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Mitral valve repair: comparison between two minimally invasive surgical approaches

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MITRAL VALVE REPAIR: COMPARISON BETWEEN TWO MINIMALLY INVASIVE SURGICAL APPROACHES

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Abstract

Background: Mitral regurgitation (MR) occurs when there is an inefficient coaptation between the two leaflets of the valve, which allows blood to reflow to the left atrium during ventricular systole. MR is currently the second cause for valve surgery in Europe, which emphasizes the relevance of studying new surgical instruments that allows for less invasive techniques. The NeoChord™ DS1000™ system can be used for repairing a flail or prolapsing valve, without the need of sternotomy, cardiopulmonary bypass or cardioplegia.

Aim: To present a single-center experience of the early results of Transapical Off-Pump Mitral Valve Repair with neochords (TOP-MINI) in the first patients operated in Portugal; and, to compare the short-term safety and efficacy of this new procedure with mitral valve repair by right anterolateral minithoracotomy.

Methods: In this retrospective study, data from CHVNG/E regarding two surgical techniques for mitral valve repair was collected between December 2016 and December 2019. A total of 45 patients, 18 intervened by Transapical Off-Pump Mitral Valve Repair with neochords and 27 by right anterolateral minithoracotomy were then compared using IBM SPSS® statistics version 26.0. Significance level (*p*) of 0.05 (5% error probability) or lower was considered.

Results: The mean age in the TOP-MINI group was 65.2 (±15.1) and 57.3 (±13.5) in minithoracotomy group, with a majority of males (72.2% vs. 85.2%, respectively). Most patients from both groups were class II in the New York Heart Association (NYHA) functional classification preoperatively (44.4% in TOP-MINI vs. 59.3% in MT). Pre-procedural mitral regurgitation grade was 3.9 ± 0.3 in the first group vs 3.7 ± 0.5 in the second one. Procedural and device success were defined as a reduction of its degree to 1+ or 0, which was achieved in 100% of TOP-MINI's cases and 96.3% of MT's.

Conclusion: In a short-term follow-up, TOP-MINI seems to be not only safe, but effective in patients with primary MR as well, and also non-inferior to mini-thoracotomy approach to repair MR, leading to a substantial decrease of the regurgitation degree. It also reduces the surgical theatre time, ICU and total hospital stay and overall complications. Avoidance of cardiopulmonary bypass is one of the most important advantages of this approach, as it eliminates the need for cardioplegia, vascular access or hemostasis revision and the associated risks.

Keywords: Echocardiography; Extracorporeal Circulation; Mitral Valve Insufficiency; Mitral Valve Prolapse; Heart surgery; Minimally Invasive Surgical Procedures

Resumo

Enquadramento: A insuficiência mitral surge quando há coaptação ineficiente entre os folhetos da válvula, permitindo regurgitação de sangue do ventrículo para a aurícula esquerda durante a sístole. Esta é atualmente a segunda causa mais frequente de cirurgia valvular na Europa, o que aumenta a importância de procurar técnicas menos invasivas. O sistema NeoChord™ DS1000™ pode ser usado para reparar uma válvula laxa ou prolapsada de forma minimamente invasiva.

Objetivo: Pretende-se apresentar os resultados da reparação transapical da válvula mitral sem circulação extracorporal com implante de neocordas (TOP-MINI) nos primeiros pacientes operados em Portugal e, em comparação com a abordagem por minitoracotomia anterolateral direita, começar a entender a segurança e eficácia a curto prazo do novo procedimento.

Métodos: Neste estudo retrospetivo, foram colhidos dados do CHVNG/E referentes ao período entre dezembro de 2016 e dezembro de 2019. Um total de 45 pacientes, 18 intervencionados por TOP-MINI e 27 por minitoracotomia, foram comparados através do IBM SPSS® statistics versão 26.0. Foi considerado o nível de significância (p) de 0,05 (5% de probabilidade de erro) ou menor.

Resultados: A idade média no grupo TOP-MINI foi de 65,2 anos (± 15,1) e 57,3 (± 13,5) no grupo das minitoracotomias, com uma maioria de homens (72,2% vs. 85,2%, respetivamente). A maioria dos pacientes de ambos os grupos era de classe II na classificação funcional da New York Heart Association (NYHA) no pré-operatório (44,4% no TOP-MINI vs. 59,3% no MT). O grau de regurgitação mitral pré-operatório foi de 3,9 ± 0,3 no primeiro grupo contra 3,7 ± 0,5 no segundo. O sucesso do procedimento e do dispositivo foi definido pela redução do grau para 1+ ou 0, o que foi alcançado em 100% dos casos de TOP-MINI e em 96,3% das minitoracotomias.

Conclusão: O procedimento TOP-MINI parece ser seguro, mas também eficaz, num *follow-up* de curto prazo, em doentes com regurgitação mitral primária. Parece ainda ser não inferior à abordagem por minitoracotomia. Comparativamente, reduz o tempo de operação e anestesia, a duração da unidade de cuidados intensivos e o tempo total de internamento hospitalar, assim como as complicações em geral. O facto de evitar a circulação extracorporal é uma das vantagens mais relevantes, pois elimina a necessidade de cardioplegia, acesso vascular ou revisão de hemostasia e os riscos a estes inerentes.

