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REVIEW

Novel Therapeutic Concepts

Percutaneous tricuspid valve therapies: the new frontier

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Moderate-to-severe tricuspid regurgitation (TR) affects ~1.6 million patients in the USA, of whom only 8000 undergo tricuspid surgery annually; this results in an extremely large number of untreated patients with significant TR. Therefore, there is a large unmet clinical need for patients with severe TR who are not referred for conventional surgery, mainly due to expected high surgical risk. Percutaneous procedures are an attractive alternative to surgery for patients deemed to be high-risk surgical candidates. Whereas over the past few years, the development and clinical use of percutaneous approaches to the aortic valve and mitral valve have been widespread, few data are available about the feasibility and the efficacy of the percutaneous tricuspid valve treatment. This review will explore the available technologies, which are today under evaluation and the preliminary clinical results.

Keywords Functional tricuspid regurgitation • Transcatheter tricuspid therapy • Tricuspid valve

Introduction

Surgical avoidance of tricuspid valve (TV) repair was for many year easily accepted in patients with functional tricuspid regurgitation (FTR) secondary to left heart disease (LHD), on the basis of the incorrect concept that tricuspid regurgitation (TR) would disappear once the primary LHD had been treated. Over the past few years, many investigators reported evidence in favour of a more aggressive surgical approach to FTR, and the most recent guidelines recommend surgical repair of concomitant TR during left valve surgery also in patients with tricuspid annular dilatation with non-severe TR.[1,2]

Although acceptable results have been reported,[3] in case of TR recurrence after left heart surgery TV surgery is usually carried out with very high morbidity and mortality (up to 25% in some series).[4,5] This largely depends on the fact that typically these patients are managed medically for a long time and they are referred to surgery only when they develop severe incapacitating symptoms of right heart failure and organ dysfunction.

Currently, moderate-to-severe TR affects ~1.6 million patients in the USA, of whom only 8000 undergo tricuspid surgery annually[6]; this results in an extremely large number of untreated patients with significant TR.

Percutaneous procedures are an attractive alternative to surgery for patients deemed to be high-risk surgical candidates.[7] Different tricuspid transcatheter devices have been developed to treat FTR, which represents the most frequent aetiology of TR, while the most of them are not appropriate for organic TR, such as leaflet flail or prolapse, rheumatic disease, carcinoid disease, or endocarditis.

However, it is important to underline that clinical and pre-clinical experiences with transcatheter TV therapies are at this stage very preliminary and only very few data are available to support any evidence of clinical efficacy.

This review will explore the available technologies, which are today under evaluation and the preliminary clinical results. To ensure that the clinical information was as current as possible, presentations from the most recent and important international interventional cardiology meetings were also considered (www.tctmd.com, www.pcronline.com).

Tricuspid valve anatomy

A detailed knowledge of the complex surgical anatomy of the TV is fundamental, in order to understand the several challenges which are encountered in developing percutaneous tricuspid therapy.

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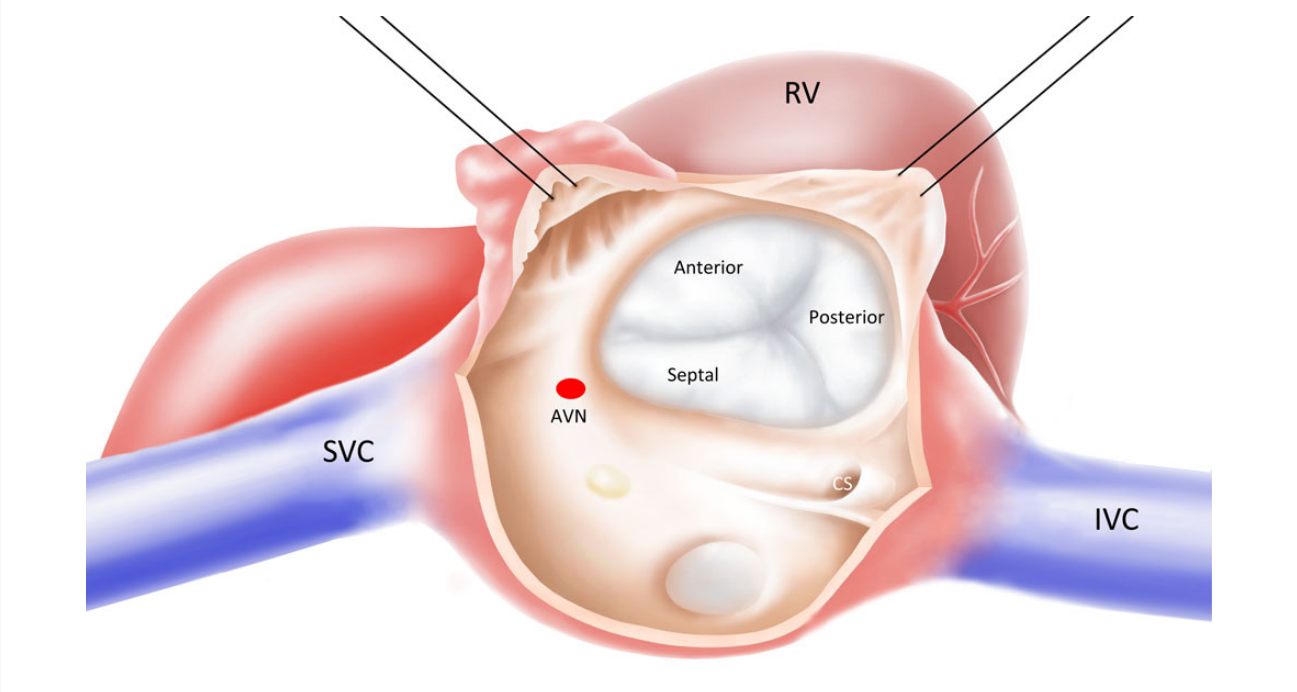

Figure 1 Surgical anatomy of the tricuspid valve. RV, right ventricle; CS, coronary sinus; AVN, atrioventricular node; SVC, superior vena cava; IVC, inferior vena cava.

