REVIEW ARTICLE

Mitral annuloplasty in the era of "ringless" MitraClip: All cats are grey in the dark

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Mitral valve repair plays a fundamental role in surgical treatment for mitral regurgitation. Regardless the type of approach or surgical technique, annuloplasty ring is an absolutely must in mitral valve repair. The annuloplasty ring forces leaflet coaptation, stabilizes the repair. Edge-to-edge mitral valve repair is a simple surgical technique to fix complex situations. However, annuloplasty ring is always needed here as well. In fact, the lack of annuloplasty by means of a prosthetic ring has been identified as one of the most powerful predictors for failure after mital valve repair. MitraClip therapy is the percutaneous equivalent to the edge-to-edge surgical mitral valve repair. Inability to safely place a ring by catheter-based techniques is the weak side of the percutaneous approach for mitral valve repair in mitral valve regurgitation. Theoretically, the lack of an annuloplasty ring allows future mitral annulus dilatation as well as stress forces to break out leaflet tissue around the MitraClip device. Up to now, there is no serious study analyzing both, MitraClip and annuloplasty ring in cases for percutaneous approach. Current running studies about MitraClip are focused only in functional mitral regurgitation comparing against medical therapy. Unfortunately, there are no well-standardized and complete trials (MitraClip and percutaneous annuloplasty at once) focused on primary disease. We are comparing apples with oranges, with no possibility to get real conclusions regarding the lack of annuloplasty ring in the era of MitraClip therapy. All cats are grey in the dark. Finally, like it or not, all roads lead to Rome, to the same point.

Key words: **Mitral valve; Mitral regurgitation; Mitral valve repair; MitraClip; Prosthetic annuloplasty ring**

La reparación valvular mitral juega un papel importante en el tratamiento quirúrgico para la reparación mitral. Independientemente del tipo de abordaje ó técnica quirúrgica, la anuloplastía con anillo es imprescindible. El anillo de anuloplastía fuerza la coaptación de las valvas, y estabiliza la reparación. La reparación mitral edge-to-edge es una técnica quirúrgica simple para solucionar situaciones complejas. Sin embargo, aún en esta técnica, también se necesita el anillo de anuloplastía. De hecho, la falta de anuloplastía con anillo protésico se ha identificado como uno de los predictores más potentes para falla después de la reparación valvular mitral. La terapia MitraClip es el equivamente percutáneo de la reparación mitral edge-to-edge quirúrgica. La incapacidad para colocar con seguridad un anillo mediante técnicas con catéter es el lado débil del abordaje percutáneo para la reparación mitral en los casos de regurgitación mitral. Teóricamente, la falta de anuloplastía con anillo permite la redilatación anular nativa en el futuro, así como también que las fuerzas de estrés rompan el tejido de las valvas alrededor del MitraClip. Los estudios actuales que se encuentran en desarrollo sobre MitraClip se centran sólo en la regurgitación mitral funcional en comparación con la terapia médica. Desafortunadamente, hasta la fecha, no existen ensayos bien estandarizados y completos (MitraClip y anuloplastía percutáneos a la vez) enfocados en la enfermedad primaria. Estamos comparando manzanas con naranjas, sin posibilidad de obtener conclusiones reales con respecto a la falta de anuloplastía con anillo en la era de la terapia MitraClip. En la obscuridad, todos los gatos son grises. Finalmente, nos guste o no, todos los caminos conducen a Roma, al mismo lugar.

Palabras clave: **Válvula Mitral; Regurgitación mitral; Reparación valvular mitral; MitraClip; Anillo protésico para anuloplasía**

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The most important concept in mitral valve (MV) repair is "remodelling on a frame". It means working with and including as a part of any MV repair a prosthetic annuloplasty ring [1]. This concept was introduced for the first time in a systematic way by Carpentier [2], giving rise to the very well-known called "French Correction" [3]. The armamentarium regarding the surgical techniques in order to get good outcomes is very extensive. Type II MV regurgitation is almost the rule in degenerative MV disease. Excesive

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motion of one or both leaflets is the common finding here. Coming to this point, it is worth saying that, as far as MV repair concerned, there are two basic principles that must not be overlooked in any way, generally speaking, viz, i) anterior leaflet prolapse is mainly handled by PTFE neo-chords plus annuloplasty ring; ii) posterior leaflet prolapse is better addressed by quadrangular resection, direct gap closure plus annuloplasty ring [4].

Capital concept playing a critical role is the annuloplasty by means of using a prosthetic ring [1,2]. This "remodelling" forces the leaflet coaptation. So, coaptation surface becomes larger. Durability of the MV repair is directly related to the annuloplasty ring usage [5,6]. The larger the coaptation surface, the longer the duration in MV repair. Indeed, the lack of annuloplasty ring has been identified as one of the most important independent risk factor for faiulre after MV repair. Edge-to-edge repair is not the exception to this rule [7-10].

