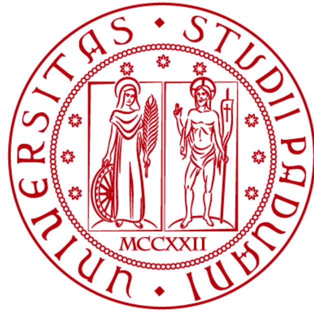

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Dipartimento di Scienze Cardiologiche, Toraciche e Vascolari

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TITOLO TESI

TRANSCATHETER ATRIOVENTRICULAR JUNCTION ABLATION: CURRENT INDICATIONS AND ANATOMO-CLINICAL CORRELATIONS

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RIASSUNTO

Introduzione:

lo scopo dell'ablazione transcatetere del nodo atrioventricolare (AV) è quello di creare una lesione del tessuto di conduzione a livello del nodo AV - fascio di His provocando il blocco AV completo. Per tale motivo è necessario un successivo impianto di pacemaker definitivo. La tecnica viene utilizzata per controllare la frequenza cardiaca in pazienti con fibrillazione atriale ad elevata risposta ventricolare, fortemente sintomatica, refrattaria alla terapia medica.

Casistica di ablazione della giunzione atrioventricolare

Nella Unità Operativa di Cardiologia dell'Ospedale di Mestre, nell'intervallo di tempo compreso tra Gennaio 2005 e Dicembre 2014, sono stati trattati con questa tecnica 62 pazienti. Le caratteristiche cliniche della popolazione presa in esame erano: un'età media di 71±5 anni, sesso maschile nel 55% (34 pz) dei casi, storia di cardiopatia ischemica nell'81% (50 pz) dei casi, fibrillazione atriale permanente nel 94% (58 pz) dei casi, 3% (2) dei pz presentavano una precedente ablazione inefficace delle vene polmonari, 9% (5 pz) erano in classe NYHA II, 77% (48 pz) in classe NYHA III, 14% (9 pz) in classe NYHA IV con una FE media del 29 ± 12, infine il 76% (47) dei pazienti erano portatori di ICD o CRTD.

La tecnica è risultata efficace in tutti i casi esaminati, con un tempo medio di procedura di 21±18 min. In nessun caso si sono verificate complicanze maggiori, mentre nel 5% (3 pz) si sono verificate complicanze minori (in tutti e tre i casi si trattava di ematoma in

sede di puntura venosa di femorale dx). Nel 69% (43 pz) dei casi si è ottenuto un ritmo giunzionale di scappamento. Nel 87% dei casi il blocco AV completo si è ottenuto con meno di 10 erogazioni di radiofrequenza sulla giunzione AV, mentre nel 13% (8 pz) dei casi sono state necessarie più di 15 erogazioni.

Esame istologico del tessuto di conduzione in quattro casi di ablazione della giunzione atrioventricolare

In uno dei quattro casi esaminati lo studio istologico seriato del tessuto di conduzione a livello della giunzione atrioventricolare, eseguito su un cuore appartenente a paziente trattato con ablazione del NAV, mostrava che la presenza di continuità anatomica tra il lembo settale ed il lembo anteriore della tricuspide aveva creato una protezione anatomica al fascio di His. Questa aveva comportato l'esecuzione di numerose lesioni ablative sia sul nodo AV che sulle branche discendenti del fascio di His (con approccio sinistro, retro aortico) prima di ottenere l'abolizione della conduzione AV.

Esame morfologico della commissura anterosettale della valvola tricuspide

Per valutare la variabilità anatomica della tricuspide (in termini di presenza o assenza di continuità tra lembo settale e lembo anteriore della valvola) abbiamo analizzato 100 cuori appartenenti all'Istituto di Anatomia Patologica dell'Università di Padova, valutando nello specifico mediante esame macroscopico la morfologia della valvola tricuspide. La presenza di continuità tra i due lembi è stata quantificata misurando la stessa in mm.

Nel 98% (98 cuori) dei casi vi era la presenza di continuità tra lembo settale e lembo anteriore della tricuspide. La misurazione media della stessa è stata di 3,8±2,9 mm.

In dettaglio, la continuità tra i due lembi è stata quantificata in ≥ 1 mm nel 98% dei casi, ≥ 2 mm nel 93%, ≥ 3 mm nel 79%, ≥ 4 mm nel 66%, ≥ 5 mm nel 36%, ≥ 6 mm nel 26%, ≥ 7 mm nel 17%, ≥ 8 mm nel 12% e ≥ 9 mm nel 6% dei casi.

