results,[2,3] but only anecdotal reports on midterm outcomes are available.[4] The evaluation of midterm data of a considerable number of patients treated with this new technology would enable optimization of indications, patient selection, procedural technique, and postprocedural follow-up (FU). Therefore, the aim of this study was to assess the clinical and echocardiographic 5-year outcomes of patients who underwent NC.

Methods

The current study included all patients who underwent NC at the Division of Cardiac Surgery of the University of Padua between November 2013 and March 2016. Data were prospectively collected in an “ad hoc” database and retrospectively analyzed. All included patients had severe symptomatic mitral regurgitation (MR) due to prolapse or flail of 1 or both MV leaflet(s). To accurately assess the severity and mechanisms of MR, preoperative transthoracic echocardiography and transesophageal echocardiography (TEE) were always performed before surgery in all patients.

The leaflet-to-annulus index (LAI) was calculated after the first 50 cases in all patients, following the standardization of the patient selection process.[5] This consists of the ratio between the sum of anterior mitral leaflet and posterior mitral leaflet (PML) lengths divided by the antero-posterior diameter. Patients with LAI !1.2 were considered to have adequate leaflet tissue to allow for sufficient postoperative coaptation.[6] All patients under- went coronary computed tomography scan or cardiac catheterization before surgery.

Inclusion criteria were mainly on the basis of a careful evaluation of MV anatomy. At the beginning of our experience, we selected patients for NC on the basis of the presence of MV prolapse and/or flail of 1 or both leaflets. With experience we then identified that isolated posterior mitral leaflet (PML) prolapse/flail with appropriate LAI was the most favorable anatomic condition. For this study and on the basis of our previous studies,[7] the study population was divided into 2 groups: favorable anatomy (FA), which included patients with isolated PML prolapse/flail, and challenging/unfavorable anatomy (UA), which included patients with anterior or bileaflet prolapse/flail, paracommissural prolapse/flail, or any type of disease with the presence of significant leaflet/annular calcifications. Exclusion criteria were severe left ventricular (LV) dysfunction (LV ejection fraction <20%), LV aneurysm, apical thrombosis, and presence of associated heart disease requiring surgical correction.

The NC procedure has been already extensively described.[7,8] In brief, the procedure is performed in a standard operating room, using general anesthesia, selective lung intubation, and real-time 2-dimensional/3D TEE guidance. Through a left anterolateral minithoracotomy in the fifth intercostal space, the LV apex is exposed. The ideal entry site is identified approximately 2 cm posterolateral from the real apex. After the insertion of the device in the left ventricle and with 3D real-time TEE guidance and 3D imaging assessment, the targeted scallop is grasped and then pierced at its edge, deploying a single pair of neochords. The device is subsequently retrieved from the ventricle and the chordal loop is exteriorized. A variable number of neochords are implanted on the basis of the extension of the prolapse/flail. The neochords are then tensioned using real-time TEE until an adequate coaptation of the leaflets is achieved. The chordal free ends are then secured to the LV wall on a polytetrafluoroethylene felt.

Outcomes

All patients were included in a specific FU protocol and underwent clinical and echocardiographic FU at 1, 3, 6, and 12 months, and annually thereafter. In particular, to standardize the observations, all surviving patients who did not receive reoperation during FU were requested to undergo echocardiography at our institution. All exams were performed by the same cardiologist (P.A.). MR severity was graded as absent/trace (0), mild (1þ), moderate (2þ), and severe (3þ) according to the American Society of Echocardiography criteria.[9] Outcomes were on the basis of the Mitral Valve Academic Research Consortium (MVARC) guidelines.[10] In particular, device success (measured at 30 days and at all later postprocedural intervals) is defined by the contemporary presence of: absence of procedural mortality or stroke; proper placement and positioning of the device; freedom from unplanned surgical or interventional procedures related to the device or access procedure; no evidence of structural or functional failure; no specific device-related technical failure issues and complications; and reduction of MR to either optimal or acceptable levels without significant mitral stenosis.

This study obtained local ethics committee approval (3360/AO/14; March 19, 2015). All patients provided written informed consent for the procedure and for data collection and analysis for scientific purposes.

Statistical Analysis

Categorical variables are expressed as percentages and continuous variables as median (interquartile range [IQR]). Survival distribution at FU was evaluated using the Kaplan–Meier (KM) method. Cumulative incidence functions were used to evaluate reoperation and MR incidence at FU to ac- count for competing risks. Statistical differences among the groups were determined using the log rank Mantel–Cox test. KM curves are presented with the number of patients at risk over the course of FU truncated at 5 years. Echocardiographic comparisons were made using the Wilcoxon signed rank test for paired samples. A Cox proportional hazard model to assess the effect of potential determinants of survival at FU was estimated. SPSS statistical software was used (IBM Corp).

RESULTS

One hundred consecutive patients underwent NC at our institution between November 2013 and March 2016. FA was detected in 81 patients (81%) whereas UA was found in the remaining 19 patients (19%). The median age was 66 years (IQR, 58-76), median Society of Thoracic Surgeons (STS) Predicted Risk of Mortality MVRe score was 1% (IQR, 0.4-1.8) and median European System for Cardiac Operative Risk Evaluation (EuroSCORE) II was 1.4% (IQR, 0.7-2.3). All baseline clinical and echocardiographic data are reported in Table 1.

TABLE 1. Baseline characteristics

Variable	Value
Age, y	66 (58-76)
Male sex	73 (73)
STS PROM MV repair, %	1 (0.4-1.8)
EuroSCORE II, %	1.4 (0.7-2.3)
<4%	90 (90)
4%-8%	6 (6)
>8%	4 (4)
Cardiovascular risk factors	
Diabetes	8 (8)
Hypertension	72 (72)
COPD	12 (12)
CAD	19 (19)
Previous PCI	9 (9)
Atrial fibrillation	10 (10)
Stroke	0 (0)
Malignancy	15 (15)
GFR mL/min	72 (52-89)
sPAP >45 mm Hg	19 (19)
NYHA functional class III or IV	80 (35)
Anatomic type	
Favorable anatomy	81 (81)
Unfavorable anatomy	18 (19)
MR grade severe	100 (100)
Prolapse/flail	
Prolapse	42 (42)
Flail	58 (58)

Values are presented as n (%) or median (interquartile range). *STS PROM*, Society of Thoracic Surgeons Predicted Risk of Mortality; *MV*, mitral valve; *EuroSCORE*, European System for Cardiac Operative Risk Evaluation; *COPD*, chronic obstructive pulmonary disease; *CAD*, coronary artery disease; *PCI*, percutaneous coronary intervention; *GFR*, glomerular filtration rate; *sPAP*, systolic pulmonary artery pressure; *NYHA*, New York Heart Association; *MR*, mitral regurgitation.

Successful repair resulting in mild or less residual MR was achieved in 98 cases (MVARC technical success: 98%). Two cases were converted to conventional surgery repair (CSR). No procedural deaths were reported. A median of 4 pairs of chords were implanted (IQR, 3-4) with a median operative time of 123 minutes (IQR, 105-150). Operative data and periprocedural adverse events are summarized in Table 2. Two in-hospital deaths occurred: an 87- year-old woman already excluded from CSR for extensive mitral annulus calcifications (postoperative severe residual MR, died from cardiac failure) and a 78-year-old man with severe comorbidities who denied surgery (Euroscore- II 8.8%; chronic obstructive pulmonary disease; previous percutaneous coronary intervention; and severe arteriopathy). He had an early NC failure, then underwent CSR and died from acute postoperative right ventricle dysfunction. Mortality at 30 days was 2% (2 patients). Two cases of early failure, detected at echocardiography during hospital stay, underwent CSR. Major device-related procedural adverse events are reported in Table 2. MVARC device and procedural early success was achieved in 94 patients (94%). Patient success at 1 year was 92%. As of December 2020, FU completeness was 99% (1 patient lost, median FU time, 61 months).

Seventy-two patients were alive and free from reoperation. Echocardiography, available in 64 of them, showed: trivial

TABLE 2. Perioperative data

Variable	Value
Neochord implanted per case	4 (3-4)
Procedural time, min	123 (110-155)
MVARC technical success	98 (98)
Intraoperative complications	
ECMO	2 (2)
IABP	1 (1)
Conversion to conventional surgery	2 (2)
Major or extensive bleeding	5 (5)
Early Mortality	2 (2)
OTI time, h	2 (1-2)
ICU stay, d	1 (1-1)
In-hospital stay, d	7 (6-9)
Periprocedural complications	
Reoperation for severe MR	2 (2)
TIA	1 (1)
Stroke	0 (0)
Myocardial infarction requiring PCI	0 (0)
Acute kidney injury stage II to III	4 (4)
Renal replacement therapy	2 (2)
New onset atrial fibrillation	28 (28)
New pacemaker	0 (0)
Cardiac tamponade	0 (0)
SAM	0 (0)
Early Reintervention	3 (3)
MVARC procedural success at 30 days	94
MVARC device success	
30 Days	94
1 Year	92
5 Years	78
MVARC patient success at 1 year	92

Values are presented as n (%) or median (interquartile range). *MVARC*, Mitral Valve Academic Research Consortium; *ECMO*, extracorporeal membrane oxygenation; *IABP*, intra-aortic balloon pump; *OTI*, orotracheal time intubation; *ICU*, intensive care unit; *MR*, mitral regurgitation; *TIA*, transient ischemic attack; *PCI*, percutaneous coronary intervention; *SAM*, systolic anterior motion.

MR in 5 patients (8%); mild MR in 33 (51%); moderate MR in 19 (30%); and severe MR in 7 (11%; Table 3).

TABLE 3. Echocardiographic parameters

Variable	Preoperative	Discharge	5 Years	*P* value
LVEF %	61 (57-67)	57 (53-60)	59 (56-64)	.09
Mitral regurgitation				
None/trace	0	30 (31)	5 (8)	
Mild	0	51 (53)	33 (51)	
Moderate	0	14 (15)	19 (30)	
Severe	100 (100)	1 (1)	7 (11)	
LVESVi, mL/m^2	33 (25-39)	29 (24-37)	25 (20-30)	<.01
LVEDVi, mL/m^2	82 (70-92)	68 (58-80)	62 (50-73)	<.001
LAVi, mL/m^2	55 (42-56)	45 (35-57)	43 (33-59)	.07
sPAP, mm Hg	33 (26-41)	29 (24-39)	25 (20-29)	<.001

Values are presented as n (%) or median (interquartile range). *LVEF*, Left ventricle ejection fraction; *LVESVi*, left ventricle end systolic volume index; *LVEDVi*, left ventricle end diastolic volume index; *LAVi*, left atrial volume index; *sPAP*, systolic pulmonary artery pressure.

A total of 14 patients died after discharge, 7 of them for cardiovascular reasons. KM analysis estimated overall survival at 5 years of 83.6% (95% CI, 76.3%-91.6%). Furthermore, no difference in terms of survival (P =0.13) between FA and UA patients was found (Figure 1). The Cox proportional hazard model confirmed that there was no association between anatomical type and survival at FU (hazard ratio, 1.42; 95% CI, 0.38-5.32; P 1⁄4 .606).

