EXPERT OPINION

Are the percutaneous techniques well enough to approach the Secondary Mitral Valve Regurgitation? Getting to the heart of it.

Nosce te ipsum

Ovidio A. García-Villarreal, MD.

Consultant in Cardiac Surgery. Monterrey, Nuevo León, MÉXICO.

Mitral valve repair has dramatically evolved over the years every since its inception from the "French Correction" by Alain F. Carpentier. The Golden rule inside this one is always working on a frame by means of a prosthetic annuloplasty ring, regardless the specific chosen technique. MitraClip is an excellent tool when correctly indicated, especially in desperate cases out of surgical treatment because a prohibitive high-risk operative mortality. However, it is still very limited since it is a ringless therapy. There are two main peaks for failure after operation when ringless condition is present; namely, at 5 years and 12 years. It's really astonishing how this of paramount significance fact has been ignored by cardiologists. This is why COAPT trial analysis at 2 years turned out to be favorable. Plain and simple!

***Key words*: MitraClip; Mitral valve; Mitral valve regurgitation, funcional; Mitral valve regurgitation, secondary; Mitral valve repair, percutaneous approach.**

La reparación valvular mitral ha evolucionado dramáticamente desde su nacimiento a partir de la "Corrección Francesa" descrita por Alain F. Carpentier. La Regla de Oro aquí es siempre trabajar sobre un marco de remodelación por medio de un anillo protésico para anuloplastía, más allá de la técnica específica empleada. El MitraClip es una excelente opción cuando está correctamente indicado, especialmente in casos desesperados con una alta mortalidad operatoria prohibitiva. Sin embargo, ésta es una terapia limitada debido a que no utiliza ningún anillo protésico. Bajo estas circunstancias, existen dos picos principales de falla posterior a la ciugía cuando no se ha utilizado anillo alguno de valvuolplastía; a saber, a 5 años y a 12 años postoperatorios. Es verdaderamente sorprendente cómo este trascendental hecho ha sido ignorado por los cardiólogos. Esta es la razón por la cual el análisis a 2 años del el estudio COAPT resultó ser favorable. Así de simple!

***Palabras clave:* MitraClip; Válvula mitral; Regurgitación de la válvula mitral, funcional; Regurgitación de la válvula mitral, secundaria; Reparación valvular mitral, abordaje percutáneo.**

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At first, everything was perfect…

In order to understand all concepts regarding the mitral valve repair, we have to go all the way back to the sixties years when Carpentier published for the first time his results in mitral valve repair using a consistent and well-designed surgical technique [1], afterwards worldwide released in 1971[2]. All these preliminary considerations set the stage and laid the foundation for the well-known and flawless "French Correction" for the mitral valve repair [3]. With this wide range armamentarium of surgical techniques, the central core and fundamental part is working on a frame by using a prosthetic annuloplasty ring. This last one remodels the native orifice (preserving the 3:4 ratio –anteroposterior:transversal diameters) while increasing the coaptation surface of both leaflet [3]. This is the key of any mitral valve repair, regardless the specific and selected chosen technique (**Fig. 1**).

Corresponding author: Dr. Ovidio A. García-Villarreal
email: ovidiocardiotor@gmail.com

Where does the MitraClip therapy come from?

After analyzing one case of native double mitral orifice, Ottavio Alfieri figured out and introduced his technique in April 25, 1991 [4]. At first glance, it seems to be a simple technique for complex situations. A strategic stitch is placed joining both mitral leaflets at the point where the prolapse is located. Thus, this can turn out to be a central stitch or a paracommissural stitch. Or put in other way, "double-orifice edge-to-edge" repair (**Fig. 2A**) and "paracommissural edge-to-edge" repair (**Fig. 2B**), respectively [5]. Nevertheless,