Abbreviations list

AFib – Atrial Fibrillation

AMI – Acute Myocardial Infarction

BMI – Body Mass Index

CHVNG/E - Centro Hospitalar de Vila Nova de Gaia e Espinho

COPD – Chronic Obstructive Pulmonary Disease

CPB – Cardiopulmonary Bypass

EACTS – European Association for Cardio-Thoracic Surgery

ECG – Electrocardiogram

ESC – European Society of Cardiology

GDMT – Guideline-directed medical therapy

ICU – Intensive Care Unit

LVEF – Left Ventricular Ejection Fraction

MR – Mitral Regurgitation

MT - Minithoracotomy

MV – Mitral Valve

MVARC – Mitral Valve Academic Research Consortium

NYHA – New York Heart Association

PISA – Proximal Isovelocity Surface Area

RBC – Red Blood Cells

sPAP - Systolic Pulmonary Artery Pressure

TACT – Transapical Artificial Chordae Tendinae

TOP-MINI – Transapical Off-Pump Mitral valve repair with Neochord Implantation

TEE – Transesophageal Echocardiography

TTE - Transthoracic Echocardiogram

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Introduction

Mitral regurgitation (MR) occurs in 9,3% of the population over 75 years of age in developed countries[1], where average life expectancy is over 80 and continues to increase[2]. It is, currently, the second most frequent indication for valve surgery in the European continent[3].

In 2017, joint recommendations from the European Society of Cardiology (ESC) and the European Association of Cardiothoracic Surgery (EACTS) on the treatment of patients with chronic mitral regurgitation were released, with different directed therapeutic approaches depending on if the condition is primary (degenerative, organic or structural) or secondary (functional) (**Figures 1 and 2**). Thus, it can be understood that this distinction currently serves as the central basis for selection of standardized care therapies, which is why it is so important to identify the dysfunction's etiology. In this light, said document recommends surgery (repair over substitution, if possible) for severe primary MR, while mostly conservative treatment for secondary MR. Focusing on primary MR correction, besides the available invasive procedures, these guidelines also mention a minimally invasive procedure known as percutaneous edge-to-edge repair[3]. In fact, the scientific and technological advancement increasingly allows for the creation and improvement of new medical and surgical instruments and, with them, gradually less invasive techniques. The intention is, of course, to reduce the risk of death inherent to the procedures, as well as the number of complications (in intra and postoperative periods), with less iatrogeny and better prognosis. It is therefore necessary to have a deeper understanding of these interventions so as to comprehend if their intention is being fulfilled.

As so, although there are several new minimally invasive procedures still under study, such as direct and indirect annuloplasty, left ventricular remodelling or leaflet plication and, last but not least, transcatheter mitral valve replacement (TMVR), the present dissertation will focus on Transapical Off-Pump Mitral Valve Repair with neochord implantation (TOP-MINI). So far, TOP-MINI has been used for the treatment of degenerative mitral insufficiency due to prolapsed or ruptured chords (primary MR, Carpentier type II), in all types of MV morphologies. The surgical technique is performed with the NeoChord™ DS1000™ device and consists on the application of transventricular polytetrafluoroethylene (PTFE) neochords between the valve and the left ventricular wall, through the left ventricle apical region, which is accessed by left minithoracotomy. Guidance of direct 2D and 3D transesophageal echocardiography (TEE) is required not only to allow for the proper use of the device and the correct implantation of the

chords, but also to regulate its length and tension to the most adequate measures in each case[4]. It is performed under general anaesthesia and haemodynamical monitorization, similarly to the classic procedure, but foregoes cardiopulmonary bypass (CPB) and cardioplegia as well as median sternotomy and further invasive accesses, such as cannulation of femoral vessels[5,6]. These are expected to be strong benefits for patients, especially for the ones with high surgical risk and multiple comorbidities, where complications during the procedure can be frequent and who are more likely to need mitral regurgitation correction. There is yet another feature that raises the interest in TOP-MINI, as when compared to all other current minimally invasive procedures, which is the fact that this is the only technique that maintains the possibility of re-intervention, if need be, by both open surgical or percutaneous options to repair or replace the valve.

According to the Mitral Valve Academic Research Consortium (MVARC), an expert consensus around the investigation on mitral valve devices, the right way to increase outcome credibility when investigating a new procedure is by comparing it to known ones, with known results[3]. In this context, between the recognized minimally invasive procedures, the right anterolateral minithoracotomy (MT) in the fourth intercostal space is currently the most used approach[7], and as such, it is going to be used as our control group.

The aim of this dissertation is to present the early results of TOP-MINI in the first patients operated with this technique in Portugal, a single-center experience, and, by comparison to MV repair by MT, to begin to understand the short-term safety and efficacy of the new procedure.

Material and methods

In Portugal, neocordoplasty without cardiopulmonary bypass for surgical repair of MR is mostly done by the Cardiothoracic Surgery department of Vila Nova de Gaia/Espinho Hospital (CHVNG/E), hence the present dissertation only considered this hospital for collecting data. CHVNG/E's ethics committee was then responsible for its approval.

This prospective study encompasses information from December 2017 up to October 2019 regarding all patients intervened by TOP-MINI in CHVNG/E. Data was also collected from December 2016 until December 2019 covering the totality of patients that underwent right anterolateral minithoracotomy at this center.

For both procedures, patients were individually selected and inclusion criteria included age equal or above 18 years, Carpentier type II MR, MR severity (3+ and 4+), all MV morphology types (A, B and C), including leaflet perforation and involvement of the commissural regions, LVEF >20%. Good potential for coaptation was required as well in the TOP-MINI group, since an annuloplasty ring is never used. Although at least 15% of tissue overlap – leaflet-to-annulus ration > 1.15 – was preferred, this ideal ratio was not found in some TOP-MINI patients who were still intervened by this technique since they were not candidates for any other procedure. In opposition, for the purpose of eliminating eventual bias, in the MT group, patients who underwent multiple valve repairs or substitutions at the same surgical moment were excluded.