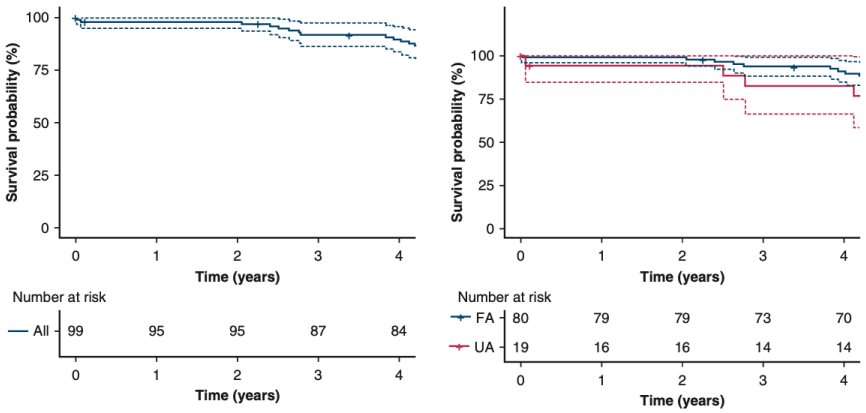

FIGURE 1. Kaplan–Meier estimates of survival in patients who underwent the neochord implantation procedure. On the left the overall population of the study. On the right patients with favorable anatomy (*FA*; *blue line*) versus those with unfavorable anatomy (*UA*; *red line*). No difference in terms of survival ($P = .13$) between FA and UA was found (95% CI indicated by *dotted lines*).

Overall cumulative incidence of severe MR recurrence was 9.2% (95% CI, 3.5%-14.9%) at 1 year, 12.3% (95% CI, 5.8%-18.8%) at 3 years, and 23.7% (95% CI, 14.9%-32.4%) at 5 years. Patients with FA compared with UA had a lower incidence of severe MR recurrence over the same period (6.2% vs 22.2% at 1 year; 7.5% vs 33.3% at 3 years; and 14.7% vs 63.0% at 5 years; P <.001; Figure 2).

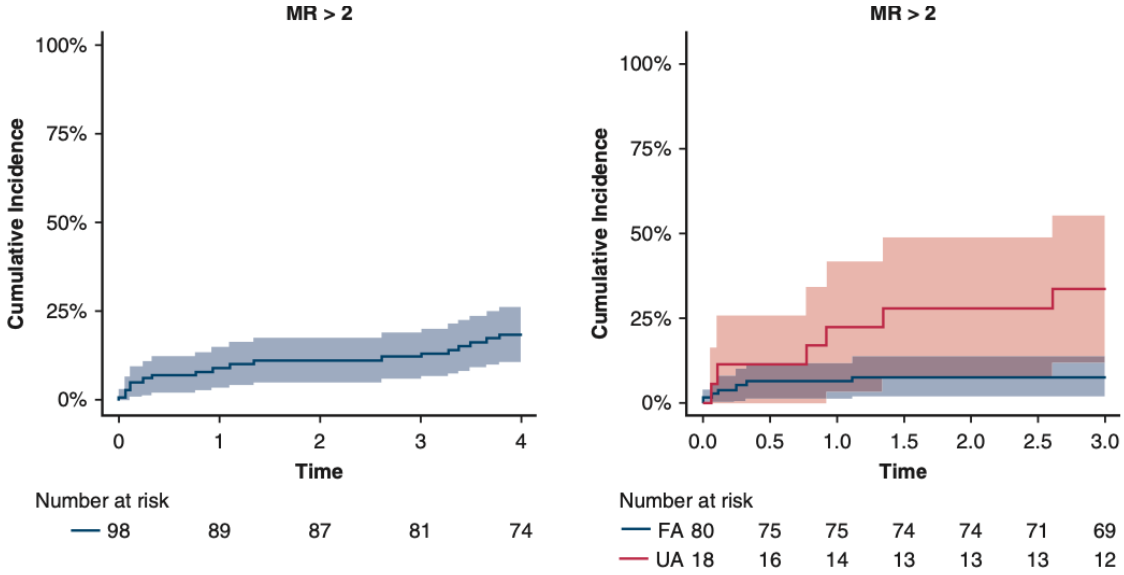

FIGURE 2. Cumulative incidence of severe mitral regurgitation (*MR*) in patients who underwent the neochord implantation procedure. On the left the overall population of the study. On the right patients with favorable anatomy (*FA*; *red line*) versus those with unfavorable anatomy (*UA*; *green line*). Patients with FA compared with UA had a lower incidence of severe MR recurrence (*shaded area* indicates 95% CI).

Twelve patients underwent CSR reoperation because of late MR recurrence. Ten of them underwent MV replacement and 2 of them underwent MVRe. Reasons for failure were: re-prolapse of the treated leaflet due to tear of the leaflet or secondary to new chordal rupture in 4

patients; relative elongation of the neochords due to LV reverse remodeling in 2 patients (one of these underwent repeat NC), and prolapse of the untreated leaflet due to native chordal rupture in the remaining 6 patients. Overall cumulative incidence of reoperation was 7.1% (95% CI, 2.0%-12.1%) at 1 year, 10.1% (95% CI, 4.2%-16.1%) at 3 years, and 16.7% (95% CI, 9.2%-24.2%) at 5 years. Patients with FA compared with UA had a lower incidence of reintervention (5.0% vs 18.8% at 1 year; 6.3% vs 26.3% at 3 years; and 14.7% vs 43.4% at 5 years; P <.001; Figure 3).

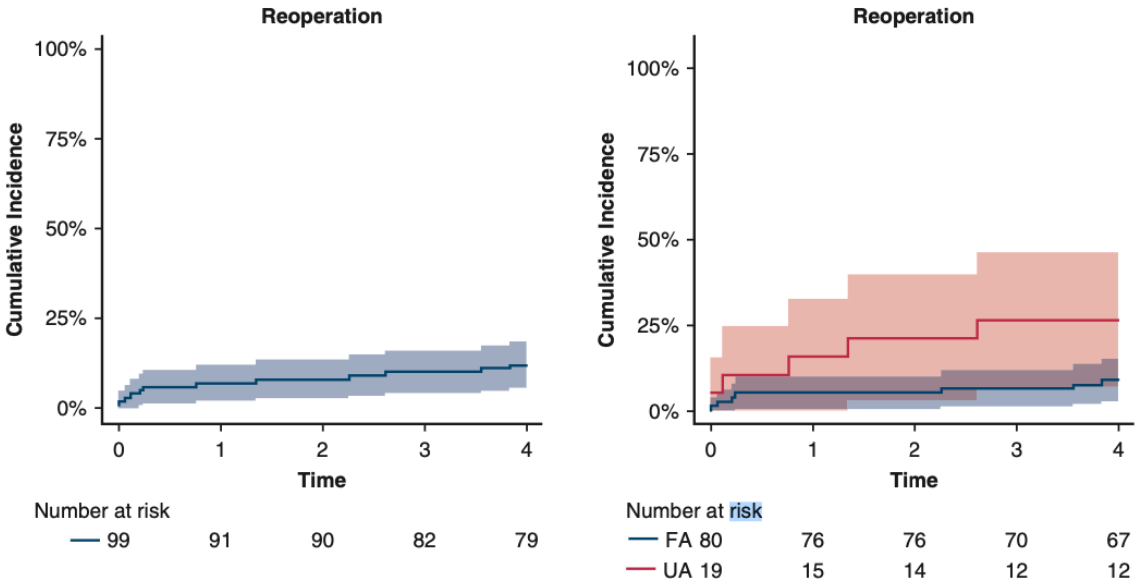

FIGURE 3. Cumulative incidence of reoperation in patients who underwent the neochord implantation procedure. On the left the overall population of the study. On the right patients with favorable anatomy (*FA*; *red line*) versus those with unfavorable anatomy (*UA*; *green line*). Patients with FA compared with UA had a lower incidence of reintervention (*shaded area* indicates 95% CI).

Significant differences between baseline and 5-year left ventricular end-diastolic volume index (82 vs 62 mL/ m^2; P<.001) and systolic pulmonary artery pressure (33 vs 25 mm Hg; P < .001) were also found (Table 3). Figure 4 shows the variation of New York Heart Association class before and after NC; at 5 years all patients were in New York Heart Association class I (78%) and II (22%).

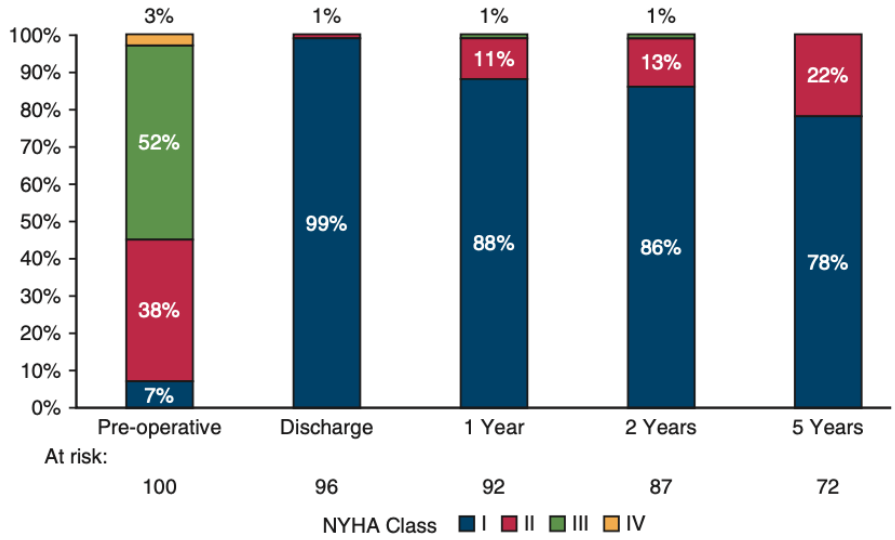

FIGURE 4. Evaluation of New York Heart Association (*NYHA*) functional class before the neochord implantation procedure and after (at discharge and at each follow-up). At the 5-year follow-up interval 78% of patients were in NYHA class I and 22% in class II.

DISCUSSION

To our knowledge, this study is the first midterm out- comes report of a large cohort of patients who underwent transapical off-pump beating-heart mitral NC for the treatment of severe MR due to leaflet prolapse/flail. The main findings of the present study are: (1) NC has a good short- and midterm safety profile; (2) NC provides satisfactory results in terms of cumulative incidence of severe MR and of reoperation in patients with FA, represented by isolated PML prolapse/flail; (3) in patients who underwent NC a significant reduction of LV volumes and of pulmonary artery pressure has been shown; (4) patients with UA should not be considered for this procedure because of a high incidence of severe MR recurrence and to a high reoperation rate. However, because there are no differences in terms of midterm survival of FA and UA patients, the latter can still be considered for NC in extremely high-risk patients on a compassionate basis.

Neochord DS 1000 was the first transapical chord im- plantation device to be introduced into clinical practice, receiving CE mark approval in December 2012.[11] Since the start of its clinical application, more than 1200 cases have been performed worldwide.[12] However, scarce midterm FU data are currently available, except for an anecdotal report by Kiefer and colleagues[4] describing good 5- year durability of NC in 3 patients.

Our results show a cumulative incidence of severe residual MR of 23.7% in the overall population and 14.7% in FA patients. The 5-year reoperation rate was 16.7% in the overall population and 14.7% in FA patients. These results appear inferior than those commonly reported from established surgical series; David and colleagues[13] reported a 20-year reoperation-free survival rate of 60.4% and a reoperation rate of 4.6% in patients with leaflet prolapse; and Glauber and colleagues[14] reported, in the setting of DMR (907 treated patients), at 5 years, survival of 93.5%, freedom from reoperation of 96.4%, and freedom from recurrent MR of 93.6%.