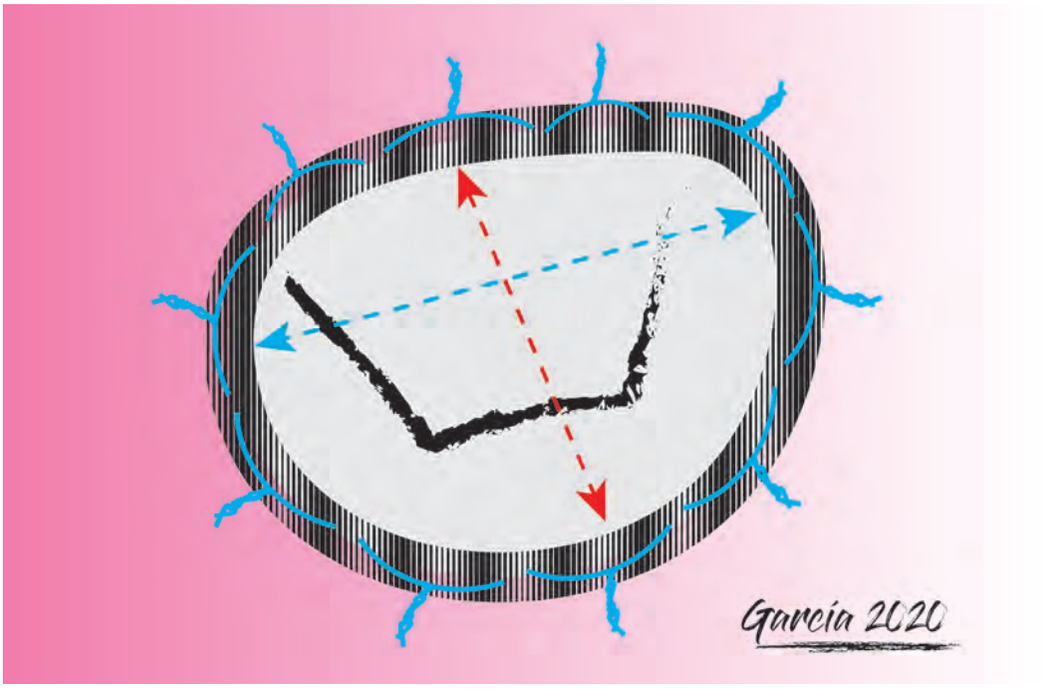

Figure 1. Schematic representation of a prosthetic annuloplasty ring once in placement. The Golden rule in mitral valve repair. Of note, the cricual idea, as it can be shown here, is the remodeling on a frame while preserving the 3:4 relation between anteroposterior diameter (blue line):transversal diameter (red line) of the mitral valve.

over the years, the first and most important condition came into the open. The most powerful predictor for failure after the "edge-to-edge" repair or Alfieri's stitch is the lack of a prosthetic annuloplasty ring. Alfieri et al. have identified the first peak for failure at 5-years of follow-up [6]. Some attempts have been done pointing towards specifically avoiding the use of any prosthetic ring. However, all attempts have been unsuccessful. The second and most important one was at 12 years after operation [6]. De Bonis et al. have clearly demonstrated that without annuloplasty ring, freedom from MR ≥ 3+ is 80% at 5 years, but decreasing up to 50% at 12 years [7]. This same working group has showed this second peak for failure after 12 years. They found that when annuloplasty is missed out, the freedom from MR ≥3 was only 39.7% at 12.5 years [8]. Therefore, making a long story short, we can clearly indetify two main peaks over the time for failure after a ringless "edge-to-edge" MV repair. Viz, the first one at 5 years follow-up, and the second and most important one is at 12 years follow-up. This is the main reason why we have to wait sufficient time before making assumptions

Things do not change: mitral annuloplasty ring remains as the Golden rule

One fact we always bear in mind is that the MitraClip therapy arrived from Alfieri's stitch concept. Plain and simple! There is no reason to believe things could turn out to be different by changing just the approach. The approach for MV repair being percutaneous or surgical has nothing whatsoever to do in respect thereof. The absolute presence of a prosthetic ring to perform a true annuloplasty remains as the Golden rule in any MV repair [9].

What about the MitraClip?

The MitraClip was designed to percutaneaously approach some specific types of mitral valve regurgitation. Firstly focused on primary mitral valve regurgitation (degenerative etiology with Carpentier's Type II) out of surgery because of a prohibitive high-risk operative mortality, it reached the target throughout the Everest II trial [10]. Even when MitraClip was safer, long-term results were much better with open surgery.