All patients have undergone diagnostic evaluation with medical history (including sex, age, BMI, cardiovascular risk factors, New York Heart Association (NYHA) classification), routine laboratory testing, electrocardiogram (ECG), transthoracic echocardiogram (TTE) and transesophageal echocardiogram (TEE), at least. They were on guideline-directed medical therapy (GDMT) before surgery. Preoperative risk was calculated individually using the European System for Cardiac Operative Risk Evaluation upgraded[8] (EuroSCORE II).

Regarding laboratory testing, in order to assess renal impairment creatinine value was used. Once it can vary according to the performing lab, the range that was considered normal was the one used in the hospital's laboratory, between 0.67-1.17 mg/dL, since it is where all analyzes were processed. For echocardiographic parameters, all were evaluated during a period of clinical stability and no procedure was made under emergency circumstances.

Primary and secondary endpoints were set according to MVARC criteria[9,10]. Primary endpoints included clinical measures such as mortality and heart failure rehospitalization. Three types of secondary endpoint were established, namely mechanistic parameters (selected echocardiographic measures), safety assess (procedure related complications) and technical success of each procedure (including reduction of mitral regurgitation severity to 1+ or 0, procedure duration and time in ICU/total hospital stay).

The follow-up period was designed as at least one image exam in a six-month time period after surgery, in order to approach both groups in a similar way, since follow up in the MT group is less strict.

Statistical analysis. Both groups were compared using IBM SPSS® statistics version 26.0. Categorical variables were compared using Chi-Square or Fisher's exact test when appropriate. For quantitative (continuous) variables, it was checked whether they had a normal distribution by the Kolmogorov-Smirnov test of normality. Then, if normal distribution was confirmed, the two groups were compared with T test (for independent samples). Otherwise, they were compared using Mann-Whitney test. Particularly regarding echocardiographic parameters that were assessed both pre and postoperatively, only patients that had results for both periods were considered, paired and included for statistical analysis. In these cases, T Test was used to compare the pairs if the distribution was normal and Wilcoxon test if not. Results with a significance level (p) of 0.05 (5% error probability) or lower were considered statistically relevant.

Results

A total of 45 patients were selected, 18 submitted to TOP-MINI and 27 to MT. This corresponds to all cases that underwent these procedures during the selected timeframe, except for one that was excluded from the MT group for being submitted to an aortic valve substitution in the same surgical moment.

For analysis purposes, four main moments of treatment are to be highlighted, namely, preoperative, acute (during procedure or within 24 h), procedural (until discharge from hospital) and follow-up (up until 6 months after intervention).

Baseline characteristics

There were no important statistical differences in cardiovascular risk factors between the groups (**Table I**). The mean age in the TOP-MINI group was 65.2 (±15.1) years and 57.3 (±13.5) in the MT group, with a majority of males (72.2% vs. 85.2%, respectively). Most patients from both groups were class II in the New York Heart Association (NYHA) functional classification (44.4% in TOP-MINI vs. 59.3% in MT). The most common following classes were, for both groups, III (33.3% vs. 22.2%) and then I (22.2% vs. 18.5%); there were no class IV patients. Overall, 77.8% of TOP-MINI patients displayed sinus rhythm, preoperatively, as well as 81.5% of MT patients. Non sinus rhythms included permanent atrial fibrillation (4 in TOP-MINI group and 3 in MT group) and paroxysmal atrial fibrillation (3 in MT).

Preoperative TTEs allowed for the description of some valve aspects (**Table II**). As mentioned, all patients had primary MR and the defects found were MV leaflet prolapse (12 before TOP-MINI and 9 before MT), chordal rupture with flail leaflet (6 before TOP-MINI and 10 before MT) or others, like poor coaptation, clefts or combinations between these faults. In the TOP-MINI group, valve morphology was mostly type A (77.8%), while in the MT group all three types were found in the same number of patients (33.3% for each type).

Clinical outcomes

At the time of hospital discharge, all patients in both groups left with a reduction of their baseline NYHA class to class I (**Table III**).

Primary Endpoints

There was no short-term mortality (including all-cause, procedure or no procedure related, periprocedural and non-periprocedural) in both groups until the end of the follow-up.

Re-hospitalization for cardiovascular cause occurred in 1 patient who underwent TOP-MINI due to a pericarditis a month after hospital discharge. In the MT group, 2 patients needed re-hospitalization, 1 for pleural effusion 2 days after hospital discharge and another for surgical drainage of right pleural effusion and pericardial effusion 15 days after the procedure.

Secondary Endpoints

As mentioned, three types of secondary endpoint were established.

Technical success (**Table III**) with procedural and device success being defined as a reduction of mitral regurgitation's severity to 1+ or 0, was achieved in 100% of TOP-MINIs and 96.3% of MTs (1 patient finished the surgery with moderate MR). As for the implant rate, the mean duration of procedure was significantly different ($p<0.001$), being 105.6 minutes (±29.6) on TOP-MINI procedure and 298.3 minutes (±43.1) on mini-thoracotomy. The mean of chords used was less in TOP-MINI (2.8 (±0.6)) than in MT (3.6 (±2.1)) ($p=0.013$). Mean length of ICU stay was 0.9 (±0.6) days after TOP-MINI and 1.4 (±0.9) after MT ($p=0.014$). Mean length of total hospital stay for TOP-MINI patients was about 5.2 days (±4.3), and 5.6 days (±2.2) for MT ($p=0.033$).