Conclusioni:

L'ablazione della giunzione AV ha ancora un ruolo di rilievo nel trattamento di pazienti con fibrillazione atriale sia per il controllo della frequenza cardiaca nei pazienti fortemente sintomatici sia per l'ottimizzazione della resincronizzazione nei pazienti con scompenso cardiaco sottoposti ad impianto di pacemaker biventricolare.

L'intervento è efficace nel 100% dei pazienti, con una incidenza di complicanze molto bassa (generalmente complicanze minori)

La variabilità anatomica della commissura tra i lembi anteriore e settale della valvola tricuspide sembra avere una importanza cruciale sull'efficacia della ablazione della giunzione atrioventricolare. La continuità' tra i due lembi e' quasi sempre presente e quando tale continuità' e' marcata può coprire e proteggere il fascio di His al punto da rendere difficile o inefficace la procedura di ablazione mediante approccio da destra. Nei casi di inefficacia diventa necessario l'approccio sinistro retro artico per ottenere il blocco AV completo.

ABSTRACT

Introduction:

The aim of transcatheter AVJ ablation is to create a lesion of the conduction system at the level of AV node- His bundle provoking AV complete block. Therefore, in necessary a subsequent pacemaker implantation. Technique is used to control heart rate in patients with atrial fibrillation with fast ventricular rate highly symptomatic refractory to drugs therapy.

AVJ ablation experience from Electrophysiological unit of the Cardiovascular Department of Hospital “All’Angelo”, Mestre (Venice) :

We analyzed data from 62 consecutive patients who underwent AVJ ablation from January 2005 to December 2014, to the EP Section of Cardiovascular Department, “Ospedale all’Angelo”, Mestre,

Characteristics of study population were: mean age was 71±5 years, male in 55% of patients, history of ischemic heart disease in 81% of patients, permanent atrial fibrillation in 94% of patients, previous pulmonary vein ablation in 3% of patients, NYHA II class in 9% of patients, NYHA III class in 77% of patients, NYHA IV class in 14% of patients, mean ejection fraction of 29 ± 12 % and 76% of patients had a previuos CRT or CRTD implantation.

Tecnique resulted efficacy in all the patients with a mean procedural time of 21±18 min. No major complication were observed, only three minor complication occurred (three gross hematoma in the site of vein puncture). In 69% of patients was present a junctional escape rhythm. In 87% of patients AV complete block was obtained with less

than 10 RF erogations while in the other 13% more than 15 erogations was necessary to obtain the AV complete block.

Cinico-pathologic study of four cases that underwent “in vivo” AVJ ablation (Cardiac Registry, Cardiovascular Pathology Unit of the Department of Cardiac, Thoracic and Vascular Sciences of Padua University)

In one of the four examined heart, histologic examination of conduction system at the level of AVJ conducted in an heart of a patients that underwent AVJ ablation showed presence of anatomic continuity between anterior and septal leaflet of tricuspid valve. This continuity protected His bundle from ablation lesions. Therefore many attempts was necessary to obtain AV complete block even at the level of AV node even at the level of left and right His brunching bundle (from retroaortic left side approach).

Anatomic study of the tricuspid valve for AV ablation: the antero-septal commissure morphology (Cardiac Registry, Cardiovascular Pathology Unit of the Department of Cardiac, Thoracic and Vascular Sciences of Padua University)

To evaluate anatomic variability of tricuspid valve in terms of presence or absence of continuity between anterior and septal leaflet, in 100 heart Attention was point to the morphology of tricuspid valve and continuity of leaflet, if present, was measured in millimeters.

In 98% of hearts there was continuity between septal and anterior leaflet of tricuspid valve. The mean value of this continuity was 3,8±2,9 mm.

More in details continuity was ≥ 1 mm in 98% of hearts , ≥ 2 mm in 93% of herats, ≥ 3 mm in 79% of hearts , ≥ 4 mm in 66% of hearts, ≥ 5 mm in 36% of hearts , ≥ 6 mm in 26% of hearts, ≥ 7 mm in 17% of hearts, ≥ 8 mm in 12% of herats ≥ 9 mm in 6% of hearts.

Conclusions:

AVJ ablation has still a relevant role in the treatment of patients with atrial fibrillation either to control the rate in highly symptomatic patients either to optimize pacing in patients affected by heart failure implanted with a CRT device.