Morphological and echocardiographic criteria for NC suitability have been constantly investigated throughout our experience. The initial identification of different anatomical types (types A, B, C, D) was followed by the distinction of FA and UA, and the introduction of LAI.[14] Therefore, some patients that have been included in the analysis, especially at the beginning of the experience, would probably no longer be considered suitable for the procedure today. However, procedural aspects underwent a similar improvement process, characterized in particular by refinements of the LV entry site, choice of the right number of chords to be deployed, and chordal tensioning. In fact, a slight overtensioning to avoid relative chordal elongation due to left ventricle reverse remodeling is now routinely performed. In particular, overtensioning is on the basis of the surgeon's eye-ball evaluation: when optimal coaptation is achieved, chords are tensioned a little more to the point that the PML results more vertical but valve competence is maintained. Although CSR has yet to be considered the first choice in patients with DMR, there are some important aspects that need to be highlighted. CSR includes several surgical options that have been per- formed and developed over the years. Moreover, these can be simultaneously combined during the same repair to achieve an optimal result. Transapical NC is a relatively new procedure that implies a completely different approach for surgeons accustomed to working on the MV through open heart access. Another important aspect of the NC procedure compared with CSR is the lack of annular stabilization by a prosthetic ring and its effect on mid- and long-term durability after MVRe. NC is a microinvasive (beating heart, off-pump) image-guided procedure that requires specific training. In particular, in our experience a double learning curve was evident: the first one related to patient selection and the second one related to the technical and procedural aspects.

In CS, the use of artificial chords is usually accompanied by an annuloplasty, added as an adjunctive "parachute maneuver" to reduce the tension on the leaflet, increase the coaptation surface, and counteract unfavorable changes of the leaflet height due to left ventricle reverse remodeling. The dogma of annular ring implantation in MVRe has been repeatedly questioned by some investigators, although no one has reported solid data to support the debate.[15-17] Although annular dimensions were not investigated in the present study, some amount of annuloplasty effect was reported with the use of another transapical NC device, the Harpoon, which resulted in a 20% reduction of the anterior-posterior diameter.[3] Nevertheless, because of the absence of clear data on annular remodeling, patients with a significantly dilated annulus should be denied for NC.

The possibility of performing a combined procedure of NC and transcatheter mitral annuloplasty has already been shown.[18,19] This would allow for transcatheter reproduction of what is commonly done during open heart surgery but through a microinvasive approach. As a matter of fact, we have already witnessed the evolution of procedures that initially had suboptimal results. However, with continued improvements in technology, technique, patient selection, imaging, and experience, they have reached the goal of becoming a gold standard therapy. Transcatheter aortic valve replacement is the best example of this triumphal growth being now in class I even in low-risk patients.[20] Trans-septal devices for beating-heart mitral NC are already under development and will likely soon be available for clinical use. This will allow for an even less invasive approach.

The ChordArt system (Coremedic) had a first- in-man study reported in September 2018 and 1-year FU data recently published,[21] which show encouraging results. Also Pipeline (Pipeline Medical Technologies/Gore Inc) recently revealed promising outcomes of first-in-human application of the Pipeline MVRe system.[22] Furthermore, the NeoChord company is working on a second- generation device and is attempting to engineer a solution allowing trans-septal access. For this reason, we believe that it is fair to discuss NC outcomes also considering those of other transcatheter microinvasive techniques, in particular edge-to-edge MVRe. The 2017 annual STS/American College of Cardiology Trans- catheter Valve Therapy Registry report[23] described outcomes of MitraClip (Abbott) MVRe in the United States, mainly in DMR-affected patients. Similarly to our results, acute procedural success (post implantation MR grade 2, no mortality, no conversion to cardiac surgery) was achieved in 91.8% and in-hospital mortality was 2.7%, whereas length of stay (2 days) was considerably shorter because of the completely percutaneous approach. At 30 days, mortality and surgery reintervention rates were 5.2% and 0.4%, respectively, whereas at 1 year death occurred in 25.8% and reintervention in 2.1%, thus reflecting a higher-risk population, with a median STS Predicted Risk of Mortality MVRe score of 6.1%. Furthermore, midterm results for MitraClip have been investigated in the Endovascular Valve Edge-to- Edge Repair Study (EVEREST) II trial,[24] in a population of 279 patients, affected mainly by DMR. At 5 years, freedom from death and from reoperation in patients who received the MitraClip was 79.2% and 72.1%, respectively. However, different from percutaneous edge-to-edge procedures in which a device is deployed on the leaflets causing an irreversible fibrotic process, NC preserves MV anatomy allowing for a possible future reintervention in case of failure, offering to the surgeon the opportunity to work on an intact MV and through a first mediastinal access, regardless of the surgical approach (full sternotomy or right anterior minithoracotomy).

Limitation

This was a single-center study and, as such, it cannot be generalizable to other centers with less experience in the use of this novel technique. The lack of a CSR control group represents one of the major limitations of this study together with the retrospective nature of data analysis. The Randomized Trial of the Neochord DS1000 System Versus Open Surgical Repair (ReChord) clinical trial (NCT02803957) is currently enrolling patients in the United States to evaluate the safety and efficacy of the NeoChord device in subjects with DMR receiving a MVRe without cardiopulmonary bypass (treatment group) versus subjects receiving MVRe through CSR with cardiopulmonary bypass (control group) but results are not yet available. Moreover, as previously mentioned, our analyzed cohort of patients included the first “roll in” cases, who did not benefit from an optimized technique and refined patient selection process. The classification of patients with FA and UA was done retrospectively, thus constituting a possible bias because authors were unblinded to clinical results. Five-year echocardiography parameters were available only for a subset of patients. However, the regression-based test for missing data mechanism showed that data were missing completely at random.

CONCLUSIONS

NC is an acceptable therapeutic option in patients with severe DMR due to PML prolapse/flail. This technology shows satisfying early and midterm results in patients with FA, providing another tool for the achievement of the ideal therapeutic combination for MVRe. Data from ongoing perspective randomized trials are required to better elucidate the potential of this procedure (Figure 5).

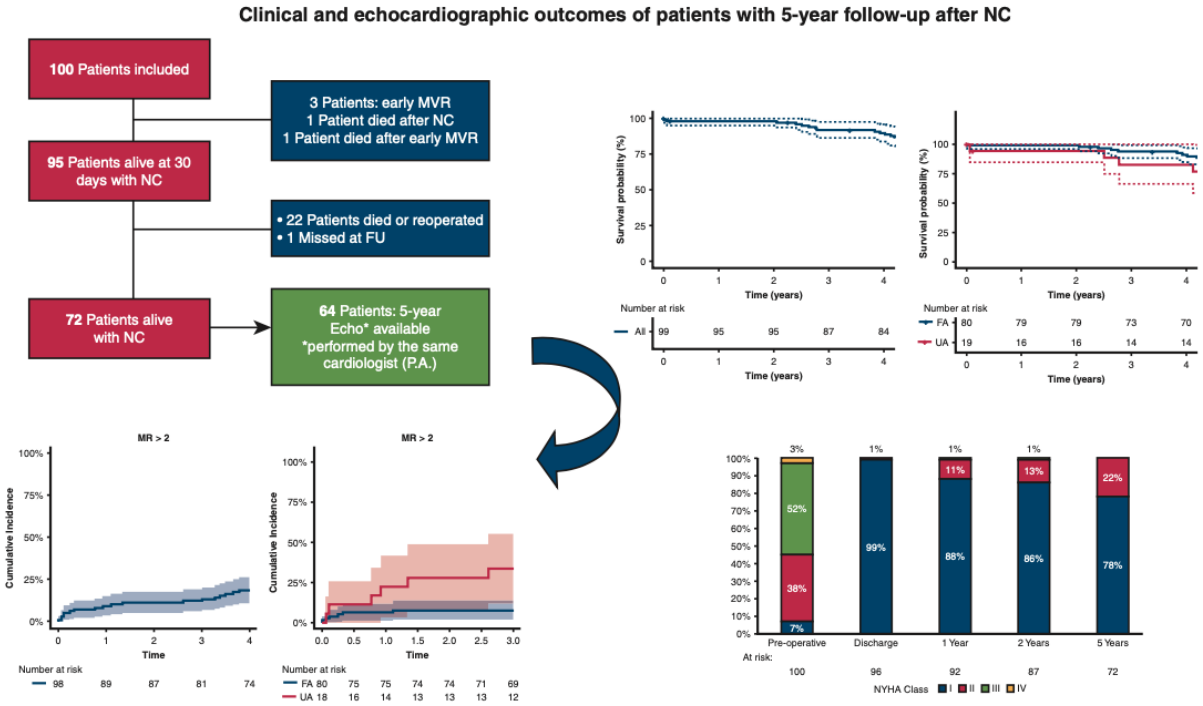

FIGURE 5. The Graphical Abstract features: Consolidated Standards of Reporting Trials diagram with the study design, early results, survival, and freedom from mitral regurgitation (*MR*) >2, and changes of New York Heart Association (*NYHA*) class during the study period. *MVR*, Mitral valve replacement; *NC*, neochord implantation; *FU*, follow-up; *FA*, favorable anatomy; *UA*, unfavorable anatomy; *Echo*, echocardiography.

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CHAPTER 4

Transapical beating heart mitral valve repair versus conventional surgery: a propensity-matched study

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ABSTRACT

OBJECTIVES: Transapical Neochordae implantation (NC) allows beating heart mitral valve repair in patients with degenerative mitral re- gurgitation. The aim of this single-centre, retrospective study was to compare outcomes of NC versus conventional surgical (CS) mitral valve repair.

METHODS: Data of patients who underwent isolated mitral valve repair with NC or CS from January 2010 to December 2018 were collected. A propensity score matching analysis was performed to reduce confounding due to baseline differences between groups. The primary end point was overall all-cause mortality; secondary end points were freedom from reoperation, freedom from moderate (2+) and

from severe (3+) mitral regurgitation (MR) and New York Heart Association functional class in the overall population and in patients with isolated P2 prolapse (type A anatomy).

RESULTS: Propensity analysis selected 88 matched pairs. There was no 30-day mortality in the 2 groups. Kaplan–Meier analysis showed similar 5-year survival in the 2 groups. Patients undergoing NC showed worse freedom from moderate MR (>_2+) (57.6% vs 84.6%; P < 0.001) and from severe MR (3+) at 5-year follow-up: 78.1% vs 89.7% (P = 0.032). In patients with type A anatomy, freedom from moderate MR and from severe MR was similar between groups (moderate: 63.9% vs 74.6%; P = 0.21; severe: 79.3% vs 79%; P = 0.77 in NC and FS, respectively). Freedom from reoperation was lower in the NC group: 78.9% vs 92% (P = 0.022) but, in type A patients, it was similar: 79.7% and 85% (P = 0.75) in the NC and CS group, respectively. More than 90% of patients of both groups were in New York Heart Association class I and II at follow-up.

CONCLUSIONS: Transapical beating-heart mitral chordae implantation can be considered as an alternative treatment to CS, especially in patients with isolated P2 prolapse

Keywords: Mitral valve repair • Surgical • Mitral valve repair • Transapical

INTRODUCTION

Surgical mitral valve repair is the gold standard treatment for degenerative mitral regurgitation (DMR), since it provides excellent long-term clinical and echocardiographic results and it is currently recommended by guidelines[1-11] .

Minimally invasive approaches showed to be a reliable option for repairing the mitral valve, gaining ever-increasing interest, even though still implying cardiopulmonary bypass (CPB) and aortic cross-clamping (CC)[12-13] .

Transapical off-pump, beating heart mitral Neochordae implantation (NC) enables the correction of DMR in case of leaflet prolapse/flail with no CPB nor aortic CC. This procedure has been recently introduced into clinical practice and has shown initial promising results[14]. There are no data about a direct comparison between NC and conventional surgery (CS) in patients with mitral prolapse/flail.

The aim of this retrospective, single-center study was to compare early- and mid-term outcomes of NC and CS in patients who underwent mitral valve repair for DMR.