The TV apparatus (*Figure 1*) consists normally of three leaflets (septal, posterior, and anterior), chordae tendineae, and usually three papillary muscles. Several structures of major surgical importance surround the TV, such as the atrioventricular (AV) node, the bundle of His, and the coronary sinus.

Differently from the mitral valve, it is more difficult to define a 'fibrous' tricuspid annulus along the line of attachment of the leaflets, although it remains identifiable. The parietal attachment of the TV is encircled by the right coronary artery, which is very often in close contiguity.

Since the right ventricle (RV) is wrapped around the left ventricle, the physiological shape of the tricuspid orifice is semilunar. Compared with the mitral, the tricuspid orifice is larger. In physiologic conditions, the tricuspid annulus has a non-planar three-dimensional configuration, which is lost in pathological conditions.[8] The non-planar and non-circular structure of the tricuspid annulus must be taken into account when considering tricuspid repair.

Mechanism of tricuspid regurgitation

The aetiology underlying TR is functional in >90% of the cases, typically due to RV dilation and dysfunction from LHD. The development of FTR is conventionally classified in three progressive stages of the disease[9] (*Figure 2*).

Stage 1: initial annular dilatation

Functional tricuspid regurgitation is invariably associated to tricuspid annular dilatation secondary to RV enlargement. In the first phase of the disease tricuspid annulus is dilated but the degree of TR is not severe yet.

Stage 2: progressive annular dilatation leads to the lack of leaflets coaptation

Progressive TV annulus enlargement prevents normal leaflet coaptation. Dilatation of the tricuspid annulus is not symmetric, since it occurs mainly in its anterior and posterior segments, which corresponds to the free wall of the RV.[10] In this phase, FTR severity become significant and there is initial RV dilatation.

Stage 3: right ventricle dilatation and dysfunction, tricuspid valve tethering

The consequence of severe FTR is progressive RV dilatation and dysfunction. Progressive RV dilatation causes papillary muscles displacement and consequent leaflets tethering. Usually, significant pulmonary hypertension is present at this stage.

Prevalence and prognostic impact of functional tricuspid regurgitation: the clinical need

About 50% of patients with mitral valve regurgitation have concomitant TR, and a consistent number of them will develop significant FTR following left-sided valve surgery (up to 40%).[11,12]

Functional TR is also frequently associated with functional MR. After mitral valve replacement, close to 50% of patients develop significant TR and its prevalence increases with time.[13] Moreover, in patients with less than severe TR, TR might progress after surgery if the TV is left untreated. Matsuyama *et al.* reported significant TR (at least grade 3) on echocardiography performed late after MVR, in 37% of the patients with grade 2 + TR before surgery.[14]

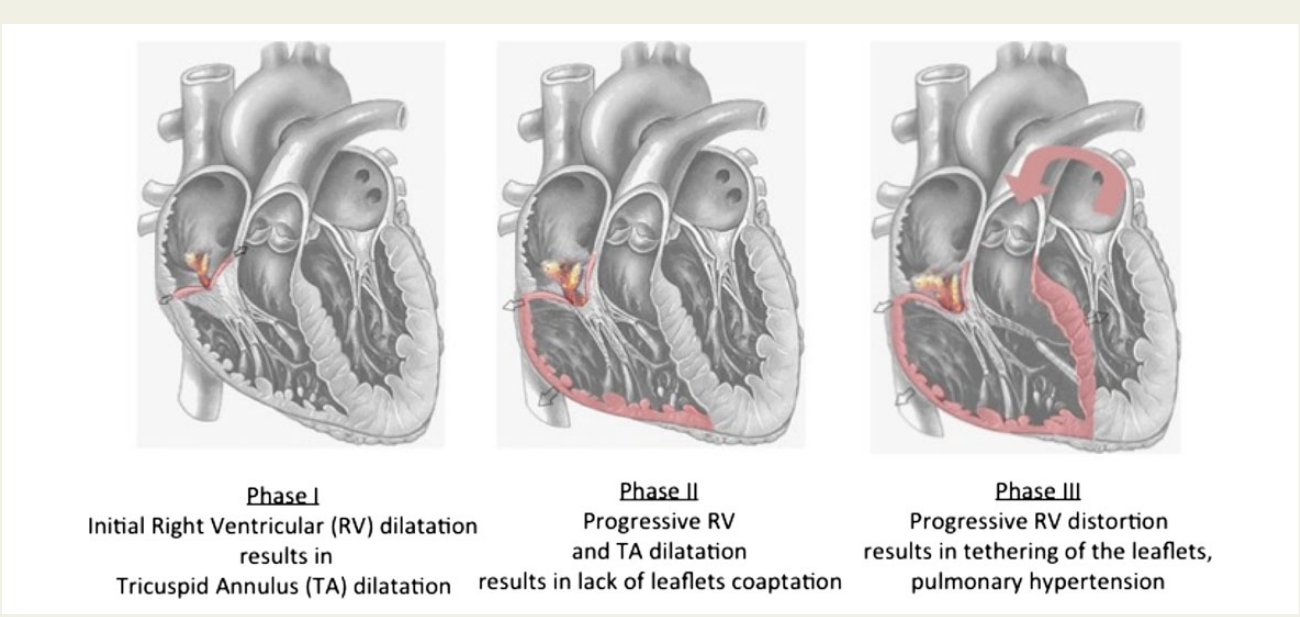

Figure 2 Pathophysiology of functional tricuspid regurgitation.