In order to analyze safety, complications are to be discriminated (**Table IV**). There were no major adverse events, such as stroke and other cerebrovascular events, myocardial infarction or major vascular complications to report. In the acute period, there were no device or procedure-related adverse events to report in the TOP-MINI group but in the MT group there was frequent need of cardioversion for new onset of atrial fibrillation (AFib) related to going out of CPB (33.3%). AFib then happened in the procedural period in 1 patient after TOP-MINI (that was successfully reverted using amiodarone) and in 2 after MT (one reverted, the other proceeding to assume a medical strategy of rhythm control). This was the only kind of arrhythmias and conduction system disturbances to report. Hemostasis revision was also needed in 3 MT patients (11.1%), 2 in the acute period and 1 in the procedural period. There was 1 patient needing 2 units of red blood cell (RBC) transfusion after TOP-MINI and 2 after MT, one needing 1 unit of packed red blood cells (PRBC), 7 units of platelets and 1 unit of fibrinogen

transfusion. In MVARC Primary Bleeding Scale, all these events are classified as minor. Between pulmonary complications, the most common was pleural effusion in both groups (5 in TOP-MINI (27.8%) versus 10 in MT (37.04%)). 1 atelectasis and 1 subcutaneous emphysema also occurred in MT patients. There were 2 pericardial effusions after TOP-MINI procedures and 3 after MT. As for acute kidney injury (AKI), there were 2 episodes in the first group (1 of them acute on chronic kidney disease), both stage I of VARC-2 classification, besides 1 urinary tract infection (UTI). 1 UTI occurred after MT as well. Others events included 1 postoperative delirium, 1 anemia needing IV iron and 1 fever without a focus, all in the MT group.

In the matter of mechanistic parameters, early success was achieved, since mean mitral regurgitation severity decreased significantly ($p<0.001$) in both groups. In TOP-MINI patients, it was 3.9 (±0.3) preoperatively, downing down to 0.6 (±0.5) postoperatively; 3.7 (±0.5) to 0.1 (±0.4) in MT patients. Throughout follow-up (**Table V**), MR grade decrease kept on being significant ($p<0.001$) on both groups. Decrease in left ventricular ejection fraction (LVEF) occurred for both groups, from 57.3% (±6.1) to 52.4% (±8.7) after TOP-MINI, and from 59.6 % (±6.4) to 56.3 % (±7.4) after MT, but was only statistically significant in the first group ($p=0.035$). Mean systolic pulmonary artery pressure (sPAP) went from 36.2 mmHg (±16.1) to 25.5 (±7.0) in the first group which was more significant ($p=0.056$) than 33.0 (±13.0) to 30.7 (±13.1) in the second one ($p=0.657$). Left chamber dimensions seem to decrease postoperatively in TOP-MINI patients and in MT patients, like perceived when looking at mean LV diameter (56.6 (±7.3) to 56.1 (±9.9) with $p=0.057$, vs. 55.6 (±3.4) to 51.4 (±5.8), with $p=0.800$). Mean LV mass went from 236.0 (±101.5) to 219.6 (±70.5) in the first approach and from 197.9 (±24.2) to 191.4 (±41.4) in the second.

As for procedure-related necessity of new surgical intervention, beside the ones mentioned during hospital stay and in re-hospitalization, until the end of the follow-up, a MT patient needed new MV surgical intervention due to MR 4+ at 3 months post-surgery and another refused reoperation that was required due to partial ring disinsertion and hemolysis at 4 months. Between patients who underwent TOP-MINI, 2 need new MV surgical intervention, both due to neochord break, at 3 months and 6 months post-surgery.

Discussion

The two groups appear to be comparable since all the pre-operative characteristics have no significant statistical differences between them. Both groups of patients were selected by experts and/or a multidisciplinary group, and as so this lack of differences can be indicative of MR patients' usual profile.

Given that TOP-MINI is the new procedure in focus, it is relevant to evaluate if success was achieved. So, as defined by MVARC (**Image 3**), technical success (measured at exit from the operation theatre), device success (measured at 30 days and at all later post-procedural intervals) and procedural success could be assessed until the 6 months' target. All criteria for technical and procedural success were met. For device success we can say that it was accomplished at 30 days, as there were no transapical technique-related adverse events (such as ventricular apex rupture, leaflet perforation or tear or left atrial perforation). However, in our population, there were 2 patients with broken native chords at 3 and 6 months after surgery.

Since the Transapical Artificial Chordae Tendinae (TACT) trial[11], an early TOP-MINI evaluation that mentioned potential for upgrading efficacy and durability, a multitude of improvements have been made. Nevertheless, the surgeon's experience has likewise influence in patient's outcome[11] and new solutions on their training have being presented, such as dynamic cardiac biosimulators[12]. In this light, a note regarding evolution of the surgical learning curve in CHVNG/E: In the early experiences using TOP-MINI the aim was to reduce MR to near zero intraoperatively. Over time, with LV remodelling and reduction of LV chamber and wall size, the neochords were loosened, and as so, less effective. After this observation, an overcorrection of MR became standard, in order to allow for chamber volume and/or wall modifications while maintaining MR reduction or annulment.

Furthermore, other studies have shown good results not only in early experiences but with a longer timeframe as well[5,6,13-15]. Kiefer et al. has the longest follow-up, showing very good long-term results at a 5-year period[15].

However, this study constitutes a direct comparison between two mitral valve repair procedures, which has not been done before, to our knowledge. Looking over the two techniques, several benefits were found on TOP-MINI over MT. Re-hospitalization was needed more often in MT patients, as well as surgical re-intervention (in all acute, procedural and follow-up periods). Minor events were found in larger number on patients who were submitted to

minithoracotomy both in the acute and procedural periods, with exception for AKI (11.1% in TOP-MINI). The probable cause for most of these findings is the necessity of CPB in the MT approach, given the fact that this technique has a multitude of steps that must be rigorously followed and surveilled and patient factors to control so the patient does not develop complications[16] and the surgery is successful. Even so, a significant number of MT patients had to be submitted to cardioversion for going into atrial fibrillation while going out of CPB and had to have acute hemostasis revision. Procedural times were significantly shorter for TOP-MINI, not only during surgery but also in ICU days and total hospital stay. A reduction of MR severity to 1+ or 0 was achieved in 100% of TOP-MINI's cases and 96.3% of MT's. These results were obtained with lesser surgical trauma (smaller incision expected, fewer chords implanted (2.8 (±0.6) vs. 3.6 (±2.1)) and no need for less invasive accesses).