MATERIAL AND METHODS

Data of patients who underwent isolated mitral valve repair with NC or CS from January 2010 to December 2018 were collected. In particular, CS data were retrospectively collected while NC data were prospectively collected in an ‘ad hoc’ database and then retrospectively analysed for this study. Data of CS patients were collected from electronic hospital records. Since November 2013, when NC was introduced at our institution, the choice be- tween NC and CS was primarily based on anatomical characteristics (prolapsing scallop/s, annular dilatation, calcifications, leaflet to annulus ratio) but also on surgeon’s and patient’s preferences. During preoperative counselling, both options (NC and CS) with pros and cons are discussed and the final decision is always shared with the patient.

Ethics statement

Patient informed consent for treatment, data collection and analysis for scientific purposes was collected in all cases. The study was approved by the local ethics committee.

Preoperative variables were defined according to European system for cardiac operative risk evaluation (EuroSCORE II) definition; the severity of mitral valve regurgitation was graded as mild (1+), moderate (2+) and severe (3+) according to the American Society of Echocardiography[15].

The anatomical classification of the valve allows to select patients according to MV morphology: type A; isolated central posterior leaflet prolapse/flail; type B, posterior multisegment prolapse/flail; type C, anterior or bileaflet prolapse/flail; and type D, paracommissural prolapse/flail or any type of disease with the presence of significant leaflet/annular calcifications[14]. We de- rived data regarding anatomical classification from transoesophageal echocardiography in all patients.

Patients with previous cardiac surgery, and combined operations were excluded from the analysis. Patients with type D mitral valve anatomy were also excluded from this analysis because in our previous studies we showed poor results[16] and, therefore, we do not consider these patients eligible for NC anymore.

Primary end point was overall all-cause mortality after NC and CS. Secondary end points were freedom from reoperation, freedom from moderate–severe mitral regurgitation (MR) and New York Heart Association (NYHA) functional class evaluation. The same end points were also specifically analysed only in patients classified as type A.

Surgical techniques

Transapical off-pump beating-heart mitral Neochordae implantation. Study device was the Neochord DS1000 (Neochord Inc., St. Louis Park, MN, USA) (Fig. 1A). Technical aspects of NC procedure have been previously described[17]. Briefly, under general anaesthesia, a minithoracotomy in the 5th intercostal space is performed and the pericardium is retracted. Two concentric purse-string sutures using 2–0 polypropylene are prepared on the left ventricular apex. An incision of the apex is performed and the instrument is inserted in left ventricle. The tip of the instrument is positioned in the left atrium passing through mitral valve leaflets. The instrument is then opened and gently retracted to catch the prolapsing segment.

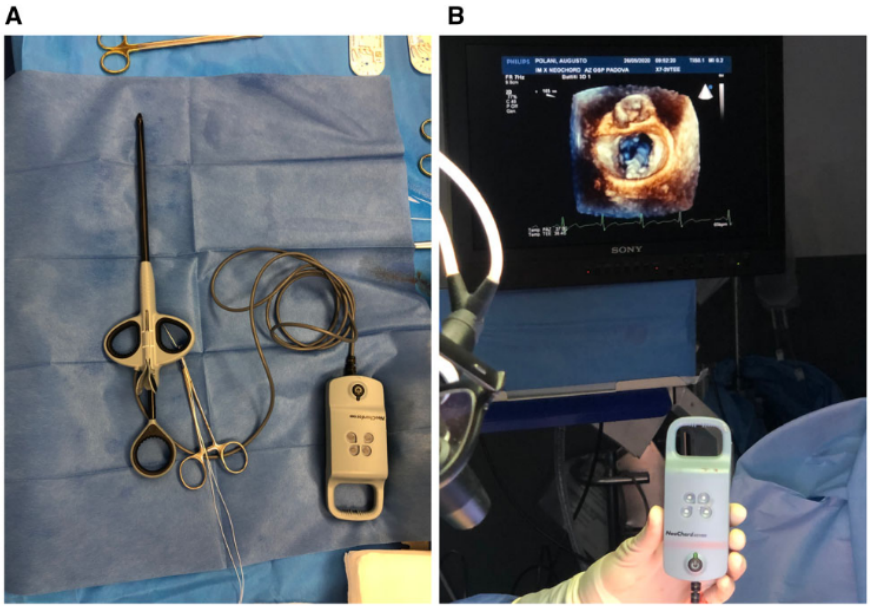

Figure 1: Neochord DS 1000 device (**A**) and appropriate leaflet grasping confirmed either by transoesophageal echocardiography imaging and by the 4 device lights turning white (**B**).

When an appropriate leaflet grasping is confirmed by the 4 de- vice lights turning white (Fig. 1B), the instrument is closed and the expanded polytetrafluoroethylene suture is passed through the free edge of the leaflet. The expanded polytetrafluoroethylene suture is then pulled out from the ventricle and secured on a mosquito. This sequence is repeated according to the number of required chordae. The number of chords is decided intraoperatively based on live 3D TEE. The implanted chordae are then tensioned until the appropriate leaflet coaptation is achieved. The entire procedure is performed under live 2D and 3D TEE guidance. If the final result was not deemed acceptable, conversion to open surgery was done. Clinical and echocardiographic assessment was performed preoperatively, at discharge, at 1, 6 and 12 months and on a yearly basis thereafter.

Conventional surgery. All procedures were performed under general anaesthesia and through full sternotomy. The technique of mitral valve repair was chosen by the surgeon according to mitral valve anatomy and to his personal preference. A mitral valve prosthetic ring was implanted in all patients. Prolapse resection and artificial chordae implantation were used alone or combined to restore a competent valve. If the final result was not deemed acceptable mitral valve replacement was performed.

Clinical and echocardiographic assessment was performed preoperatively, at discharge and then at least on a yearly basis.

Follow-up data were collected through hospital records visualization, referring cardiologist or general practitioners or through telephonic interview when necessary.

Statistical analysis

Continuous variables were reported with I quartile, median and III quartile, and categorical variables with percentage (relative frequencies). Differences between distributions of continuous variables were assessed using the Kruskal–Wallis test and Chi-square test or Fisher's exact test was used for categorical variables.

A propensity score (PS) matching analysis was performed to reduce confounding due to differences in preoperative variables between groups. The criterion for selecting variables for PS analysis was based upon clinical factors. The individual PS was estimated using the covariate balancing PS. The matched set of subjects was formed using 1:1 nearest neighbour matching without replacement and with a calliper set equal to 0.20 of the standard deviation of the PS distribution on the logit scale. Missing baseline covariates were imputed before PS estimation using an unsupervised machine learning approach based on the random forest algorithm. The balance of preoperative characteristics was assessed using standardized mean differences of variables distributions between compared groups of subjects.

On the matched set of patients, Kaplan–Meier curves were estimated in the 2 groups for the following long-term end point: overall survival, freedom from reoperation and freedom from severe MR. The effect of the surgical approach on follow- up end points. Differences in the Kaplan–Meier curves were assessed using the log-rank test. Wilcoxon signed-rank test was used to evaluate differences in the distribution of NYHA class between follow-up and baseline in the 2 groups on the matched set of subjects.

All the analyses were performed using the R software for statistical computing (version 4.0.0). Individual PS was estimated using the CBPS R package (version 0.21) and the matched set of patients was formed using the MatchIt R package (version 3.0.2).

RESULTS

The overall number of included patients was 372, 191 (51.3%) and 181 (48.7%) for NC and CS, respectively. Type D mitral valve anatomy, combined procedures and history of previous cardiac surgery were present in 34 (9.1%), 35 (9.4%) and 22 (5.9%) patients, respectively, and these were excluded from the analysis. The remaining 281 patients represent the population of this study. In particular, 169 (60%) and 112 patients (40%) underwent NC and CS, respectively. Propensity matching selected 88 pairs of patients.

Preoperative variables

Preoperative clinical and echocardiographic characteristics of the unmatched and of the matched cohorts are shown in Table 1.

Unmatched cohort

Before matching NC patients were more likely to have anatomical type A valve: 93 patients (55%) vs 39 (35%); $P < 0.001$; whereas type C was more represented in the CS group: 20 patients (18%)

vs 12 patients (7%); P < 0.001. Patients in the CS group had worse NYHA functional class. Preoperative risk profile was similar between groups: ES II: 0.85% (0.6–1.53) vs 0.78% (0.67–1.07) (P = 0.22) in the NC and CS groups, respectively.

Matched cohort

After matching the 2 groups appeared well balanced in terms of preoperative variables with similar risk profile as shown by logistic EuroSCORE values. Importantly, no differences were observed regarding anatomical types: type A was present in 43 (49%) and 37 (42%) in NC and CS, respectively.

Early outcomes

Perioperative clinical and echocardiographic outcomes in the matched population are depicted in Table 2 and 3. The surgical procedure was significantly faster in the NC group (2 vs 4 h; P < 0.001). Intraoperative conversion rate was low (1 patient in the NC group was converted to conventional mitral repair; 1 patient in the CS group converted to valve replacement; P = 1). Surgical revision due to pericardial effusion was very low and not significant in both groups; 2 patients (1%) in NC and 4 patients (4%) in CS, respectively (P = 0.4). Intensive care unit stay was significantly shorter in the NC group (1 day, IQR 1–1 vs 1 day, IQR 1–2; P = 0.004), as well as the duration of mechanical ventilation: 2 h (IQR 1–3) vs 8 h (IQR 5–12) in the NC and CS groups, respectively (P = 0.004). Furthermore, patients undergoing NC had a significantly lower incidence of new- onset atrial fibrillation (5 patients, 6% vs 30 patients, 34%; P < 0.001).

In-hospital length-of-stay was significantly shorter in NC patients: 7 days (IQR 6–8) vs 8 days (7–10) (P = 0.004). Moderate and severe MR occurred in 8 patients (9%) in the NC group and in 1 patient (1%) in the CS group (P = 0.084). In particular, moderate MR was found in 4 (5%) and in 1 (1%) patients while severe MR was found in 4 (5%) and in no patients in the NC and FS groups, respectively. There was no 30-day mortality in the 2 groups.

Table 1: Baseline variables

Variables	Overall (281)	NC (169)	CS (112)	*P*-Value	NC (88)	CS (88)	*P*-Value
Gender_male, *n* (%)	213 (76%)	135 (80%)	78 (70%)	0.067	68 (77%)	64 (73%)	0.6
Age	53.8/63.0/72.2	54.0/63.0/72.0	53.7/62.9/72.4	0.9	54.0/62.0/70.0	52.9/61.0/71.4	0.9
BSA	1.7/1.8/1.9	1.7/1.8/1.9	1.7/1.8/1.9	0.06	1.7/1.8/1.9	1.7/1.8/1.9	0.1
Hypertension, *n* (%)	148 (53)	95 (56)	53 (47)	0.17	37 (42)	42 (48)	0.5
Diabetes, *n* (%)	11 (4)	4 (4)	7 (4)	1	2 (2)	4 (5)	0.6
Dyslipidaemia, *n* (%)	65 (23)	29 (49)	16 (14)	0.009	14 (16)	14 (16)	1
COPD, *n* (%)	23 (8)	17 (10)	6 (5)	0.177	2 (2)	5 (6)	0.4
CAD disease, *n* (%)	38 (13.5)	24 (14.2)	14 (12.5)	0.72	11 (12)	11 (12)	1
ES II	0.61/0.81/1.3	0.6/0.8/1.5	0.6/0.7/1.0	0.2	0.5/0.7/1.0	0.6/0.7/1.0	0.6
EF (%)	59/64/68	58/64/67	60/64/69	0.8	59/64/68	60/64/69	0.9
Type A, *n* (%)	132 (47)	93 (55)	39 (35)	<0.001	43 (49)	37 (42)	0.4
Type B, *n* (%)	117 (42)	64 (38)	53 (47)		39 (44)	40 (45)	
Type C, *n* (%)	32 (11)	12 (7)	20 (18)		6 (7)	11 (12)	
NYHA class I, *n* (%)	39 (13.8)	39 (23)	0	0	33 (37.8)	18 (20)	<0.001
NYHA class II, *n* (%)	79 (28.1)	69 (40.8)	10 (8.9)		31 (35.4)	64 (72.9)	
NYHA class III, *n* (%)	152 (54)	56 (33.1)	96 (85.7)		24 (26.8)	6 (7.1)	
NYHA class IV, *n* (%)	11 (3.9)	5 (2.9)	6 (5.3)		0	0	

BSA: body surface area; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; CS: conventional surgery; EF: ejection fraction; ES II: EuroSCORE II; NC: Neochord; NYHA: New York Heart Association.