The presence of significant TR has a negative prognostic impact on survival and is independently associated with a 1.5- to 2-fold increased risk of cardiovascular events. Similarly, the late development of FTR after left-sided valve surgery is also associated with reduced survival.[15]

The consequence of these observations is that there is a large number of patients that could potentially benefit from a less invasive transcatheter TV therapy.

Standard surgical treatment

The standard surgical treatment of FTR is tricuspid annuloplasty. The rational behind annuloplasty is to fix the annular dimensions, to force the leaflets coaptation reducing the anteroseptal diameter of the TV and counteracting further annular dilatation. Long-term studies have suggested that repair with a prosthetic ring is more durable than suture repair techniques, with a freedom from recurrent TR of ~85% 10 years after surgery.[16,17]

Percutaneous tricuspid devices and preliminary results

Some of the concepts that have been developed for the percutaneous treatment of mitral regurgitation may be adapted to percutaneous repair of the TV, such as the percutaneous annuloplasty approach (*Table 1*). However, anatomical diversity between the two AV valves makes a direct translation of a mitral into a tricuspid application improbable.

Transcatheter tricuspid annuloplasty

The experiences with percutaneous TV therapies are very preliminary. While different approaches have been tested in pre-clinical setting, one of the most promising concept in this field seem to be the annuloplasty concept, since it addresses annular dilatation by reducing the anteroseptal distance. Different annuloplasty devices are under pre-clinical and clinical evaluation.

Mitralign system

The Mitralign device (Mitralign, Inc. Tewksbury, USA), which was originally designed for the treatment of functional mitral regurgitation,[18] has recently been used to treat FTR performing a transcatheter bicuspidization of the TV though transvenous jugular approach.[19] A steerable catheter is advanced in the RV across the TV and positioned under echocardiographic guidance. An insulated radiofrequency wire is then advanced from the base of the leaflet and within the annulus, directed toward the right atrium (RA) in the desired position in correspondence of the anteroposterior commissure. Once the wire is through the annulus, a pledget delivery catheter is advanced over the wire from the RA across the annulus to the RV (*Figure 3A*). The steps are then repeated on the opposite anatomic site of the posterior commissure. A dedicated plication lock device is used to bring the two pledgeted sutures together, plicating the annulus and effectively bicuspidizing the TV (*Figure 3B*). Preliminary results obtained in seven high-risk patients with symptomatic FTR have been reported. Implant was feasible in 5/7 patients with no reported adverse events. Tricuspid annular dimension was observed in all the implanted patients, with an acute reduction of TR in 4/5 patients (Groothuis A. Direct annuloplasty for the treatment of TR. Paris, EuroPCR 2015). In particular, in the first case performed, a 57% reduction in annular area (from 14.1 to 6.05 cm^2) and a 53% reduction in effective regurgitant orifice area (1.35–0.62 cm^2) were documented. Right atrial pressure decreased from 22 to 9 mmHg and the left ventricular stroke volume improved from 42 to 72 mL.[19]

Table 1 Summary of the different transcatheter tricuspid therapies

	Pro	Cons
Mitralign system	Surgical background proved the procedural and clinical outcomes High safety profile in the initial experience Good outcomes in the first patients	Concerns if local access injuries (jugular area) Risk of leaflets or right coronary injuries during procedure Slow and technically challenging procedure
TriCinch device	Surgical background proved the procedural and clinical outcomes High safety profile in the initial clinical experience Fully retrievable an technically not demanding Good clinical outcomes at 6 months in the first three patients	Risk of leaflets or right coronary injuries during procedure
TRAIPTA concept	Preclinical experience documented safety of the implants Significant improvement of leaflet coaptation and TV area/ diameters reduction observed in 9 animals	Absence of surgical background Limited clinical applicability because of the need of free pericardial space (Redo patients excluded)
Millipede system	Repositionable and retrievable complete ring	Potential high risk of complete AV block
CAVI concept	Promising RV function improvements reported Technically easy to perform	Palliative treatment Absence of surgical background
FORMA device	Preliminary results in seven high-risk patients reported successful device implantation with at least one grade acute TR reduction 30 days results showed clinical improvements and stable TR reduction	Surgical pocket Very large devices needed for patients with advanced tricuspid annular dilatation Absence of surgical background
Mitraclip	Large clinical experience in mitral valve Many operators are confident with the device	Absence of a concomitant tricuspid annular remodelling could limit this procedure targeting solely the leaflets Three-leaflets configuration of the valve
Transcatheter TV replacement	Good outcomes reported at short term by the Valve-in-Valve International Registry Fast procedure	Currently only for valve-in-valve application The unfavourable narrow angle between the IVC and the TV could be technically challenging, limiting the transfemoral approach