The main disadvantage in the use of TOP-MINI is that it should not be used in an emergency setting. The inability to correct clefts on MV leaflets or advanced annular dilatation can also be questioned, but a solution can be found in combining this method with others, as has already been already done and reported by von Bardeleben et al., where the MV was repaired with a combination between direct ring annuloplasty and TOP-MINI[17], maximizing the strongest advantages from each technique. Other combos have been described like TOP-MINI and TAVI in a single moment[18] and maybe that's the future on risky multiprocedures at the same moment.

Limitations of this study. This study had some limitations. Being a single-center study led to a small number of patients, only allowing for preliminary inferences. The absence of a standardized guide to record patients' clinical information led to a lack of various echocardiographic parameters. Leaflet-to-annulus index seems to be an important postoperative predictor[19] that we could not report.

Conclusion

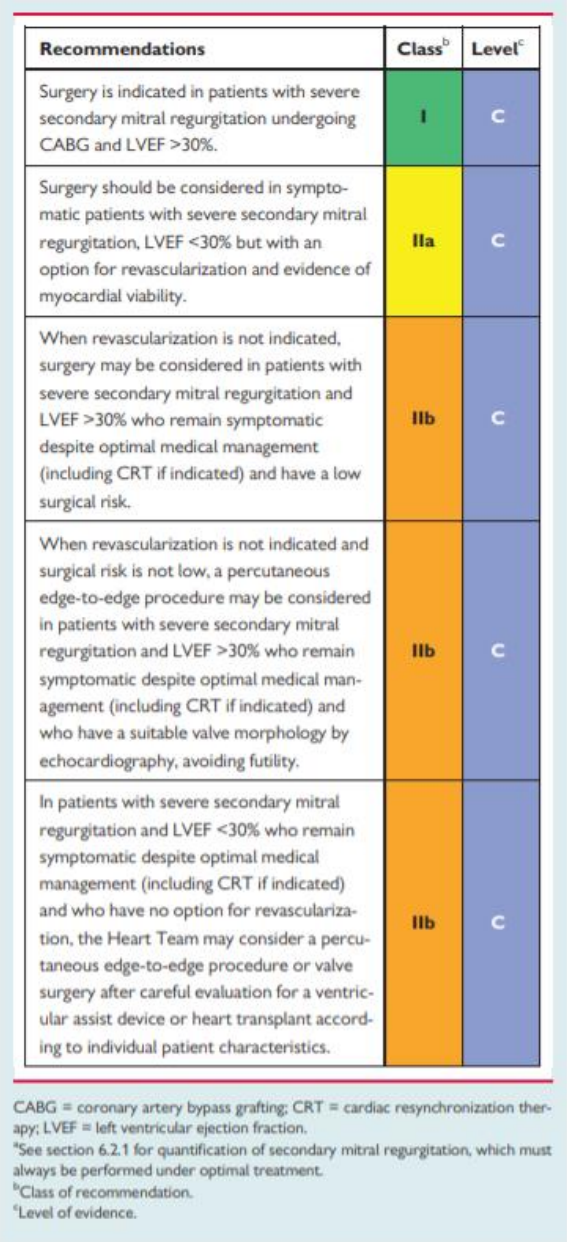
Neochordal replacement was popularized by David *et al*.[20] and has since provided excellent short and long-term results[5]. This study wasn't any different, with the recent technique of transapical off-pump mitral valve repair with neochord implantation. In the short term, it seems to be not only safe, but effective in patients with primary MR as well, and also at least non-inferior to the mini-thoracotomy approach to repair MR. It not only leads to a substantial decrease in the degree of mitral regurgitation, but also reduces surgical times, length of ICU and total hospital stay and overall complications. Avoidance of cardiopulmonary bypass is one of the most important advantages of this approach, as it eliminates the need for cardioplegia, vascular access or hemostasis revision and the associated risks. This acquires special significance for patients in higher surgical peril. Although results seem promising at short and even maybe at medium term[15], studies including more cases and longer follow-up are needed so the technique's durability and long-time patient's wellbeing can be assessed, after which, this technique can eventually be considered as standard of practice in new guidelines for mitral regurgitation correction.

Appendix

Recommendations	Class[a]	Level[b]
Mitral valve repair should be the preferred technique when the results are expected to be durable.	I	C
Surgery is indicated in symptomatic patients with LVEF >30%.[121,131,132]	I	B
Surgery is indicated in asymptomatic patients with LV dysfunction (LVESD ≥45 mm[c] and/or LVEF ≤60%).[122,131]	I	B
Surgery should be considered in asymptomatic patients with preserved LV function (LVESD <45 mm and LVEF >60%) and atrial fibrillation secondary to mitral regurgitation or pulmonary hypertension[d] (systolic pulmonary pressure at rest >50 mmHg).[123,124]	IIa	B
Surgery should be considered in asymptomatic patients with preserved LVEF (>60%) and LVESD 40–44 mm[c] when a durable repair is likely, surgical risk is low, the repair is performed in a heart valve centre and at least one of the following findings is present: • flail leaflet or • presence of significant LA dilatation (volume index ≥60 mL/m^2 BSA) in sinus rhythm.	IIa	C
Mitral valve repair should be considered in symptomatic patients with severe LV dysfunction (LVEF <30% and/or LVESD >55 mm) refractory to medical therapy when the likelihood of successful repair is high and comorbidity low.	IIa	C
Mitral valve replacement may be considered in symptomatic patients with severe LV dysfunction (LVEF <30% and/or LVESD >55 mm) refractory to medical therapy when the likelihood of successful repair is low and comorbidity low.	IIb	C
Percutaneous edge-to-edge procedure may be considered in patients with symptomatic tion (LVEF <30% and/or LVESD >55 mm) refractory to medical therapy when the likelihood of successful repair is low and comorbidity low.	IIb	C
Percutaneous edge-to-edge procedure may be considered in patients with symptomatic severe primary mitral regurgitation who fulfil the echocardiographic criteria of eligibility and are judged inoperable or at high surgical risk by the Heart Team, avoiding futility.	IIb	C