Table 2: Perioperative outcomes

Variables	Overall (176)	NC (88)	CS (88)	*P*-Value
Surgery_duration_h	2.0/3.0/4.0	1.8/2.0/2.5	3.5/4.0/4.0	<0.001
Conversion to repair, *n* (%)	0	1 (1)	0	1
Conversion to replacement	0	0	1 (0)	1
30-Day mortality	0	0	0	
ICU–stay, mean (days)	1/1/1	1/1/1	1/1/2	0.003
Intubation time, mean_h	2.0/3.5/7.0	1.0/2.0/3.0	5.0/7.5/12.0	0.003
Reexploration for bleeding, *n* (%)	4 (2)	0 (0)	4 (5)	0,2
CVVH, *n* (%)	1 (0)	0 (0)	1 (1)	1
AF, *n* (%)	35 (20)	5 (6)	30 (34)	<0.001
Wound inf, *n* (%)	1 (0)	0 (0)	1 (1)	1
In-H stay_ days	7-7-9	6/7/8	7/8/10	0.003

AF: atrial fibrillation; CS: conventional surgery; CVVH: continuous venovenous hemodiafiltration; ICU: intensive care unit; NC: Neochord.

Results at follow-up

The median follow-up was 3.4 years (IQR 2.14–4.39) and 6.6 years (IQR 2.37–8.17) in the NC and CS groups, respectively. Follow-up was 99% complete (2 patients missed). Overall all-cause mortality was similar between groups. Kaplan–Meier analysis shows 5-year survival of 92.1% [confidence interval (CI) 82.1–100] and of 95.5 (CI 90.6–100) in the NC and FS groups, respectively (P = 0.94). Similarly, in patients with type A anatomy, survival was 100% (CI 100–100) vs 92.8% (CI 83.7–100) in the NC and FS groups, respectively (P = 0.27) (Fig. 2). Echocardiographic variables at follow-up are shown in Table 3.

Table 3: Echocardiographic variables at baseline, discharge and at follow-up

Variables	Preoperative			Discharge			Follow-up[a]		
	NC (88)	CS (88)	*P*-Value	NC (88)	CS (88)	*P*-Value	NC (87)	CS (87)	*P*-Value
MR, *n* (%)									
0–1+	0	0	1	80 (90.9)	87 (98.9)	0.084	64 (73.6)	71 (81.6)	0.079
2+	0	0		4 (4.5)	1 (1.1)		11 (12.6)	10 (11.5)	
3+	88 (100)	88 (100)		4 (4.5)	0 (0)		12 (13.8)	6 (6.9)	
LVEF (%)	59/64/68	60/64/69	0.9	51/55/60	50.7/55.5/61	0.867	55.5/59/62.5	55/60/64	0.89
iLVEDV[ab] (ml/m^2)	67.3/82/95	71/79/95	0.884	58.5/76/86.5	50/62.5/72	0.001	66/66/72	62/60/65	0.009

[a]Last available follow-up was considered for each patient.
[b]iLVEDV observations were available for 166 patients at baseline, 156 patients at discharge and 122 patients at follow-up.
CS: conventional surgery; iLVEDV: indexed left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; MR: mitral regurgitation; NC: Neochord.

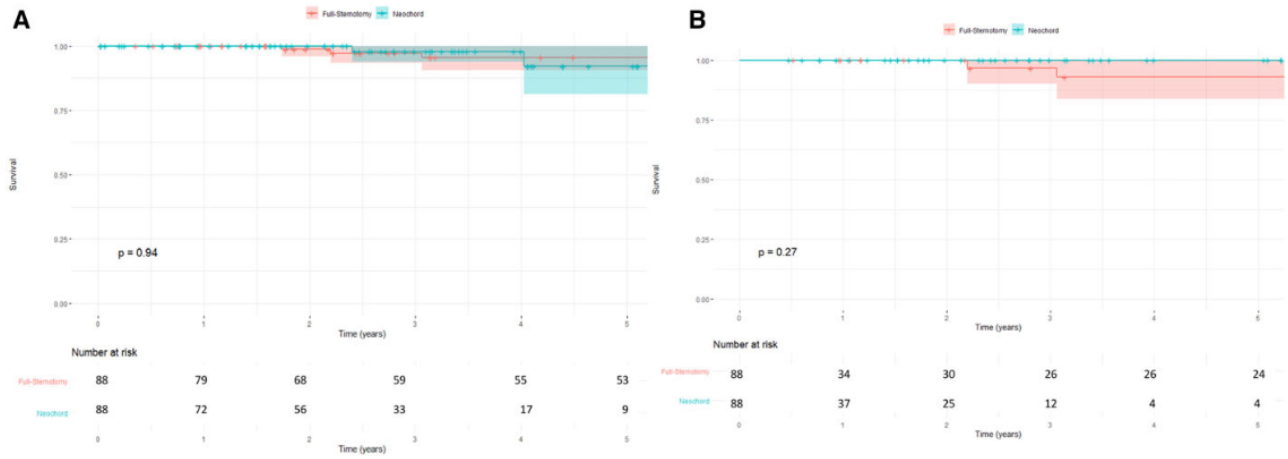

Figure 2: Overall survival in the matched cohort (**A**) and in type A patients (**B**).

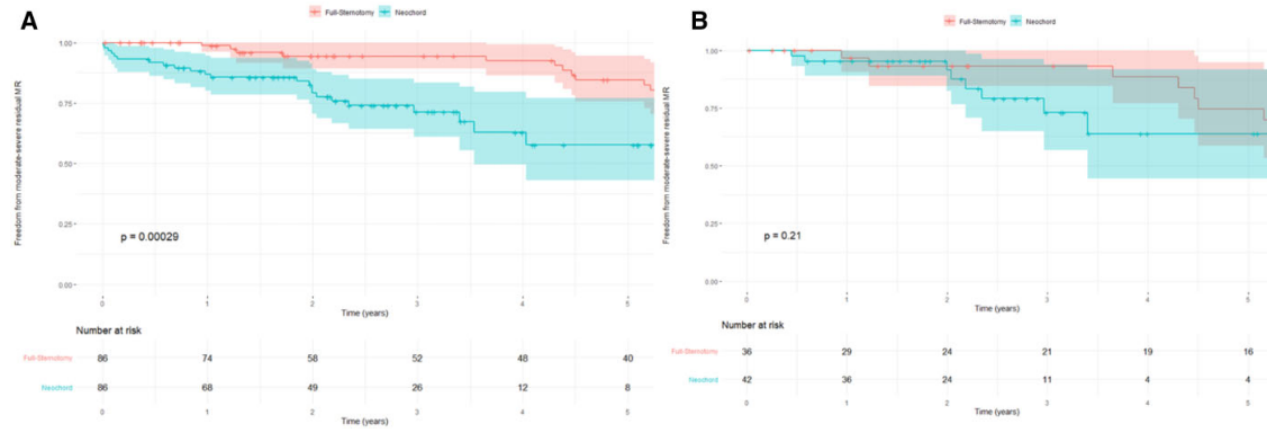

Figure 3: Freedom from moderate mitral (2+) regurgitation in the matched cohort (**A**) and in type A patients (**B**).

Patients undergoing NC showed worse freedom from moderate MR (>_2+) at 5-year follow-up: 57.6% (CI 43–77.1) vs 84.6% (CI 75.6–94.6) in the NC and CS groups, respectively (P < 0.001), and also worse freedom from severe MR at 5-year follow-up: 78.1% (CI 65.4–93.2) vs 89.7% (CI 82–98, P = 0.032).

However, in patients with type A anatomy, freedom from moderate MR was similar between groups: 63.9% (CI 44.4–91.8) vs 74.6 (CI 58.7–94.8) (P = 0.21) (Fig. 3) and also severe MR was similar between groups 79.3% (CI 60.8–100) vs 79% (63.9–97.6) in the NC and CS groups, respectively (P 0.77).

Freedom from reoperation was lower in the NC group: 78.9% (CI 65.7–94.8) vs 92% (CI 85.4–99.1) (P = 0.022) but, in type A patients, it appeared to be similar between groups: 79.7% (CI 57.9–100) and 85% (CI 72.4–99.9) in the NC and FS groups, respectively (Fig. 4). During follow-up, 11 patients of the NC group underwent reoperation; of these, 4 were re-repair, 6 were replacements and 1 was a re-NC. On the other hand, 5 patients of the FS group underwent reoperation; of these, 2 were re- repair and 3 were replacements. Reasons for failure in the NC group were re-prolapse of the treated leaflet due to tear of the leaflet or secondary to new chordal rupture in 4 patients; relative elongation of the Neochords due to left ventricular reverse remodeling in 2 patients (one of these underwent re-NC); and prolapse of the untreated leaflet due to native chordal rupture in the remaining 5 patients. Significant improvement of NYHA functional class with respect to baseline was observed in both groups (P < 0.001) with >90% of patients in NYHA class I and II at follow- up (Fig. 5).

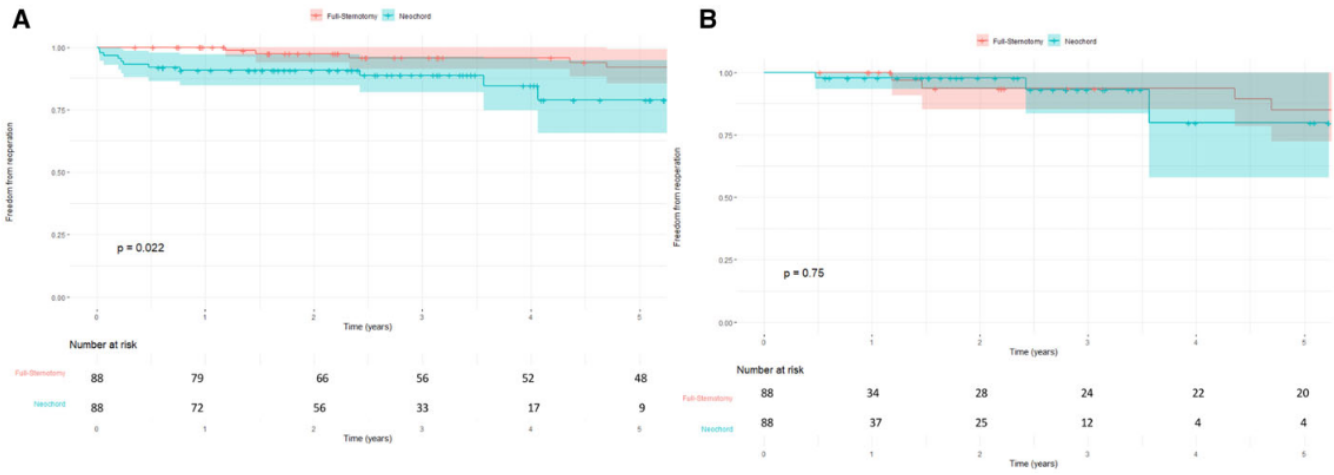

Figure 4: Freedom from reoperation in the matched cohort (**A**) and in type A patients (**B**).