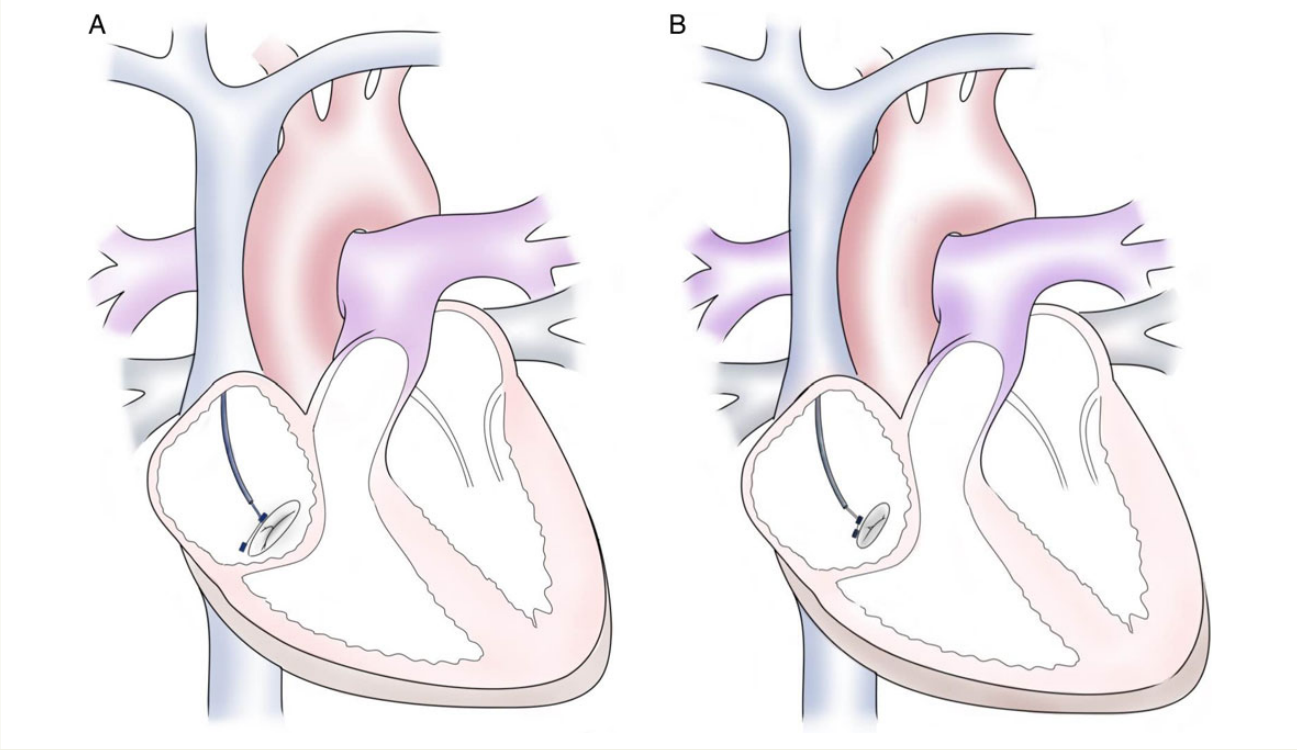

Figure 3 (*A* and *B*) The Mitralign concept. (*A*) The pledget delivery catheter is advanced over the wire from the right atrium. (*B*) Plication of the annulus and reduction of its dimension.

The main advantage of this approach is that it is based on a proven surgical background, since it reproduces the Kay bicuspidization, which has been associated with satisfactory long-term results.[20,21] Transjugular access is a relatively safe option, since most of the operators are confident with central venous line positioning and it allows fast mobilization of the patients.

A possible drawback of the Mitralign procedure is that it is technically challenging and requires advanced 3D echocardiography imaging guidance.

The risk of leaflet or right coronary artery damage due to the positioning of the transannular pledgets and to the annular plication has to be assessed on a large basis.

The TriCinch device

The TriCinch (4Tech Cardio, Galway, Ireland) is a catheter-based device designed to perform tricuspid annular cinching, in order to reduce anteroseptal annular dimension and reduce TR improving leaflet coaptation. A steerable catheter is introduced in the femoral vein and delivered to the tricuspid annulus on beating heart condition.[22] The tip of the steerable catheter is positioned between the antero-posterior commissure and the mid-anterior annulus. A corkscrew is implanted in the proximity of the mid part of the anterior tricuspid annulus (*Figure 4A*). Right coronary artery angiography is performed to exclude coronary damages. Once the corkscrew is secured, the delivery system is retrieved and a self-expandable nitinol stent is introduced over the wire and coupled to the implant. The whole system is then tensioned to reshape the TV promoting annular cinching and to increase the leaflet coaptation, on beating heart, under live echo guidance. Finally, the stent is deployed in the inferior vena cava (IVC) to maintain the tension applied (*Figure 4B*). Multicentre CE Mark trial is on-going (PREVENT trial). Preliminary results obtained in the first three successfully implanted patients showed stable reduction of the septolateral dimension of the tricuspid annulus 6 months after the implantation, with sustained clinical and functional improvements. In particular, septolateral annular dimension decreased from 46 $\pm$ 6 to 38 $\pm$ 6 mm. All patients were in NYHA class I–II 6 months after the procedure, with a mean improvement of 172 m at 6-min walk test compared with baseline (Maisano F. Fortech Percutaneous Annuloplasty for Tricuspid Regurgitation. Chicago, TVT 2015).