Technique has an efficacy of about 100% with a very low rate of complications (generally minor complications).

The anatomic variability of the commissure between anterior and septal leaflets of tricuspid valve seems to have a crucial importance on the ablation procedure. A continuity between the two leaflet is almost ever present and, when remarkable, could cover and protect the His bundle from attempts of ablation. Therefore when, as usual, AVJ ablation is approaching from the right atrium this anatomic variability could explain the cases in which the procedure results more difficult, longer or inefficient. In these last cases can be necessary to switch to left side retroaortic approach to obtain the complete AV block.

1. **Anatomy and Histology of AVJ**

The AVJ are the areas of the heart where the atrial musculatures insert into the circumferences of the mitral and tricuspid valves.

The basic arrangement is well seen when the base of the ventricular mass is viewed from its atrial aspect. On the right atrium the atrial myocardium is in potential continuity with the ventricular wall throughout the circumference of the tricuspid valve, apart from the small area occupied by the membranous septum. This fibrous septal component is crossed by the attachment of the septal leaflet of the tricuspid valve, with the location of the valvar hinge determining the extent of the AV and interventricular components of the septum.

The septal component of the junctions achieves its importance because it is the site of the only muscular structure which conducts the cardiac impulse from the atriums to the ventricles. Hecht and his colleagues (1), defined this muscular axis for conduction as the "specialized AVJ." The architecture of this phenotypically specialized myocardium was first described, with great accuracy by Tawara (2).

A century ago he likened the AV system to a tree, with its roots in the atrial septum, and its branches ramifying within the ventricles. He recognized a collection of histologically distinct cells at the base of the atrial septum that he termed the "knoten", and that has subsequently become known as the AV node.

Being the atrial component of the AV conduction system, the AV node receives, slows down and conveys atrial impulses to the ventricles. It is an interatrial structure located on the right side of the central fibrous body and when considered from the right atrial aspect it is situated within the triangle of Koch. The triangle described by Koch (3) is bordered anteriorly by the 'annulus' of the septal leaflet of the tricuspid valve, posteriorly by the tendon of Todaro that runs within the sinus septum (Eustachian ridge

or crista dividens), and inferiorly by the orifice of the coronary sinus and the atrial vestibule (Figure 1). The vestibule is recognized by arrhythmologists as the so-called 'septal isthmus'. This is the target for ablating the slow pathway in patients with AV nodal reentrant tachycardia (6). The central fibrous body itself is comprised of a thickened area of fibrous continuity between the leaflets of the mitral and aortic valves, termed the right fibrous trigone (Figure 2), together with the membranous component of the cardiac septum. The tendon of Todaro inserts into the central fibrous body that lies at the apex of the triangle (Figure 3 e 4) (7). The 'annulus' of the septal leaflet of the tricuspid valve crosses the membranous septum (Figure 5).

Figure 1: triangle of Koch; A) coronary sinus, B) septal leaflet of tricuspid valve, C) AV node, D) tendon of Todaro, E) penetrating His bundle