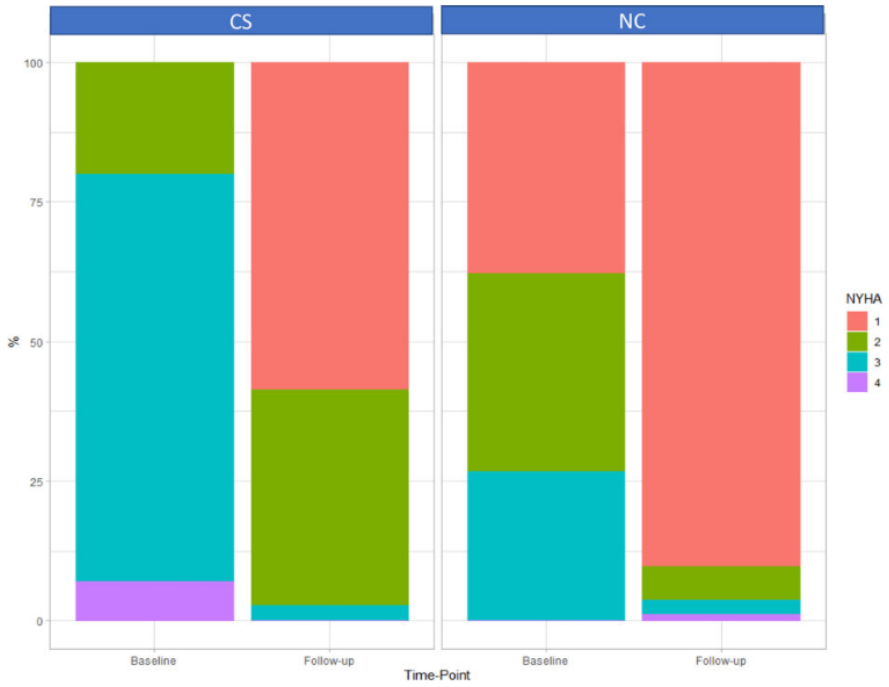

Figure 5: New York Heart Association functional class at baseline and at follow-up in patients undergoing conventional surgery and Neochord operation.

DISCUSSION

The main findings of this propensity-matched study are: (i) we could not find any difference in terms of mortality and major postoperative complications between CS and NC; (ii) patient selection plays a major role since it significantly affects postoperative outcomes in term of freedom from moderate and severe MR and from reoperation; and (iii) patients undergoing both approaches showed a significant improvement of NYHA functional class.

This is the first study comparing transapical beating heart mitral chordae implantation with Neochord device and CS mitral valve repair in patients suffering from degenerative MR with leaflet prolapse/flail. The first consideration is that these 2 approaches are completely different under many points of view. First, NC is a relatively new procedure with about 1000 operations performed worldwide while CS is well standardized and routinely performed everywhere and therefore it should be considered as the benchmark for every new technique; second, NC is performed with no need for CPB nor CC[18] while CS, although it may be carried out through minimally invasive access, always requires CPB and CC; third, NC does not imply prosthetic mitral ring implantation while this is always implanted during CS.

This analysis includes all patients undergoing treatment with Neochord procedure in our center since the beginning of the program, in 2013, when both technical and patient selection were still under definition. After the introduction of a new procedure in clinical practice, it is of utmost importance to assess its safety and to define its learning curve. Our results show that NC can be safely performed and that there are no differences in terms of early mortality and postoperative complications if compared with CS. The NC low mortality rate confirms the findings of a multicenter study that reported 1.9% mortality rate at 30 days[14]. It has been shown that the

learning curve of Neochord procedure is characterized by 3 phases of experience: an initial 'learning phase' (first 20 procedure), a second 'intermediate' phase and a final 'expert' phase. The learning phase is characterized by a relatively high actual probability of failure (25%), whereas the 'expert' phase demonstrates a decrease in failure probability near to 5%. The cumulative SUM failure analysis showed that after the 49th case, the expert phase begins[19]. Furthermore, this phase is a period of good performance because it reflects a refinement in patient selection criteria. An appropriate anatomical classification (type A, B, C, D) and leaflet-to- annulus index threshold value (1.25) are required in order to im- prove the possibility of favourable results[20]. Therefore, 2 different learning curves should be considered for NC: the 'technical' learning curve, related to the acquisition of new technical skills (completely different from those needed for CS) and the 'patient- selection' learning curve.

Therefore, it is not surprising that, in the matched cohort that includes types A, B and C, NC shows worse results than CS. The fact that type A patients have encouraging results in the NC group highlights the importance of an accurate patient selection process. This has already been demonstrated in previous NC series and it can be explained mainly by anatomical reasons: the central scallop of the posterior leaflet is the easiest target for NC because it is straight from the apical access and also because it has sufficient amount of tissue for secure grasping.

Once established that NC can be performed with mortality and complication rate comparable to CS, it is necessary to focus on NC efficacy in the treatment of DMR. CS efficacy is excellent and consequently some questions arise: what is the unmet need in surgical valve repair? Why do we need an alternative technology? The key factor is represented by the no need for CPB and CC since it has been clearly demonstrated that they have both a non-negligible impact on postoperative outcomes. In fact, CC duration is correlated with mortality, while CPB generates a systemic inflammatory response with the production of cytokines and potential harmful effects on organ function[21-25].

Beating heart mitral valve repair represents a very physiological approach to the mitral valve. Moreover, the beating heart allows a 'real-time' evaluation of the treatment efficacy in reducing DMR through live 3D TEE assessment: 'Eyes-wide-open' to- wards a 'thorax-wide-shut'. To further reduce the invasiveness of this procedure, a transseptal device for mitral chordae implantation is currently under development[26]. This will allow to perform the procedure in a completely percutaneous fashion with no need for left minithoracotomy.

One of the major concerns related to the NC procedure is the absence of annular stabilization with prosthetic ring. However, it has been demonstrated that although annuloplasty is not ap- plied, annular remodeling is observed and to date there is no evidence of annular dilatation over time in patients treated with NC procedure[27]. Furthermore, in patients treated with another beating heart transapical device (Harpoon, Edwards Lifesciences, Irvine, CA, USA), annular remodeling has been shown to occur 1 year after Neochordae implantation[28]. This may be a consequence of an indirect annuloplasty effect due to post-procedural left ventricular remodeling. Nevertheless, early referral

allows to treat patients with only leaflet disease and preserved left ventricle volumes and not dilated annuls[29].

The mechanism of mitral valve regurgitation recurrence after NC that has been identified at follow-up are re-prolapse of the treated leaflet due to tear of the leaflet or secondary to new chordal rupture; relative elongation of the Neochords due to left ventricular reverse remodeling; and prolapse of the untreated leaflet due to native chordal rupture. Although we have never found severe central MR recurrence due to annular dilatation, recurrence of MR may be associated to a decreased degree of coaptation and excessive tension to the supported leaflet causing rupture of neo- or native chordae. As far as reoperation is concerned, our data show that, due to the small manipulation of valve leaflets as well as of the mitral annulus, mitral valve re-repair is feasible after a failed NC procedure.

Limitations

This study has several intrinsic limitations that are mainly related to its retrospective nature; in particular, we cannot exclude bias of classification, diagnosis and memory that could affect comparison between cohorts. Patient selection bias is likely because patients underwent anatomical screening before NC procedure. Neochord procedure was strictly followed up through clinical and echocardiographic assessment at scheduled timepoints; on the other hand, CS patients were followed up mainly by their referral cardiologists and, therefore, a possible underestimation of valve-related adverse events in the CS population cannot be excluded. This has also a consequence on follow-up echo data of the CS population that is often lacking of parameters related to left ventricular remodeling such as volumes, diameters and right ventricular parameters. Furthermore, as expected, the PS matching procedure resulted in a proportion of patients discarded from the analysis, which is one of the main limitations of PS matching analysis, limiting the generalizability of study results. Not least, results of the subgroup analysis on type A patients should be taken with caution because, even though subgroup analyses are common in biomedical research, their validity is limited. Furthermore, as expected, the PS matching procedure resulted in a non-negligible proportion of patients discarded from the analysis, which is one of the main limitations of PS matching analysis. The resulting small sample size would affect the generalizability of the study results and the type II error prob- ability. Another limitation is represented by the absence of an echocardiographic core laboratory.

CONCLUSION

In conclusion, according to our data, in patients with DMR, trans- apical beating heart mitral chordae implantation provides early results similar to CS; patients with isolated P2 prolapse/flail had similar freedom from severe MR and from reoperation in the 2 groups and, therefore, they should be considered as the ideal candidates for this procedure. In patients with isolated P2 pro-lapse/flail, transapical beating heart mitral chordae implantation provides similar results to CS in terms of freedom from recurrent MR and from reoperation. On the other hand, in more complex

mitral anatomies, CS repair still proves to be superior. Therefore, accurate patient selection is crucial to achieve optimal results.

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CHAPTER 5

Feasibility of percutaneous coronary intervention before mitral NeoChord implantation: Single-center early results

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The preliminary results of this study have been presented as poster at the 2019 AATS Mitral Conclave, New York, NY, USA.

ABSTRACT

Background and Aim of the study: Micro-invasive cardiac surgery identifies procedures performed off-pump, on beating heart. Aim of this single-center retrospective study was to assess early outcomes of a totally micro-invasive strategy (percutaneous coronary intervention—PCI—followed by transapical off-pump NeoChord mitral repair) in patients with concomitant coronary artery disease (CAD) and degenerative mitral regurgitation (MR).
Methods: We analyzed early and 1-year follow-up data of patients who underwent a NeoChord procedure between November 2013 and May 2020, and preceded by PCI. Outcomes were defined according to Mitral Valve Academic Research Consortium (MVARC) definitions.
Results: Among 220 patients who underwent NeoChord repair in the study period, 17 (7.7%) underwent PCI previously. CAD was an accidental finding during pre- operative mitral evaluation in nine patients (52.9%; Group 1; with PCI occurring 2 months before NeoChord, interquartile range [IQR] = 1.0–2.7), while it was part of the past medical history in the remaining eight patients (47.1%; Group 2; with PCI occurring 30 months before NeoChord, IQR = 24.5–64.0). Twelve patients (70.6%) presented single-vessel disease, two patients (11.8%) triple-vessel disease. No surgical revisions for bleeding were required after NeoChord. At 1-year follow-up (n = 16), all patients were alive and did not experience major adverse events except for one reoperation due to late NeoChord failure. None required additional PCI. Conclusion: In our experience, PCI before NeoChord seems safe and effective, and performing PCI before NeoChord might not affect outcomes. A totally micro-invasive strategy in selected patients suffering from MR and CAD should be considered as a reasonable alternative to conventional surgery.

KEYWORDS: coronary artery disease, micro-invasive surgery, valve repair/replacement

INTRODUCTION

Recently, the new concept of micro-invasive cardiac surgery has been introduced to identify procedures performed off-pump, on beating heart (e.g., transcatheter aortic valve replacement, transcatheter mitral valve repair or replacement).[1,2]

Mitral valve repair can be performed either with open-heart procedures (full sternotomy or minimally invasive cardiac surgery) or through micro-invasive transapical neochordae implantation. The former has shown well-established early and long-term results, while the latter has demonstrated promising early and 5-year outcomes.[3]

Although open-heart cardiac surgery remains the gold standard for patients with combined coronary artery disease (CAD) and mitral regurgitation (MR), a totally micro-invasive strategy (percutaneous coronary intervention—PCI—+NeoChord) might allow to optimize outcomes especially in selected patients.