The TriCinch concept is based on the surgical background of annular remodelling. The main advance of this device is that it is retrievable in case of right coronary artery damage or in case of unsatisfactory TR reduction observed under tension, before the implantation of the stent. The procedure is technically not demanding. However, advanced imaging guidance and proper patients selection are key elements to reach the annular target. Another potential issue is that in patients with advanced RV dysfunction usually IVC are very dilated, requiring very large caval stent and this aspect may limits the eligibility of the patients. Further results should exclude the risk of stent dislocation.

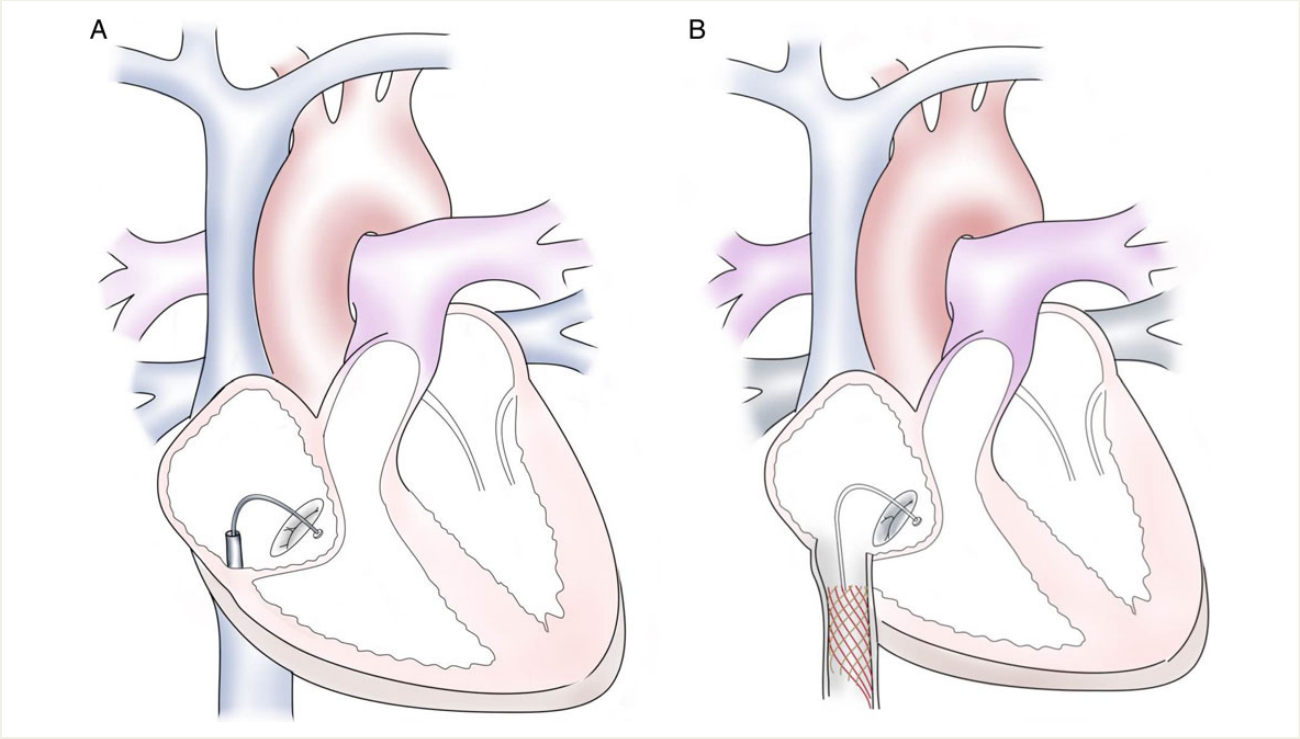

Figure 4 (*A* and *B*). The TriCinch concept. (*A*) The corkscrew is implanted in the target zone. (*B*) The system is tensioned to reshape the annulus. The stent is deployed in the IVC to maintain the tension applied.

Transatrial intrapericardic tricuspid annuloplasty (TRAIPTA concept)

A different approach is used by the TRAIPTA concept (transatrial intrapericardial tricuspid annuloplasty).[23] Pericardial access is obtained puncturing the RA appendage from within, after transfemoral venous access. A circumferential implant, which exerts compressive force over the annulus, is delivered along the AV groove within the pericardial space (*Figure 5A*). Tension on the implant is then adjusted interactively to modify tricuspid annular geometry and reduce therefore TR (*Figure 5B*). The RA puncture is then sealed using off-the-shelf nitinol closure devices. The procedure is mainly guided by fluoroscopy. Pre-clinical experience showed safety of the implant. Pericardial access via a right appendage puncture was uncomplicated in all cases. In nine animals, tricuspid leaflet coaptation length was increased by 53% ($P < 0.001$). Septolateral dimension and annular area were reduced by 49 and 59% compared with baseline, respectively ($P < 0.001$).[23]

The major limitation of this approach is that it requires a free pericardial space. Therefore, it cannot be used in patients with previous heart surgery. This aspect may reduce the adoption of the TRAIPTA device, since patients with late recurrence of FTR after mitral surgery represent a big proportion of the potential candidates for percutaneous TV annuloplasty.

The Millipede system

The Millipede system (Millipede, LLC, Ann Arbor, Michigan) is a repositionable and retrievable complete ring, which can be implanted surgically or transcatheter on the atrial side of the native tricuspid annulus, in order to restore its shape and diameter.[10] No updated pre-clinical feasibility or safety data are so far available.