BSA = body surface area; LA = left atrial; LV = left ventricular; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; SPAP = systolic pulmonary artery pressure.
[a]Class of recommendation.
[b]Level of evidence.
[c]Cut-offs refer to average-size adults and may require adaptations in patients with unusually small or large stature.
[d]If an elevated SPAP is the only indication for surgery, the value should be confirmed by invasive measurement.

Image 1. ESCS/ESCTC indications for intervention in severe primary mitral regurgitation. *Source: courtesy of Dr. Helmut Baumgartner; adapted from « 2017 ESC/EACTS Guidelines for the management of valvular heart disease».*



Recommendations	Class[b]	Level[c]
Surgery is indicated in patients with severe secondary mitral regurgitation undergoing CABG and LVEF >30%.	I	C
Surgery should be considered in symptomatic patients with severe secondary mitral regurgitation, LVEF <30% but with an option for revascularization and evidence of myocardial viability.	IIa	C
When revascularization is not indicated, surgery may be considered in patients with severe secondary mitral regurgitation and LVEF >30% who remain symptomatic despite optimal medical management (including CRT if indicated) and have a low surgical risk.	IIb	C
When revascularization is not indicated and surgical risk is not low, a percutaneous edge-to-edge procedure may be considered in patients with severe secondary mitral regurgitation and LVEF >30% who remain symptomatic despite optimal medical management (including CRT if indicated) and who have a suitable valve morphology by echocardiography, avoiding futility.	IIb	C
In patients with severe secondary mitral regurgitation and LVEF <30% who remain symptomatic despite optimal medical management (including CRT if indicated) and who have no option for revascularization, the Heart Team may consider a percutaneous edge-to-edge procedure or valve surgery after careful evaluation for a ventricular assist device or heart transplant according to individual patient characteristics.	IIb	C

CABG = coronary artery bypass grafting; CRT = cardiac resynchronization therapy; LVEF = left ventricular ejection fraction.
[a]See section 6.2.1 for quantification of secondary mitral regurgitation, which must always be performed under optimal treatment.
[b]Class of recommendation.
[c]Level of evidence.

Image 2. ESCS/ESCTC indications for intervention in severe secondary mitral regurgitation.
Source: courtesy of Dr. Helmut Baumgartner; adapted from « 2017 ESC/EACTS Guidelines for the management of valvular heart disease».

TABLE 10 Technical, Device, Procedural, and Patient Success

I. Technical success (measured at exit from the catheterization laboratory)
All of the following must be present:
I. Absence of procedural mortality; and
II. Successful access, delivery, and retrieval of the device delivery system; and
III. Successful deployment and correct positioning of the first intended device; and
IV. Freedom from emergency surgery or reintervention related to the device or access procedure.

II. Device success (measured at 30 days and at all later post-procedural intervals)
All of the following must be present:
I. Absence of procedural mortality or stroke; and
II. Proper placement and positioning of the device; and
III. Freedom from unplanned surgical or interventional procedures related to the device or access procedure; and
IV. Continued intended safety and performance of the device, including:
a. No evidence of structural or functional failure (see Table 11, part I)
b. No specific device-related technical failure issues and complications (see Table 11, part II)
c. Reduction of MR to either optimal or acceptable levels* without significant mitral stenosis (i.e., post-procedure EROA is ≥1.5 cm^2 with a transmitral gradient <5 mm Hg), and with no greater than mild (1+) paravalvular MR (and without associated hemolysis)

III. Procedural success (measured at 30 days)
All of the following must be present:
I. Device success (either optimal or acceptable),† and
II. Absence of major device or procedure related serious adverse events, including:
A. Death
B. Stroke
C. Life-threatening bleeding (MVARC scale)
D. Major vascular complications
E. Major cardiac structural complications
F. Stage 2 or 3 acute kidney injury (includes new dialysis)
G. Myocardial infarction or coronary ischemia requiring PCI or CABG
H. Severe hypotension, heart failure, or respiratory failure requiring intravenous pressors or invasive or mechanical heart failure treatments such as ultrafiltration or hemodynamic assist devices, including intra-aortic balloon pumps or left ventricular or biventricular assist devices, or prolonged intubation for ≥48 h.
I. Any valve-related dysfunction, migration, thrombosis, or other complication requiring surgery or repeat intervention

IV. Patient success (measured at 1 year)
All of the following must be present:
I. Device success (either optimal or acceptable), and
II. Patient returned to the pre-procedural setting: and
III. No rehospitalizations or reinterventions for the underlying condition (e.g., mitral regurgitation, heart failure); and
IV. Improvement from baseline in symptoms (e.g., NYHA improvement by ≥1 functional class); and
V. Improvement from baseline in functional status (e.g., 6-min walk test improvement by ≥50 m); and
VI. Improvement from baseline in quality-of-life (e.g., Kansas City Cardiomyopathy Questionnaire improvement by ≥10)