Nevertheless, with secondary mitral valve regurgitation, things can turn out to be much more demanding and complicated. Carpentier's Type IIIb is not about any prolapse but tethering segment (usually located on the interscallop between P2-P3). As a matter of fact, this kind of MV regurgitation is surgically approached in a different way than the classic Type II (prolapse). In 1995, Steve Bolling proposed the concept of the "restrictive annuloplasty" in order to reduce and tackle this condition. By downsizing one or two sizes the original measurement of the native mitral annulus, a more than perfect coaptation is almost always obtained [11,12]. Of note, once again the golden rule is the prosthetic annuloplasty ring. We will lay aside all the other more complex techniques for the secondary or functional MV regurgitation, such as papillary muscle cinching, leafleat augmentation, among many others because this is not the scope of this manuscript.

Heart failure is present in approximately 5 million of American people. Half of them have low ejection fraction, of which at least half have some degree of secondary (functional) MV regurgitation [13]. In first place it was designed for this specific purposes the MITRA-FR trial comparing MitraClip plus medical management versus only medical therapy.

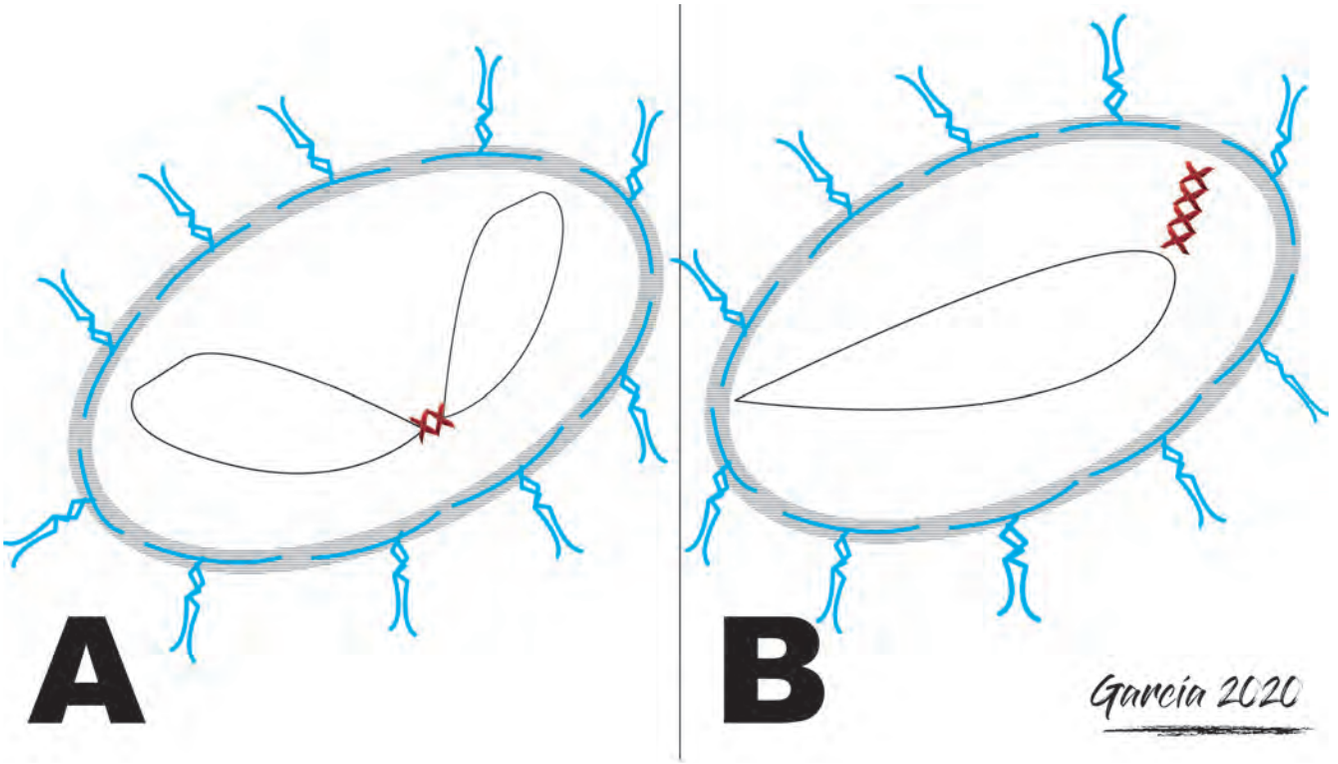

Figure 2. *Two main types of Alfieri's stitch technique. (A) Double-orifice edge-to-edge" repair, and (B) paracommissural edge-to-edge repair. A very important and remarkable facts is always preserving ≥ 2.5 cm² of mitral valve area, regardless the type of Alfieri's stitch. A prosthetic annuloplasty ring is always present.*