Although the Millipede device is an appealing technology, since it is repositionable and retrievable, the risk of complete AV block seems to be very high, depending on the shape of the device and on the anchoring system.

Caval valve implantation for treatment of severe tricuspid regurgitation: the Caval Valve Implantation concept

An alternative approach to percutaneous treatment of TV is to implant a transcatheter prosthesis in IVC (single valve approach) or in combination with a superior vena cava (SVC) valve (dual valve) to prevent damage to the liver and other organs (*Figure 6*). In the presence of advanced RV dysfunction, the single valve approach seems to be safer compared with the dual-valve approach since it less increases RV preload. However, no data are available on which should be the optimal treatment (single vs. dual valve).[24,25]

The rational of this procedure is to reduce hepatic, abdominal, and peripheral venous congestion leading to amelioration of right heart failure. Since the prostheses are implanted in a low-pressure venous system, lifelong anticoagulation would be probably required. However, most of the patients would receive anticoagulants anyway, due to previous mitral replacement or associated atrial fibrillation.

Different devices have been implanted using this approach and there is no consensus on what would be the ideal Caval Valve Implantation (CAVI) prosthesis.[24,25] Promising preliminary clinical results have been recently reported in 10 patients treated with the Sapiens XT valve. A self-expandable stent has been implanted in the IVC to prepare the landing zone for the balloon expandable prosthesis. Thirty days clinical and RV longitudinal function improvements were observed, with a significant reduction of the retrograde flow in the IVC (Laule M. Caval Sapien Valve Implants. Chicago, TVT 2015).

Acute haemodynamic as well as clinical improvements at follow-up have been also reported with the self-expandable prosthesis in five patients, three treated with dual valve and two with single valve

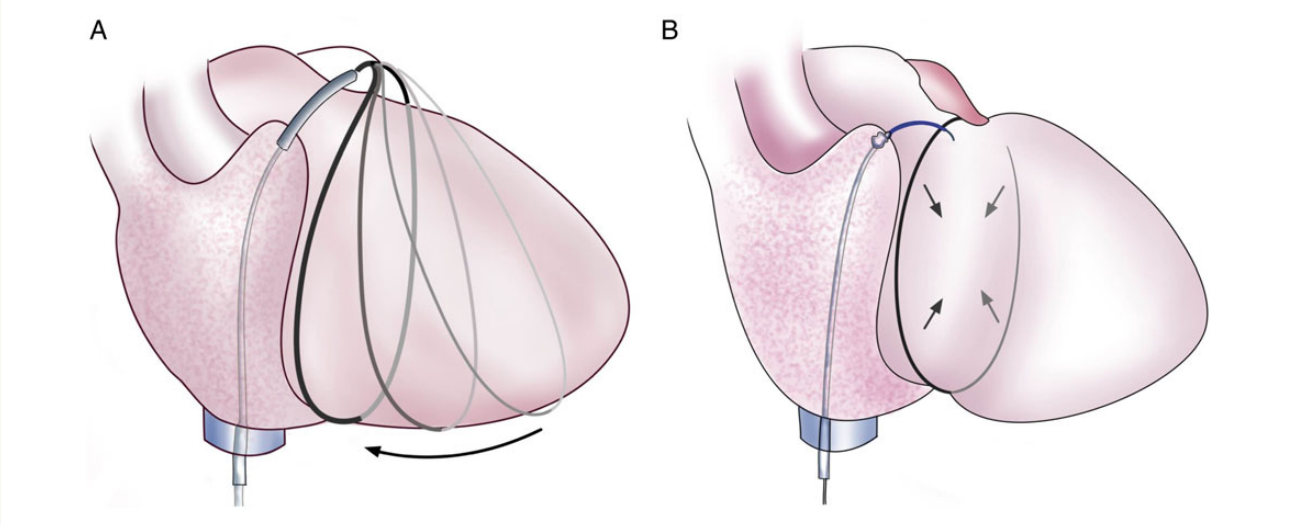

Figure 5 (*A* and *B*). The transatrial intrapericardic tricuspid annuloplasty concept. (*A*) A circumferential implant is delivered along the atrioventricular groove. (*B*) Tension on the implant is then adjusted to modify annular geometry.

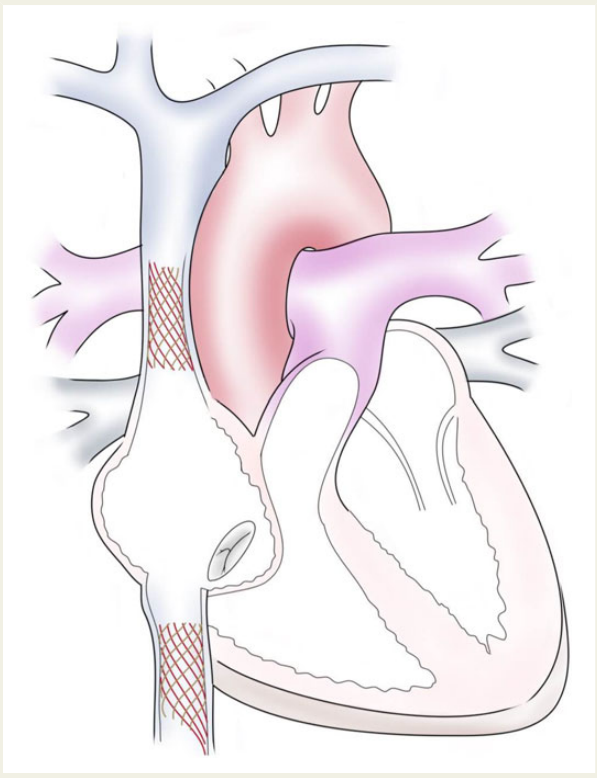

Figure 6 The 'caval valve implantation' concept. Transcatheter prosthesis is implanted in inferior and superior vena cava.

approach [Lauten A. Caval Valve Implantation (CAVI) for Treatment of Severe TR. San Francisco, TCT 2014].