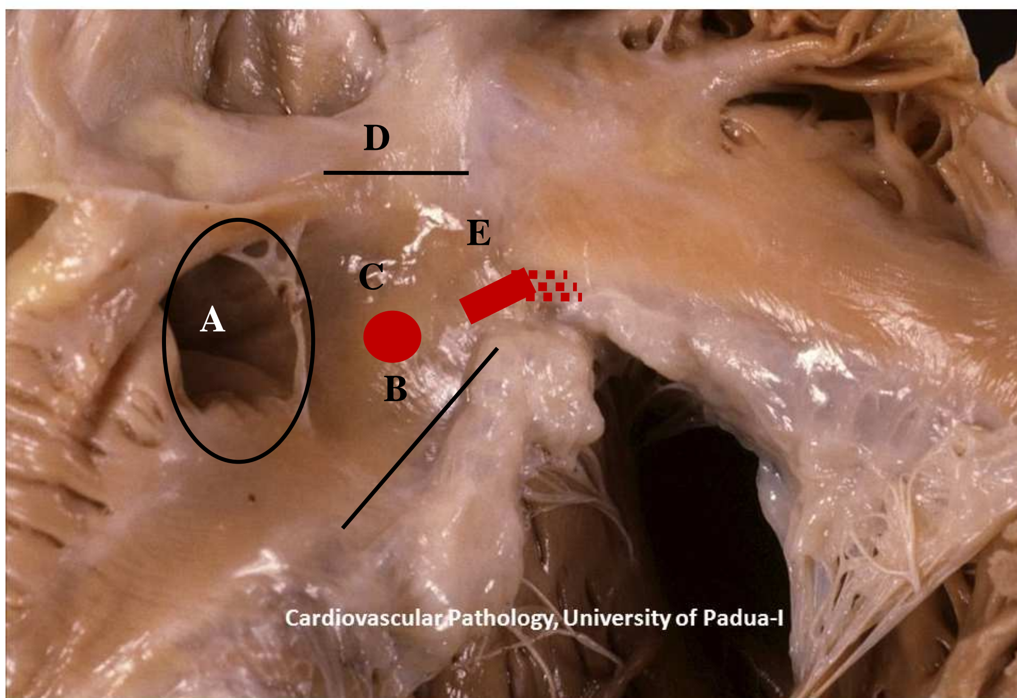


Figure 2: AV node located on the right side of the central fibrous node (5)

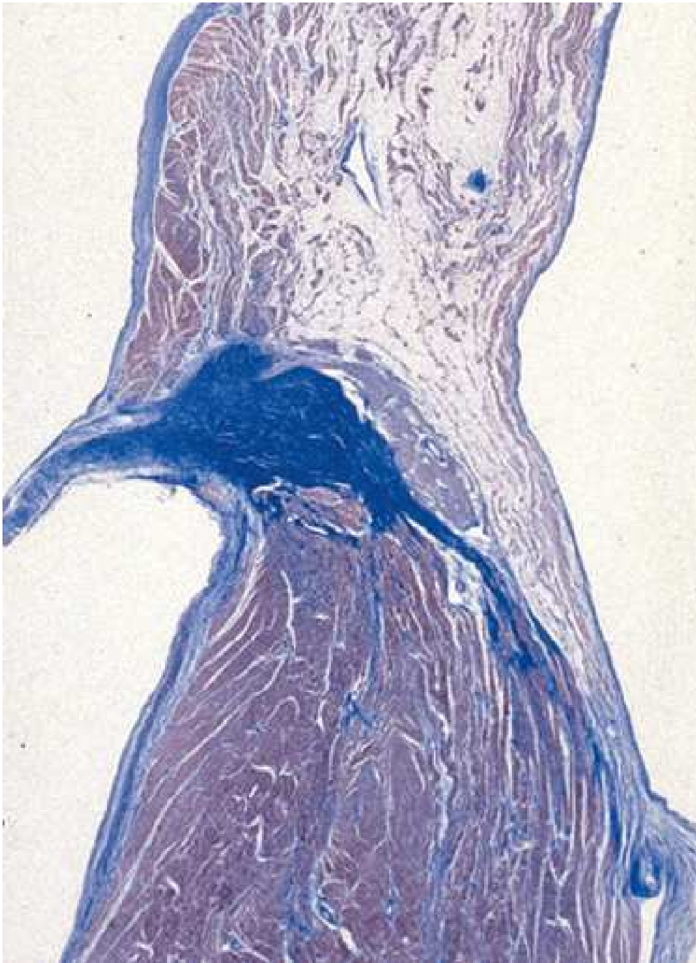


Figure 3: Penetrating AV bundle: note on the top the tendon of Todaro, approximating the central fibrous body (5)