MATERIALS AND METHODS

In the present single-center, retrospective study, we aimed to analyze the early clinical outcomes of PCI followed by transapical off- pump NeoChord mitral valve repair in patients with CAD and degenerative MR.

Among all patients who underwent a NeoChord mitral repair procedure at the Padova University Hospital, we retrospectively analyzed early and 1-year clinical and echocardiographic outcomes of those subjects who also underwent a previous PCI.

All enrolled patients had indications for surgical mitral repair due to degenerative MR according to current guidelines.[4] Functional MR cases were excluded.

The choice to perform a NeoChord mitral repair was based on the following anatomical criteria: a mitral tissue overlap to obtain a potential postoperative coaptation length of 3–5 mm and the leaflet- to-annulus index (LAI) with a cutoff value of >1.25; the “surgically derived” morphological classification which includes four anatomical types (type A: isolated central posterior leaflet prolapse/flail; type B: posterior multisegment prolapse/flail; type C: anterior, bileaflet, or paracommissural disease; type D: leaflet and/or annular calcifica- tions); cases showing mitral annular calcifications were excluded.[5]

All patients gave their informed consent for the procedure and for data collection for scientific purposes. Data collection of NeoChord procedures has been approved by the local Ethical Committee (No. AOP-1772).

Outcome definitions were based on the Mitral Valve Academic Research Consortium (MVARC) guidelines.[6] The primary endpoint was 1-year MVARC patient success, and secondary endpoints

were MVARC technical and procedural success (intraoperatively and at 30 days, respectively), and failure of the mitral repair (MR = severe). Clinical and echocardiographic follow-up was performed for all pa- tients at discharge and 1 year after NeoChord implantation. Post- operative MR was assessed with transthoracic echocardiograms according to the standard American Society of Echocardiography (ASE) modified criteria.[7] MR was qualitatively defined by means of transthoracic echocardiography as trivial, mild, moderate, and severe.

INDICATIONS TO PCI, PCI PROCDURE, NC TECHNIQUE

PCI was performed according to the current guidelines.[8,9] Dual anti- platelet therapy (DAPT) had been started in each patient at the time of PCI, and continued for at least 6 months after the coronary proce- dure.[10,11] PCI was performed through a femoral or radial artery access.

The mitral NeoChord implantation is performed with the patient under general anesthesia, and access to the left heart is achieved through a left lateral mini-thoracotomy in the fifth intercostal space. Two purse-string sutures are placed 2–4 cm postero-lateral from the apex of the left ventricle to pass in between the papillary muscles. After ventriculotomy, the NeoChord DS1000 device (NeoChord, Inc.; Figure 1A) is inserted in the left ventricle, and 2D- and 3D-transesophageal echocardiographic imaging is used to guide the device to the prolapse/flail leaflet and implant the neochordae (Figure 1B). When the proper number of neochordae needed to correct MR has been implanted, they are tensioned under direct live-3D

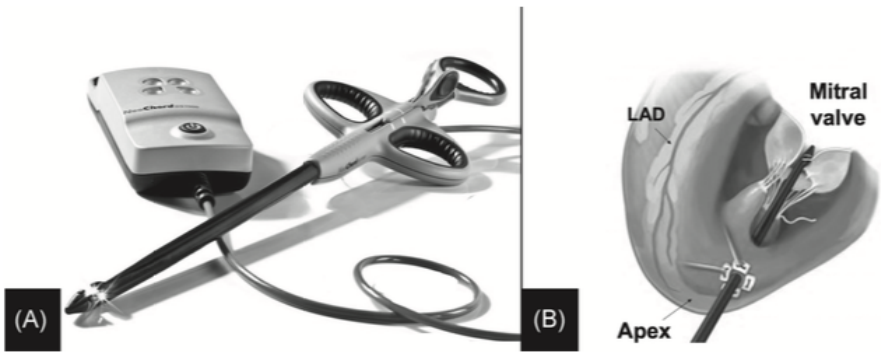

FIGURE 1 (A) Picture showing the NeoChord DS1000 device (NeoChord, Inc.). (B) Draw representing the device into the left ventricle and through the mitral valve, ready to release the *neochordae*. LAD, left anterior descending

transesophageal control. Finally, the tensioned neochordae are secured to the left ventricular epicardium using Teflon pledgets.[12]

2.2 | Statistical analysis

Baseline and demographic categorical data were expressed as absolute

numbers and percentages, while quantitative variables were expressed as medians (interquartile range [IQR]) or mean±standard deviation as ap- propriate. Wilcoxon–Kruskal–Wallis test was performed for continuous variables and Pearson Chi-square test for categorical ones. A p value of

.05 was considered statistically significant. Computations have been performed using R 3.5.2 System and rms package.

3 | RESULTS

Among 220 consecutive patients who underwent mitral repair with NeoChord implantation between November 2013 and May 2020, 17 patients (7.7%) were included in the analysis (mean age = 73 ± 9 years; M = 94%) and represent the population of our study. The median time between PCI and NeoChord repair was 4.9 months (IQR = 2.0–29.6). In nine patients (52.9%; Group 1), CAD was an incidental finding during the preoperative screening of the mitral valve disease, with a median time of 2 months between PCI and NeoChord repair (IQR = 1.0–2.7). Conversely, in eight patients (47.1%; Group 2), CAD was found as part of the past medical history, with PCI occurring 30 months before NeoChord repair (IQR=24.5–64.0). In all these eight cases CAD was diagnosed in the context of an acute coronary syndrome. These patients underwent a re- catheterization before the mitral procedure, showing patent stents and consequent no need for additional revascularization. Preoperative data have been summarized in Tables 1 and 2. Twelve patients (70.6%) presented with single-vessel disease, 3 patients (17.6%) presented with two- vessel disease, and 2 patients (11.8%) presented with triple-vessel disease. CAD involved the left anterior descending artery in 10 patients (58.8%). Ten patients (58.8%) were on DAPT at the time of the mitral repair procedure (9 in Group 1, and 1 in Group 2). According to the anatomical classification,[4] patients were distributed as follows: type A, eight patients (47.1%), type B, six patients (35.3%), and type C, three patients (17.6%). No type D patients were included.

During the mitral procedure, the mean cell-saved, processed blood volume for the study population was 499 ± 347 ml, with no differences between the two groups (p = .85). Five patients required blood transfusion with a maximum of two units transfused during the hospital stay. Remarkably, we did not encounter intraoperative complications related to DAPT and to CAD such as bleeding or intraoperative acute myocardial infarction. Only two patients (11.8%) presented minor bleeding according to the MVARC bleeding scale. Furthermore, we did not observe any major complications related to the preoperative PCI (acute myocardial infarction, cerebrovascular accident, vascular complications, and acute kidney injury). No patient required >24 h of invasive ventilation.

TABLE 1 Preoperative demographic and clinical data

Variable	*n* (%), mean ± *SD*		
	Elective PCI during preoperative mitral workup (*n* = 9)	Past medical history of PCI (*n* = 8)	*p*
Age (years)	71 ± 9	75 ± 10	.48
Males	9 (100%)	7 (87.5%)	.27
Arterial hypertension	5 (55.6%)	7 (87.5%)	.15
Dyslipidemia	3 (33.3%)	8 (100%)	.00-4*
Diabetes	1 (11.1%)	1 (12.5%)	.93
H/o smoking	1 (11.1%)	2 (25.0%)	.45
Peripheral artery disease	1 (11.1%)	2 (25.0%)	.45
Cerebrovascular disease	0	0	
Preoperative serum creatinine (mg/dl)	1.0 ± 0.2	1.0 ± 0.3	1
Preoperative hemoglobin (g/dl)	14.0 ± 1.3	12.7 ± 1.9	.20
Preoperative BMI (kg/mq)	26 ± 1	26 ± 3	.89
Preoperative EF (%)	65 ± 6	58 ± 8	.11
Euroscore II (%)	1.3 ± 0.9	3.7 ± 2.8	.04*
STS score (%)	1.4 ± 1.4	3.9 ± 4.7	.07
Preoperative NYHA III–IV	3 (33.3%)	6 (75.0%)	.09
Preoperative CCS angina > 1	0	1 (12.5%)	.27

Note: Variables are expressed as number of patients, *n* and percentages, %, or mean ± *SD*.

Abbreviations: BMI, body mass index; CCS, Canadian Cardiovascular Society; EF ejection fraction; H/o, history of; NYHA, New York Heart Association; SD, standard deviation; STS, Society of Thoracic Surgery.

*Statistically significant *p* values.

One high-risk patient (EuroScore II=8.7%) with severe right ventricular dysfunction, high pulmonary pressure, and COPD experienced sudden cardiac death during the hospital stay. The remaining 16 patients had an uneventful hospital stay and were discharged in good clinical conditions (Table 3).

Variable	*n* (%), mean ± *SD*, median (IQR) Elective PCI during preoperative mitral workup (*n* = 9)	Past medical history of PCI (*n* = 8)	*p*
Time between PCI and NeoChord repair (months)	2.0 (1.0–2.7)	30.0 (24.5–64.0)	<.001*
Preoperative CAD			
One-vessel	8 (88.9%)	4 (50.0%)	.08
Two-vessels	1 (11.1%)	2 (25.0%)	.45
Three-vessels	0	2 (25.0%)	.11
PCI (*n is referred to vessels, no patients)			
Left anterior descending	4	6	.20
Circumflex artery	5	4	.82
Right coronary artery	1	4	.08
Bare metal stent	0	1	.39
Drug-eluting stent	10	13	.39
DAPT at the time of mitral repair	9 (100%)	1 (12.5%)	<.001*

Note: Variables are expressed as number of patients, *n* and percentages, %, median and IQR, or mean ± *SD*.

Abbreviations: CAD, coronary artery disease; DAPT, dual antiplatelet therapy; IQR, interquartile range; PCI, percutaneous coronary intervention; SD, standard deviation.

*Statistically significant *p* values.

At 1-year follow-up, all 16 patients were alive; of these, 15 were in good clinical status (NYHA Class I, CCS Class 1); one patient had severe MR due to recurrent prolapse after 2 months and underwent a successful transcatheter edge-to-edge repair. Thirteen patients (81.3%) presented with residual trivial/mild MR and 2 patients (12.5%) presented as asymptomatic with residual moderate MR.

None of the patients presented acute coronary syndromes or ischemic symptoms, and none required coronary reintervention.

Variable	*n* (%), mean ± *SD*		
	Elective PCI during preoperative mitral workup (*n* = 9)	Past medical history of PCI (*n* = 8)	*p*
NeoChord implanted on PML	4 ± 1	3 ± 1	.17
NeoChord implanted on AML	3 neochordae in only 1 pt	1 ± 1	
NeoChord procedural time (min)	129 ± 30	116 ± 22	.61
Cell-saved blood volume (ml)	483 ± 339	522 ± 389	.85
RBC transfusions (U)			
0	7	5	.49
1	0	2	.11
2	2	1	.60
Mechanical ventilation time (h)	3 ± 1	4 ± 7	.61
MVARC technical success	9 (100%)	8 (100%)	
MVARC bleeding			
No	0	0	
Minor	1 (12.5%)	1 (12.5%)	.93
Major	0	0	
Extensive	0	0	
Life-threatening or fatal	0	0	
MVARC vascular complications and access-related complications	0	0	
MVARC neurological events	0	0	
MVARC acute myocardial infarction	0	0	
MVARC acute kidney injury	1 (12.5%)	1 (12.5%)	.93
New onset atrial fibrillation	4 (44.4%)	3 (37.5%)	.77
Deep wound infection	0	0	
ICU stay days > 1	0	1 (12.5%)	.27
Total hospital length of stay (days)	7 ± 2	8 ± 2	.82
Device related death	0	0	
Postoperative in-hospital mortality	0	1 (12.5%)	.27
MVARC procedural success	9 (100%)	7 (87.5%)	.27
MR ≤ mild at discharge	9 (100%)	7 (87.5%)	.27

Note: variables are expressed as number of patients, *n* and percentages, %, or mean ± *SD*.