At the moment, two different clinical CAVI trials are enrolling high-risk patients with severe symptomatic TR: the TRICAVAL in Europe and the HOVER trial in USA.

The main advantage of the CAVI is that is technically very easy to perform. Although preliminary results are very promising, the main disadvantage of this approach is the complete the absence of a clinical or surgical background. Moreover, the effects of a 'ventricularization' of the RA are unknown at long term. Dedicated CAVI devices are under pre-clinical development.

Tricuspid valve spacer: the FORMA device

The FORMA Repair System (Edwards Lifescience, Irvine, USA) is a valve spacer, which is positioned into the regurgitant orifice in order to create a platform for native leaflet coaptation. The device is delivered through transubclavian venous access and is then distally anchored to the RV apex (*Figure* 7). Proximal fixation is obtained in a small surgically prepared pocket. Preliminary results in seven high-risk patients have been recently reported. In all the patients, the device was successfully implanted without major complications, obtaining an at least one grade acute reduction in TR. Thirty-day results, available for four patients, showed clinical improvements and stable TR reduction (4/4 patients had moderate TR with <2 mmHg trans-valvular gradient). All patients had reduction of peripheral oedema, while in 2/4 patients it was possible to reduce the dosage of furosemide. No

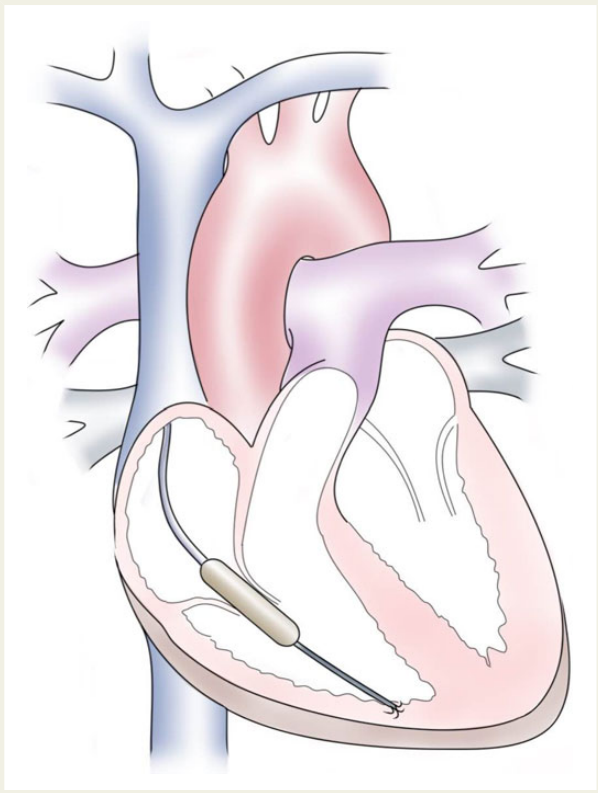

Figure 7 The FORMA concept. A spacer is positioned into the tricuspid regurgitant orifice and distally anchored to the right ventricle, to create a platform for native leaflet coaptation.

rehospitalizations were observed (Josep Rodés-Cabau, Edwards FORMA Repair System. TVT Meeting 2015, Chicago).

The main concern regarding this approach is that usually in patients with severe FTR the regurgitant orifice is huge, and consequently the lack of leaflet coaptation is very wide. Therefore, very large device would be required in order to fill such a large gap.

Mitraclipping in tricuspid position

Since the surgical edge-to-edge repair in tricuspid position has been associated with satisfactory results at mid-term follow-up,[26] the use of the MitraClip device (Abbott, Abbott Park, Illinois) in tricuspid position is an appealing concept.

However, MitraClip therapy has not yet been translated successfully for use in the normal tricuspid position. Several open challenges and drawback include logistic problems due to the use of such a long device through transjugular approach, the three-leaflets configuration of the TV, the presence of huge annular dilatation, the different tissue properties of the tricuspid leaflets.

Transcatheter tricuspid valve replacement

The feasibility of TV-in-valve or valve-in-ring to treat the degeneration of a surgically implanted bioprosthesis or after a failing surgical annuloplasty has been reported with different prosthesis and different access (transfemoral, transjugular, and direct transatrial).[27–32] The more conventional and intuitive transfemoral approach may be

technically challenging in most cases, due to an unfavourable narrow angle between the IVC and the TV. In total, 156 patients who underwent TV-in-valve or valve-in-ring have been included in the Valve-in-Valve International Registry (D. Dvir. Tricuspid valve-in-valve: Update from VIVID registry and technical strategies to improve clinical outcomes. Chicago, TVT 2015). Different authors reported acute satisfactory results,[27–31] but no data are available so far about long-term outcome.

Currently, there are no reports of transcatheter TV replacement in native TV in human.