MitraClip therapy (Abbott Vascular, IL, USA) is the percutaneous approach of performing the edge-to-edge MV repair. However, this device only addresses the leaflet component. Several devices have served this purpose [11-13]. Nevertheless, results have been not as encouraging.

The purpose if this review is to make clear how much the lack of the annuloplasty ring affects the long-term durability of the MitraClip therapy in the real world, regardless the type of patient being treated by this method.

The facts about mitral valve repair/annuloplasty ring

MV regurgitation is classified according to Carpentier's functional classification [2], namely, i) Type I (normal leaflet motion), ii) Type II (excesive leaflet motion), and iii) Type III (restrictive leaflet motion) which in turn can be IIIa (to diastole) or IIIb (to systole) (**Fig. 1**).

A very full and ambitious description with regard to these surgical techniques have been described by Carpentier et al. [14]. Talking about Type II of MV regurgitation (as mainly seen in degenerative MV regurgitation), the core of all this set of techniques can be summarized in two main well-standardized kind of procedures. For anterior leaflet prolapse, PTFE neo-chords plus annuloplasty ring is preferred. For posteror leaflet prolapse, quadrangular resection and direct gap closure plus annuloplasty ring is the best choice. The common ground in both techniques is the annuloplasty with a prosthetic ring. Several authors have demonstrated that the lack of annuloplasty ring is one of the most important predictors for failure after MV repair [5,6].

Using an annuloplasty ring is not so inoccuous. There are so many useful tips in order to get the best results after placing a prosthetic ring. However, surgeon must know all the tricks of the trade before intending. A simple example about that is the way of choosing the size of the ring [14]. The most apropriate way to do that is dependent not only the intertrigonal distance, but on the height of the anterior leaflet. Moreover, the ultimate size of the ring depends on how much the anterior leaflet protrudes beyond the inferior border of the sizer. In an effort to go into a bit more detail about it, if the anterior leaflet does not protrude anything over the inferior border of the sizer, we choose the same number as the intertrigonal distance (for example 32 mm); if it does protrude but no more than 5 mm, we choose the next higher one (34 mm); if it does protrude more than 5 mm, we choose a Carpentier´s classic ring anteriorly opened, so we can get even more exposition by opening this anterior section. The way of placing each of the sutures in order to anchor the ring is extremely so specific as well [14]. Basically, these two techniques to handle the mitral leaflets we described above are well-standardized. Nothing is improvised. The less you improvise, the greater the success rate.

Edge-to-edge surgical MV repair and MitraClip therapy

Edge-to-edge MV repair was first used and described by Alfieri et al [7]. This is a simple technique for complex situations. This is an excellent technique for difficult cases in which surgical situation is not the best; viz, inadequate surgical exposure, very low left ventricle ejection fraction, calcified native annulus of the MV, amongst many others. In this technique, one or several stitches are placed face-to-face in both mitral leaflets in order to tie them. There are two modalities: double-orifice technique (central stitch), and paracommissural technique [15]. The percutaneous approach to perform the edge-to-edge MV reapir is called MitraClip therapy. The first percutaneous mitral repair procedures using the MitraClip device were done in 2003. MitraClip received CE mark approval in Europe in 2008 and was approved by the U.S. FDA in 2013 for use in patients with degenerative MR, who are at prohibitive risk for conventional mitral valve surgery [16]. However, FDA obligated the company to run post-marketing studies to confirm the safety and efficacy of the device. It is worth highlighting that the sole and only authorisation for MitraClip therapy in USA was given exclusively for such cases with extremely high surgical risk with primary degenerative MV regurgitation [17]. In such a way that there is not any reason to use this device in cases other than primary disease.

Ringless MitraClip therapy: The inability to place a true ring

The main criticism about MitraClip therapy is that there is a lack of a complete technique in order to repair the MV. Percutaneous approach just addresses the leaflet component but not the annular one. In other words, the behavior pattern of the MV regurgitation is exactly the same, regadless the approach. It does not change. Working merely on the mitral leaflets is not sufficient to correct nor prevent MV regurgitation at an enough long follow-up. As we previously cited, several authors have demostrated that the lack of annuloplasty ring is one of the most (if not the most) predictors for failure after MV repair [5,6]. The same concept must be kept in mind when choosing MitraClip therapy for a given case. I would like to make very clear the concept about "ringless" MitraClip therapy. Certainly, annuloplasty ring has not been widely