Abbreviations: AML, anterior mitral leaflet; ICU, intensive care unit; MR, mitral regurgitation; MVARC, Mitral Valve Academic Research Consortium; PML, posterior mitral leaflet; RBC, red blood cells; SD, standard deviation.

4 | DISCUSSION

The main finding of the present study is that a total micro-invasive strategy for selected patients with associated CAD and MR is safe and effective.

Furthermore, a history of PCI before NeoChord mitral repair, regardless of timing, does not affect post-procedural outcomes. In fact, there are no differences in terms of postoperative morbidity and mortality as well as 1-year follow-up outcomes between the two groups.

According to STS adult cardiac surgery database, traditional surgical mitral repair shows 1.1% mortality, which increases to 6.2% when associated with CABG.[11] For this reason, intraoperative and postoperative risks related to combined mitral and CAD surgery may be reduced by favoring lower-risk procedures such as PCI and micro- invasive mitral repair techniques in selected patients.

Among different mitral repair strategies for patients who present degenerative MR, the micro-invasive off-pump NeoChord mitral repair has shown to be a safe, and reproducible technique, with good outcomes at discharge, and clinical efficacy maintained up to 5 years of follow-up.[12,13]

In the setting of CAD and mitral valve disease, the less invasive strategy of PCI followed by minimally invasive valve surgery has also

demonstrated positive early and midterm results.[14,15] However, these recent works have not considered micro-invasive mitral procedures, which constitute a rapidly expanding field, and have the potential of being adopted as a valuable alternative to conventional or minimally invasive surgery in selected patients.[16] Patient selection is crucial to understand who will benefit from these techniques. Regarding the NeoChord procedure, several echocardiographic parameters (LAI, morphological classification, and length of coaptation prediction index) have been introduced to help to standardize preoperative selection. The most recent evidence shows that NeoChord repair can be a reasonable alternative to conventional surgery for a subset of patients with MR in an early phase when the disease is limited to the leaflets and not extended to the annulus and/or to the left ventricle.[12] In this study, the procedures were performed by the same operator (Gino Gerosa) and all cases were performed after the initial 40 cases (recognized by the CUSUM analysis as the threshold to standardize the procedure in all its technical aspects).[17]

In our cohort, a micro-invasive treatment strategy resulted satisfactory in terms of reduced blood transfusions, reduced ventilation, and hospitalization times.

STS database demonstrates not only a higher mortality (6.2%) in patients undergoing MV repair and CABG, but also a significant higher rate of major bleedings (5.5%) and stroke (2.8%) than those observed in the present report.[18]

In patients with the previous PCI, undergoing minimally invasive mitral valve repair, Santana et al.[15] showed promising outcomes in terms of postoperative cerebrovascular accident (1.1%), acute kidney injury (2.2%), and reoperation for bleeding (4.3%), with a low post- operative mortality (4.3%),[15] similarly to our study. However, a fair comparison is not possible because of the limited number of patients treated in both series.

Albertini et al.[19] have recently shown the feasibility of combining minimally invasive direct CABG (MIDCAB) with the NeoChord mitral repair procedure as a potential strategy to treat combined CAD and MV disease.

These two reports highlight the concept that the availability of innovative surgical procedures, along with PCI, makes this association a very attractive strategy, since it can combine the advantages of the two approaches.

This study carries important limitations; first, it was a retrospective analysis of a small study cohort. Besides, PCI procedures were performed at different centers, and it was not possible to

perform a SYNTAX score analysis for all patients. Follow-up testing for residual CAD disease such as stress test or coro-CT scan was also lacking.

5 | CONCLUSIONS

In conclusion, according to our data, PCI before NeoChord mitral repair procedures is a safe and effective strategy, and performing PCI before NeoChord does not affect outcomes. Therefore, a totally micro-invasive strategy in selected patients suffering from MR and CAD should be considered as a reasonable alternative to conventional surgery.

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CHAPTER 6

FINAL DISCUSSION

This project was ambitious and even provocative for the international scientific community. Cardiac surgery interventions, as conventionally conceived, require invasiveness, open-field and blood loss with temporary controlled arrested heart.
The concept of "less-invasive" was initially related to a smaller skin incision, always requiring the disadvantages related to CPB and CC (with LOS and time of Intubation quite similar to conventional surgery).

As stated by Gerosa et al. the first Big Bang in cardiac surgery was the advent of the heart-lung machine which allowed surgeons to perform unthinkable interventions. CPB and CC were considered essential requirements for cardiac surgeons[1].

Minimally invasive surgery represented an important step forward for cardiac surgery: realizing a "standard intervention" through a minimal incision was considered very impressive: 4 or 5 cm to repair a mitral valve or to perform a MIDCAB with dedicated instruments without touching the sternum was challenging but enthusiastic for surgeons and well accepted by patients.

The second Big Bang arrived after 70 years. The possibility to perform the same interventions without arresting the heart. Transcatheter aortic valve replacement allowed to shift the paradigm of conventional and minimal cardiac surgery towards a different goal: we have to realize now the impact of the (r)evolution of techniques and technologies in cardiac surgery focusing to the best result intended as the least invasive at all.

Our Institution was a pioneer in this field: adopting the Neochord procedure on consecutive patients allowing the refinement of several aspects, such as ventricular access, patient-specific modifications based on the MV morphology tensioning protocol; improving the echocardiographic guidance protocol and standardizing patient selection criteria (leaflet-to-annulus index and MV anatomical classification).

This thesis resumes the efforts to prove the efficacy of the "micro-invasive" approach through the implant of artificial chordae in mitral position.

TECHNICAL ASPECTS: weak points

The concept of micro-invasive interventions does not mean an "easier" intervention. It requires attention and accurate planning of every step. Several aspects have been investigated as cause of recurrence of MR after NC.

The ventricular access, the correct tensioning, the cautious navigation into the ventricle are only few elements that need attention because they should compromise early and late outcomes.

The mechanisms of recurrence of MR after NC have been investigated by Colli et al.[2]

The rate of NESLR (Not-Expected Surgical Like Result) was 32%: requiring reintervention (NESLR-Redo) rate was 7.7%.

These results should be explained as follows.

An innovative transcatheter device with no expertise in technical aspects nor in selection of patients need several refinements.

A lack of experience of the surgeon-navigator or an incorrect entry site should involve a damage of the subvalvular apparatus due to an excessive posterior access or an incorrect navigation of the instrument into the LV cavity; the re -prolapse of the first pathologic leaflet explained by the progression of the underlying primitive disease should lead to a native chordal rupture; mechanism more frequent in complex anatomical type (type B multi-segment and type C bileaflet); furthermore, the LV remodeling causes a reshaping of all structure leading to an elongation of the NC.

Another NESLR cause identified is the "curling" mechanism: mostly prevalent in type A and B patients. A phenomenon first described by Gilbert in which the LV postero-basal wall abnormally moves causing an excessive movement of the posterior annulus. The lack of the movement downward and anteriorly explains the late end-systolic prolapse of the posterior leaflet.[3]

Furthermore, one of the major concerns related to NC procedure is the absence of annular stabilization. However, it has been demonstrated that although annuloplasty is not applied, annular remodeling is observed and to date there is no evidence of annular dilatation over time in patients treated with NC procedure.

Transcatheter edge-to-edge repair is currently performed without need of annular stabilization; this aspect seems not to worry cardiologists who are expanding indications for this procedure.

Analyzing our data, nothing support that the lack of annular stabilization should be the failing cause of NC procedure, considering that ventricular and consequently annular remodeling occurs in NC patients. Stating to our data, near 10% of type A patients experience recurrence of moderate MR after NC compared to CS. This result should not be interpreted in a sterile way. They include the learning curve phases and we must not forget that this procedure is performed on beating heart, without CPB and this represent a real advantage compared to CS. The same extraordinary advantage shown by the transcatheter aortic valve replacement, which started with suboptimal results and that now become the gold standard for treating aortic stenosis in high-risk patients.

Nowadays, early referral allows to treat patients with only one leaflet disease and preserved left ventricle and not dilated annulus. Moreover, as already shown, LV dimensions reduce during follow up.

Points of strength

This technique is just the harbinger of what is yet to come.

It mirrors the (r)evolution intended in extensive terms for every field of cardiac surgery. Every technique just presented are accepted with skepticism, the first not-expected results do not influence in good terms the community.

With our project we tried to show that several factors need to be ameliorate, nothing is well established, because the perfect intervention for each patient maybe does not exist but the best should be .

This technique has demonstrated very satisfying results also for repairing failed Mitral valve repair. In a recent multi-center study by Gerosa et al.[4] 15 cases have been treated with NC after a primary failed mitral valve repair. In these patients the presence of a previous prosthetic ring to stabilize the annulus revealed to be advantageous ensuring more durability. Patient Success, was 92.3% and 83.9% at 1 and 2-year FU. Moreover, freedom from more than moderate MR and freedom from more than mild MR were 92.3% and 83.9% at 1 and 2-year FU respectively, the same as patient success, while the authors did not observe any rehospitalization, death or NYHA class worsening apart from those relative to the patients who presented severe MR recurrence.

NC showed to be another possible strategy to treat patients in this challenging clinical scenario.

CONCLUSION

Microinvasive NC could be another option for patients with degenerative MR. Gaining skills, improving technical aspects and optimizing patient selection are *sine qua non* conditions to improve results. A cardiac surgeon who is able to perform conventional MVR, minimally invasive MVR, and now also microinvasive MVR, can choose the most appropriate strategy for every single patient in a totally unbiased manner with a tailored way.

As Freddie Mercury' song says "open heart and surgery, that's Miracle": stopping the heart-beat, repairing defects than restarting the native contractility was seen as a "Miracle" in the 90 's. We believe that, if the great Freddie Mercury was still alive would be captivated by the progresses of this chapter of science.

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ACRONYM

AV: Atrio-Ventricular
CAD: Coronary Artery Disease
CC: Cross-Clamping
CPB: Cardiopulmonary Bypass
CS: Conventional Surgery
DAPT: Dual AntiPlatelet Therapy
DMR: Degenerative Mitral Regurgitation
FA: Favorable Anatomy
FED: FibroElastic Deficiency
FMR: Functional Mitral Regurgitation
FV: Femoral Vein
LOS: Length of stay
LV: Left ventricle
LVEF: Left Ventricle Ejection Fraction
LVEDD: Left Ventricle End Diastolic Diameter
LVESD: Left Ventricle End Systolic Diameter
LVOT: Left Ventricle Outflow Tract
MA: Mitral Annulus
MR: Mitral Regurgitation
MVARC: Mitral Valve Academic Research Consortium
MVR: Mitral Valve Repair
NC: Neochordae
NYHA: New York Heart Association
PCI: Percutaneous Coronary Intervention
SPAP: Systolic Pulmonary Arterial Pressure
TA: Trans-Apical
TAVI: Transcatheter Aortic Valve Implantation
TMVr: Transcatheter MV repair
TEE: Trans-Esophageal Echocardiography
TSP: Trans-septal
UA: Unfavorable Anatomy

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