Percutaneous replacement of native TV presents several technical challenges to be overcome before entering in the clinical armamentarium, such as the fixation within the large dimension of the tricuspid annulus, the risk of paravalvular leak, the slow flow of the right heart side, the trabeculated structure of the RV, the angulation of the annulus in relation to the SVC and IVC which can prevent optimal coaxiality with large and rigid delivery system, the frail and thin RV apex in case of transapical access just to name the most obvious. The presence of transtricuspidal pacemaker leads could represent an adjunctive issue.

Discussion

Although only very preliminary data are available so far, transcatheter-based techniques for the treatment of TR have been rapidly evolving in the last years. Initial experiences showed that percutaneous TV repair seems to be feasible. However, it is important to point out that at the present stage of the development of these therapies, since really few data are available, it is not possible to support any clinical efficacy or safety. Some of these novel devices are based upon well-known surgical techniques that have subsequently progressed to less invasive approaches, other ones are completely new concepts that should be validated in the clinical setting.

The experience with aortic and mitral valve percutaneous interventions showed us that many years are required before TV transcatheter technology would become a routine therapeutic option in the everyday clinical practice.

Beside technological issues, most importantly there are several clinical open issues. First of all, at the moment it is very difficult to identify the ideal patients that could benefit from transcatheter TV treatment, in terms of prognostic and clinical benefit. In fact, in patients with advanced heart failure, the severe TR is likely to be a marker of disease severity, rather than an incremental risk factor that could be treated and revert the natural history.[33,34] In this regard, proper timing of the treatment would play a fundamental role, and several clinical data will be needed in order to clarify this aspect.

The second important open issue refers to anatomical patients selection, and is obviously related to the TV imaging. While transthoracic and transoesophageal echocardiography are the most important diagnostic tool to assess TV,[35,36] Angio-CT is acquiring increasing importance in patients' selection and procedural planning of TV percutaneous strategy. Although few data exist at the moment,[37] Angio-CT allows the operator to assess tricuspid annular dimension and anatomy, to identify the target zone to implant some annuloplasty device, to assess the angle between IVC, SVC, and TV plane, to assess the distance between the right coronary artery and the valve annulus and assess the risk of injury, to measure IVC and SVC dimensions (*Figure 8*). Three-dimensional echocardiography will play as well an important role, since it allows accurate assessment of the morphology of the valve and of the quantification of TR. Imaging will play an important role also in procedural live guidance, and is probable that Intra Cardiac Echography will be complementary to transoesophageal 3D echocardiography in this purpose.

Data from the on-going and upcoming clinical trials will provide in the next years all of this still missing information. It is expected that after the initial proof of feasibility, improvement in the device technology as well as in integrated pre-procedural and intra-procedural imaging will help to provide an effective tool to treat a huge number of patients.

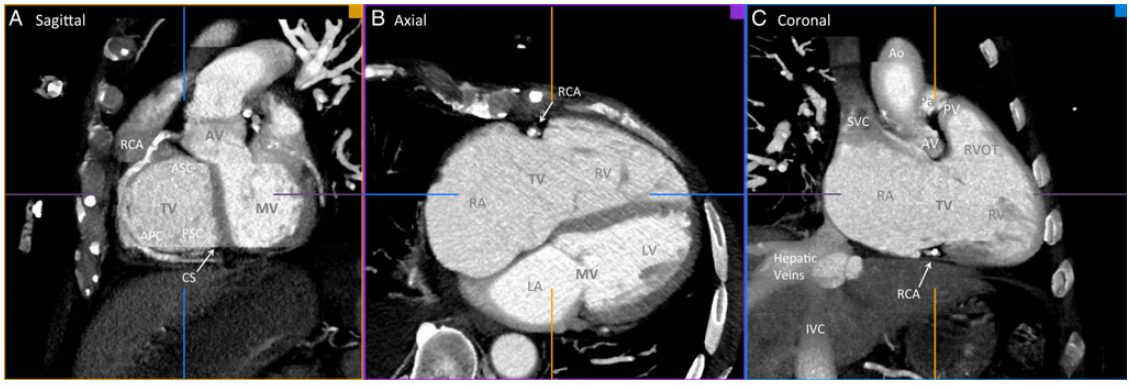

Figure 8 Angio-CT Tricuspid Valve and Right Heart structures characterization for pre-procedural planning. (*A*) Sagittal Plan = for tricuspid valve characterization (annulus, commisures, leaflets, and CS), right coronary artery vicinity, Ao relation; (*B*) axial plane = for right chambers dimensions, annulus characterization; (*C*) coronal view = for inferior vena cava and superior vena cava analysis, right chamber dimensions and structures identification. TV, tricuspid valve; APC, antero posterior commissure; PSC, postero septal commissure; ASC, antero septal commissure; CS, coronary sinus; RCA, right coronary artery; AV, aortic valve; MV, mitral valve; RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle; SVC, superior vena cava; IVC, inferior vena cava; RVOT, right ventricular outflow tract; Pa, pulmonary artery; PV, pulmonary valve.

Authors' contributions

F.M., F.N., O.A., S.B.: handled funding and supervision and made critical revision of the manuscript for key intellectual content; M.T., F.M., A.G.: conceived and designed the research; M.T., A.G., A.P.: drafted the manuscript.

Conflict of interest: F.M. is co-founder of 4Tech; A.G. has a financial relationship with 4Tech.

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