*MR reduction is considered *optimal* when post-procedure MR is reduced to trace or absent. MR reduction is considered *acceptable* when post-procedure MR is reduced by at least 1 class or grade from baseline *and* to no more than moderate (2+) in severity. For clinical trials and registry studies, assessment of baseline and post-procedure MR must be made by an echocardiographic core laboratory. For large observational databases, baseline and post-procedure MR may be assessed by physicians trained in echocardiographic evaluation. †For 30-day evaluation of device success, the results from an immediate post-procedural transesophageal echocardiogram and from a transthoracic echocardiogram taken within 24 to 48 h post-procedure may be used if the 30-day echocardiogram is absent. Device success determinations at post-procedural intervals beyond the initial 30 days should reflect findings from the patient history and an echocardiographic study obtained within the relevant pre-specified follow-up window.

CABG = coronary artery bypass grafting; EROA = effective regurgitant orifice area; MR = mitral regurgitation; MVARC = Mitral Valve Academic Research Consortium; NYHA = New York Heart Association; PCI = percutaneous coronary intervention.

Image 3. MVARC's criteria on technical, device, procedural and patient success.

Source: adapted from «Clinical Trial Design Principles and Endpoint Definitions for Transcatheter Mitral Valve Repair and Replacement: Part 1: Clinical Trial Design Principles - A Consensus Document From the Mitral Valve Academic Research Consortium». Copyright © 2015, Oxford University Press. License of use number 4805370044511

Table I. Population description: baseline characteristics and surgical risk.

		TOP-MINI (n=18)	MT (n=27)	*p*
Baseline characteristics	**Mean age (SD), years**	65.2 (±15.1)	57.3 (±13.5)	0.056**
	Males (%), n	13 (±72.2)	23 (±85.2)	NS
	Mean weight (SD), kg	73.8 (±12.8)	73.7 (±12.2)	NS
	Mean height (SD), cm	167.5 (±10.0)	170.0 (±8.1)	NS
	Mean BMI (SD), kg/m^2	26.4 (±4.7)	25.5 (±3.4)	NS
Preoperative NYHA grade (%), n	**- I** **- II** **- III** **- IV**	- 4 (22.2) - 8 (44.4) - 6 (33.3) - 0 (0.0)	- 5 (18.5) - 16 (59.3) - 6 (22.2) - 0 (0.0)	NS
Cardiovascular risk factors (%), n	**Hypertension**	12 (67.7)	16 (63.0)	NS
	Coronary heart disease	3 (16.7)	3 (11.1)	NS
	Dyslipidemia	10 (55.6)	11 (40.7)	NS
	Diabetes Mellitus	4 (22.2)	1 (3.7)	0.053
	Pulmonary Hypertension	7 (38.9)	5 (18.5)	NS
	COPD	2 (11.1)	1 (3.7)	NS
	Renal impairment	2 (11.1)	6 (22.2)	NS
	History of tobacco use	4 (22.2)	13 (48.1)	0.079
	Ex-smokers	3 (16.7)	9 (33.3)	NS
	Overweight	9 (50.0)	14 (51.9)	NS
	Previous AMI	0 (0.0)	1 (3.7)	NS*
	Previous stroke	1 (5.6)	2 (7.4)	NS
	Previous cardiac surgery	0 (0.0)	2 (7.4)	NS*
	Malignancy	1 (5.6)	1 (3.7)	NS*
	Sinus rhythm on ECG	14 (77.8)	22 (81.5)	NS
Mean EuroSCORE II (SD)		1.09 (±0.48)	1.24 (±1.44)	NS**

AMI – acute myocardial infarction; BMI – body mass index; COPD – chronic obstructive pulmonary disease; ECG – electrocardiogram; NS – non significant; * Fisher's Exact test **Mann-Whitney U test

Table II. Preoperative echocardiographic findings.

	TOP-MINI	MT
Morphology valve type (%), n		
- **A**	14 (77.8)	9 (33.3)
- **B**	2 (11.1)	9 (33.3)
- **C**	2 (11.1)	9 (33.3)
Valve defects, n		
- **Leaflet prolapse**	12 (67.7)	9 (33.3)
- **Chord rupture**	6 (33.3)	10 (37.0)
- **Others**	0 (0.0)	9 (33.3)
Preoperative MR grade (%), n		
- **1+**	0 (0.0)	0 (0.0)
- **2+**	0 (0.0)	0 (0.0)
- **3+**	2 (11.1)	8 (29.6)
- **4+**	16 (88.9)	19 (70.4)
Mean preoperative MR grade	3.9 (±0.3)	3.7 (±0.5)
Preoperative PISA (SD), cm^2	0.6 (±0.2)	0.5 (±0.2)

Type A – Isolated central posterior leaflet prolapse or flail (P1, P2 or P3); Type B – Posterior multi-segment involvement (P1, P2 and/or P3); Type C – Anterior leaflet involvement (A1, A2 and/or A3), paracommissural or calcified leaflets involvement. MR – mitral regurgitation; PISA – Proximal Isovelocity Surface Area

Table III. Secondary endpoints - technical success.