Negative results were obtained at 1-year follow-up, 54.6% versus 51.3%, for MitraClip plus medical management versus only medical therapy, respectively (OR 1.16, 95% CI [0.73 to 1.84], p=0.53) [14].

Then, the COAPT trial was designed. With a too stringent and demanding protocol, this trial was reported in 2018 [15]. The first results are now coming into the open. Hospitalization rate for heart failure within 24 months was 35.8% per patient-year for MitraClip plus medical therapy while 67.9% per patient-year for patients only with medical therapy (hazard ratio, 0.53; 95% CI, 0.40 to 0.70; P<0.001). Death from any cause within 24 months was 29.1% against 46.1%, respectively (hazard ratio, 0.62; 95% CI, 0.46 to 0.82; P<0.001) [16]. Primary and secondary end point effectiveness were both attained. Certainly, some other echocardiographic values such as LVESV and LVEDV did not improve over time, but keep increasing. However, they were better for MitraClip plus medical management than medical therapy alone. LVEF reduction was less for MitraClip group than the other one [17].

A horse of a different color…

However, in stark contrast with the golden rule for any surgical MV repair, all this kind of trials are missing the concept of the annuloplasty on a frame with a prosthetic ring. MITRA-FR failed out presumptively because a too weak and relaxed protocol as well as the shortage of the follow-up [18]. COAPT trial has proven apparently good outcomes. Nonetheless, we cannot get lost in the timeframe this trial has been run no longer than 2 years [16]. In the light of the foregoing and understanding that only a comprehensive analysis for longer can be useful by identifying the risk of lacking a prosthetic annuloplasty ring, I wouldn't claim victory so quickly. Going beyond 5-years of follow-up is the most appropriate way to show the true results for ringless MitraClip therapies.

What's the solution then?

Cardioband and some other kind of devices for percutaneous annuloplasty might be the big solution [19]. Of course, we still do not have any sufficient long randomized control trial to be able to conclude this concerning fact. Nonetheless, when making some special comparisons between both devices for functional MV regurgitation, the results seem to support our take. Indeed, all-cause rehospitalisation and mortality within 12 months were lower in Cardioband patients than MitraClip (mortality: OR 0.30, CI: 0.09-0.98, p=0.032; rehospitalisation: OR 0.57, CI: 0.28-0.97, p=0.03) [20]. By adding the Cardioband to the MitraClip seems to be the big-time gig. However, some other concepts begin to arise. The preservation of a true functional MV area (larger than 2.5 cm2) would seem to be the most worrying issue here.

Another challenging issue is the type of ring used for Cardioband. It is a well-known fact that the best results in surgical approach for restrictive annuloplasty are obtained by using a complete ring instead of a partial ring as Cardioband [19].

Getting the hang on it…

Suddenly, the main objective of MitraClip therapy, which is to improve the quality of life of patients with secondary MV regurgitation, has been lost sight of. This is a ventricular disease that yields through the MV by insufficiency. This is a matter of time in all meanings, both actually and figuratively. Five years will be the first hurdle to overcome, let alone about 12 years of follow-up after operation.

There is no question that the key challenge is how to harness knowledge for development. All facts listed above, all of them are high value conditions, with special remark on using a prosthetic annuloplasty ring as the core part of any mitral (or tricuspid) valve repair. Nevertheless, they often require specialist expertise to harness the full potential. We still can go over options. Otherwise, it would be a useless utter nonsense. And as a final outcome, in all likelihood, we will pay the price in the coming times.

As a way of conclusion, are we really ready for the big challenge? I'd rather think twice before clamming any victory.

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