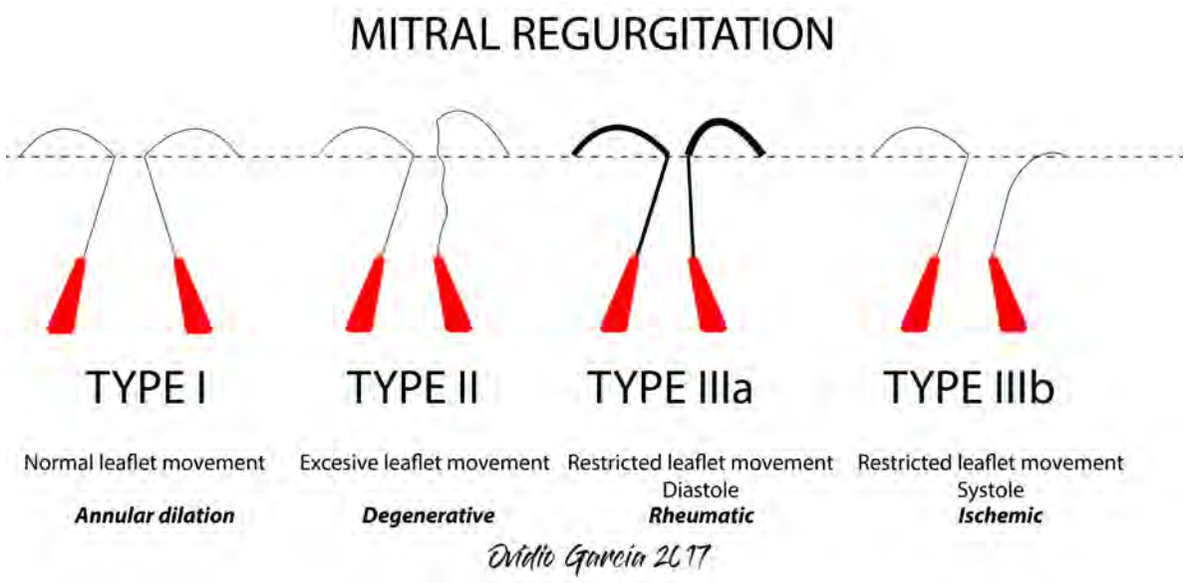

Figura 2. Functional classification by Carpentier, based on the mitral valve leaflets motion [2].

used in percutaneous approach because it is very difficult to get adequate results in most cases. So, the main reason for this lack of annuloplasty ring in MitraClip therapy is for technical reasones. Some truly creative attempts have been invented, as placing the device into the coronary sinus, called Carrillon system (Carrillon® Mitral Contour System® Model XE2; Cardiac Dimensions., Kirkland, WA, USA) [11,12]. This implies several disadvantages, like circumflex coronary artery compression near P1. Circumflexe artery lies between the coronary sinus and the MV annulus in 86% of the cases [18]. Maselli et al. [19] have found out that main circumflex artery, or its branches were located between coronary sinus and MV annulus in 16.4% and 63.9% of cases, respectively.

Cardioband (Valtech Cardio, Or Yehuda, Israel) has been developed as an alterntive device for percutaneous MV repair which functions as a percutaneous annuloplasty band. When analyzing the outcome with Cardioband, Nickening et al. [13] found that at 6 months follow-up, moderate MR in 31.8%, and severe MR in 13.6%. In a stand close scrutiny, just 54.6% were free from any important degree of recidivant/resudual MV regurgitation at 6 months. At glance, results seem not to be extraordinary good. However, once again, we have to wait for better, stronger results at an enough long follow-up.

I would like to empashize that at the beginning, before Carpentier's era, MV repair was harshly criticised because of poor consistent results. It has become strongly evident that annuloplasty ring turned out to be the central part, the fundamental key of all these surgical procedures [2]. So, we have to call a spade a spade: annuloplasty ring is an absoulte must in the course of any edge-to-edge MV repair, beyond and regadless the type of approaching.

How about we avoid using the annuloplasty ring?

After analyzing all this above, speaking about edge-to-edge MV repair, the question that really leaps out is how much does the lack of annuloplasty ring affect the true outcome in these kind of primary cases having degenerative MV regurgitation, at an enough long follow-up. In this regard, Alfieri et al. [7] found that at five years, there was a statistically significant difference between placing or not an annuloplasty ring after edge-to-edge MV repair. De Bonis et al. [8] have clearly established that, when initial residual MV regurgitation after operation is ≤ 1+ (only 52.1%) at hospital discharge, without annuloplasty ring, freedom from MR ≥ 3+ is 80% at 5 years, but decreasing up to 50% at 12 years. The same working group, in another study found that when annuloplasty is missed, the freedom from MR ≥3 only 39.7% at 12.5 years [9]. There is no reason to believe things could turn out to be different because of changing just the approach for this kind of cases. The approach for MV repair being percutaneous or surgical has nothing whatsoever to do in respect thereof.