		TOP-MINI (n=18)	MT (n=27)	*P*
Surgery related parameters	**Mean duration of procedure (SD), min**	105.6 (±29.6)	298.3 (±43.1)	**<0.001**
	Mean ECC time (SD), min	NA	186.7 (±33.4)	NA
	Mean aorta clamping time (SD), min	NA	121.8 (±22.0)	NA
	Mean of chords used (SD)	2.8 (±0.6)	3.6 (±2.1)	**0.013***
	Mean of ring strings used (SD)	NA	12.9 (±1.3)	NA
	Mean mitral ring size (SD)	NA	32.4 (±2.1)	NA
	Intraoperative complications (SD)	0.0 (±0.0)	0.4 (±0.5)	**0.003**
	Conversion to conventional surgery, n	0.0	0.0	NS
	Intraoperative final MR grade (%), n			NS
	- **1+**	10 (55.6)	1 (3.7)	
	- **2+**	0 (0.0)	1 (3.7)	
	- **3+**	0 (0.0)	0 (0.0)	
	- **4+**	0 (0.0)	0 (0.0)	
Mean RM grade decrease (SD)		3.3 (±0.1)	3.7 (±0.1)	**<0.001***
Hospital stay occurrences	**Mean length of hospital stay, (SD), days**	5.2 (±4.3)	5.6 (±2.2)	**0.033***
	Mean length of ICU stay (SD), days	0.9 (±0.6)	1.4 (±0.9)	**0.014***
	Complications during total hospital stay (%), n	8 (44.4)	18 (66.7)	NS
	NHYA grade at hospital discharge, n			NS
	- **I**	18	27	
	- **II**	0	0	
	- **III**	0	0	
	- **IV**	0	0	

*Mann-Whitney U test; NA – non applicable; NS – non significant

Table IV. Secondary endpoints - Safety analysis: Complications in acute and procedural periods.

	TOP-MINI (n=18)	**MT (n=27)**	***p***
Death, n	0	0	NS
AMI, n	0	0	NS
Stroke, n	0	0	NS
Major vascular complications, n	0	0	NS
Bleeding (%), n			
- **Minor**	1 (5.6)	2 (7.4)	NS
- **Major**	0 (0.0)	0 (0.0)	NS
- **Extensive**	0 (0.0)	0 (0.0)	NS
- **Life-threatening**	0 (0.0)	0 (0.0)	NS
- **Fatal**	0 (0.0)	0 (0.0)	NS
Transfusions (%), n	1	2	NS
- **PRBC**	1** (5.6)	2*** (7.4)	NS
- **Platelets**	0 (0.0)	1**** (3.7)	NS*
- **Fibrinogen**	0 (0.0)	1** (3.7)	NS*
Conduction disturbances (%), n			
- **Onset on acute period**	0 (0.0)	9 (33.3)	**0.006**
- **Onset on procedural period**	1 (5.6)	2 (7.4)	NS
- **Transient**	1 (5.6)	10 (37.0)	**0.016**
- **Permanent**	0 (0.0)	1 (3.7)	NS*
- **Need for permanent PM implantation**	0 (0.0)	0 (0.0)	NS
Pericardial effusion (%), n			
- **Minor**	2 (11.1)	3 (11.1)	NS
- **Major**	0 (0.0)	0 (0.0)	NS
Pulmonary complications (%), n			
- **Subcutaneous emphysema**	0 (0.0)	1 (3.7)	NS*
- **Pleural effusion**	5 (27.8)	10 (37.0)	NS
- **Atelectasis**	0 (0.0)	1 (3.7)	NS*
AKI, n			
- **Stage I**	2 (11.1)	0 (0.0)	NS*
- **Stage II**	0 (0.0)	0 (0.0)	NS
- **Stage III**	0 (0.0)	0 (0.0)	NS
Others, n			
- **ITU**	1 (5.6)	1 (3.7)	NS
- **Postoperative delirium**	0 (0.0)	1 (3.7)	NS*
- **Fever without a focus**	0 (0.0)	1 (3.7)	NS*
- **Anemia needing IV iron**	0 (0.0)	1 (3.7)	NS*

Note: Bleeding according to MVARC Primary Bleeding Scale[10]; AKI Stages according to VARC-2 classification[10]. NS – non significant
* Fisher's Exact Test ** 2 units; *** 1 unit each; **** 7 units

Table V. Echocardiographic comparison: preoperative vs. follow-up.

	TOP-MINI		*p*	MT		*p*
	Preoperative	Postoperative		Preoperative	Postoperative	
Mean MR grade (SD)	3.9 (±0.3)	1.9 (±1.1)	**<0.001**	3.7 (±0.5)	1.5 (±1.1)	**<0.001***
LVEF (SD), %	57.3 (±6.1)	52.4 (±8.7)	**0.035***	59.6 (±6.4)	56.3 (±7.4)	NS
sPAP (SD), %	36.2 (±16.1)	25.5 (±7.0)	0.056	33.0 (±13.0)	30.7 (±13.1)	NS
Mean LV diameter on diastole (SD), mm	56.6 (±7.3)	56.1 (±9.9)	0.057	55.6 (±3.4)	51.4 (±5.8)	NS
Mean LV mass (SD), g	236.0 (±101.5)	219.6 (±70.5)	NS	197.9 (±24.2)	191.4 (±41.4)	NS
Mean aorta diameter (SD), mm	35.2 (±4.8)	34.0 (±5.3)	NS	32.7 (±4.0)	28.6 (±5.0)	**0.048**
Mean LA diameter (SD), mm	45.8 (±8.5)	48.4 (±10.3)	NS	42.9 (±5.9)	43.0 (±5.3)	NS
Mean IVS thickness (SD), mm	11.7 (±2.0)	11.4 (±2.0)	NS	10.5 (±1.4)	11.2 (±2.6)	NS
Mean PW thickness (SD), mm	9.8 (±1.8)	9.9 (±0.8)	NS	9.1 (±1.4)	9.7 (±2.3)	NS

IVS – intraventricular septum; LA – left atrium; LV – Left ventricle; LVEF – left ventricle ejection fraction; MR – mitral regurgitation; PW – posterior wall; sPAP – systolic pulmonary systemic pressure; NS – non significant. *Wilcoxon test

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