The reality

When comparing surgery versus percutaneous approach, freedom from ≥ 3+ MV regurgitation at 4 years is 92 ± 3% vs 68.7% ± 7% (p = 0.002), respectively. In fact, the use of MitraClip turned out to be the most powerful predictor for recurrent ≥3+ MV regurgitation, in both univariate and multiuvariate analyses [HR: 4.4 and 6.1, respectively] [10]. In another study, analyzing the same issue, 94 ± 3.3% vs 75 ± 7.6%, respectively, in favor of surgical procedure. Multivariate analysis identified the use of MitraClip as an independent predictor of recurrence of ≥ 2+ MV regurgitation [Hazard ra-

tio (HR): 2.1, 95% confidence interval (CI): 1.1-3.9, P = 0.02] [20]. In a metaanalysis, Tagaki et al. [21] confirmed that, taking into consideration the recurrent ≥ 3+ MV regurgitation after surgical vs percutaneous edge-to-edge MV repair, the evidence is in favor of using surgical approach (HR= 4.8; 2.58-8.9, 95%CI). Looking for the same issue, but now considering freedom from recurrent ≥2+ MV regurgitation, HR increased up to 20.72 (4.91-87.44, 95%CI) (p< 0.001) being surgery quite superior than MitraClip therapy alone [22].

Analyzing the EVEREST II trial, Feldman et al. [23] have come to the conclusion that even when surgery is better than MitraClip therapy regarding freedom from ≥3+ MV regurgitation at 1 year, evolution from MitraClip patients seems to be good with no additional risk at four years follow-up.

In cardiac surgery, a word is enough to the wise. So, much ado about nothing. These findings couldn't be reproduced by De Bonis et al. Previous observations reported in the Everest II randomized controlled trial indicated that, if the MitraClip therapy was initially successful, the results were sustained at 4 years. In addition, when compared with the surgical edge-to-edge combined with annuloplasty, MitraClip therapy provides a much lower efficacy at 4 years [24].

The heart of the matter with MitraClip therapy

The true heart of the matter about the questionable durability of MitraClip therapy at a truly long enough follow-up has been identified by Votta, et al. [25]. In normal conditions, native MV annulus dilates on diastole increasing size for an adequate ventricular filling. In somehow or other, annuloplasty ring can avoid this dilation. In addition, a 20% dilation of the annulus was found to increase stresses both in the annular region and close to the edge-to-edge suture. And this is the turning point. If no annuloplasty ring is added to the MitraClip, theoretically, stress forces will end up breaking the leaflet tissue around the MitraClip device.

Trials running and comming soon

Some of the trials still running in order to study the effect of MitraClip in funcitonal MV regurgitation are, COAPT, RESHAPE-HF2, MITRA-FR, MATTERHORN, to name but a few [26]. Of all of them, only the last one presents comparison against a control group of MV repair. And to top it all off, only the first one exhibits an enough long-term follow-up at five years. Once again, speaking about surgery, we are comparing apples with oranges. Exception for MATTERHORN, we cannot get strong conclusions about the real effect of the MitraClip teraphy because the argument to compare with is medical treatment instead of surgery. It is clear that the primary goal of this kind of therapy is to treat a very special pool of severe ill high-risk surgical patients, with no other option beyond medical therapy. Nevertheless, we are facing on a dilemma. We are getting lost in the dark. The central core of all this discussion above is the efficacy of the MitraClip therapy without annuloplasty ring. Contrarily, what we are seeing here is a comparison between two groups where ventricular disease is conducting the orchestra. So, the main objective to compare once and for all in a full way how effective is the ringless MitraClip therapy in MV regurgitation it will reiamn unclear. Nevertheless, this does not mean that we should neglect our commitment to understand what about ringless MitraClip therapy. At least one arm of the trials designed for surgery might be extremely useful in order to get stronger conclusions than currently.

Conclusions

Now, after all this gathered information, I make no bones about it: until now, there is no evidence coming from any serious study using both, MitraClip as well as annuloplasty band/ring at once through percutaneous approach, indicating the true long-term durability of the MV repair in degenerative MV regurgitation as a primary disease.

We have been giving the benefit of the doubt. However, experience is the mother of knowledge. We have come a long way in surgery. In turn, there is still a long way to go in catheter based techniques for MV repair. No changes are allowed. All that glitters is not gold. All cats are grey in the dark. Finally, all roads lead to Rome, to the same point.

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