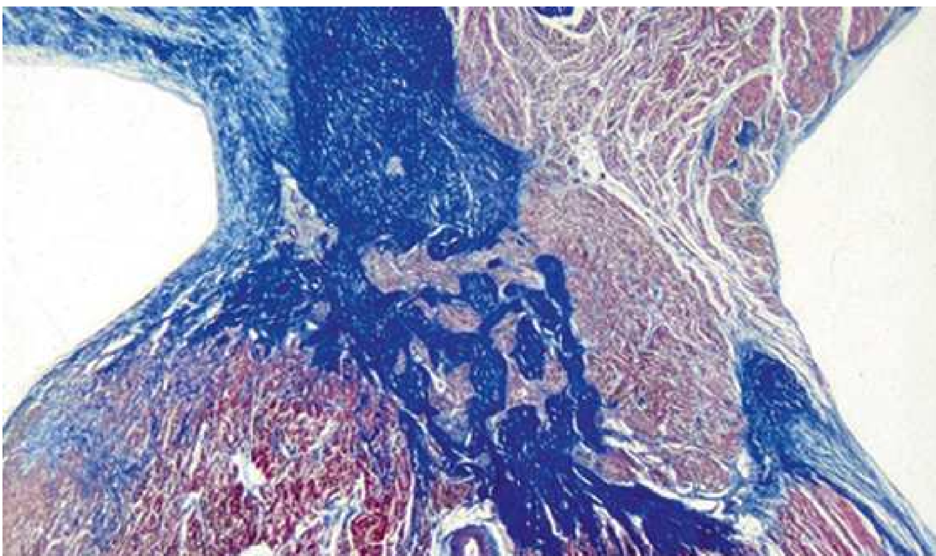


Figure 4: common AV bundle running within the fibrous body on the right side and surrounded by a fibrous sheat (4)

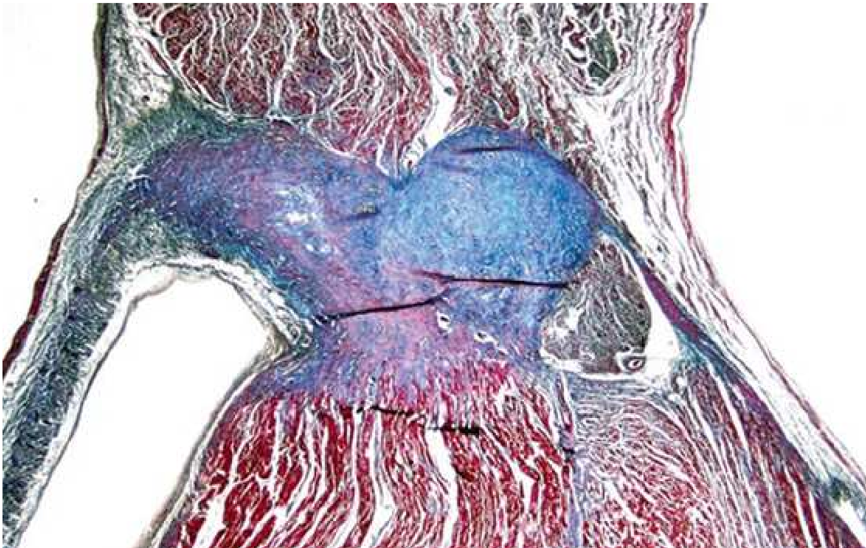
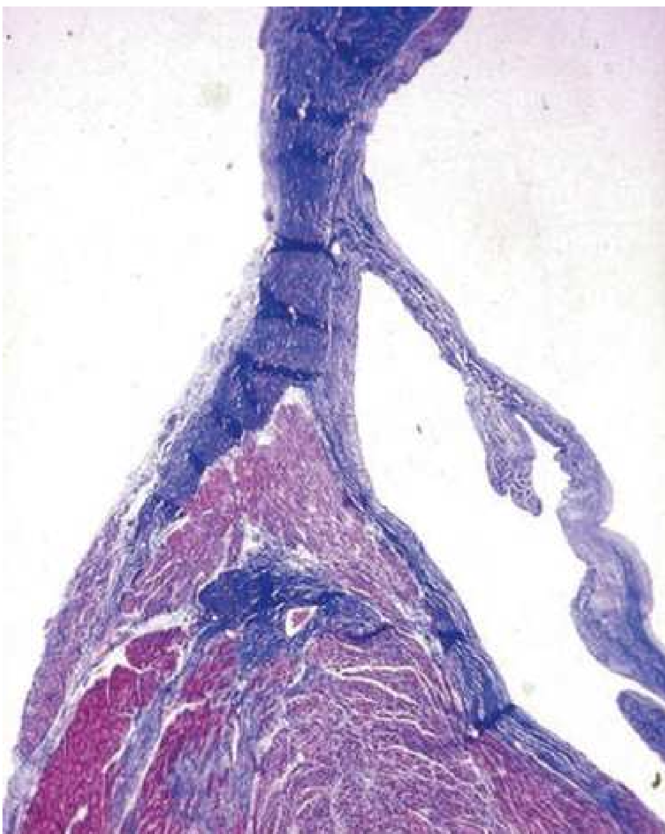


Figure 5: Bifurcating bundle astride the ventricular septal crest, underneath the membranous septum: note the insertion of the septal leaflet of the tricuspid valve dividing the membranous septum in interventricular and AV components (4)



In the original description by Tawara, it is reported that "*the system is a closed muscle bundle that resembles a tree*, *having a beginning*, *or root*, *and branches… The system connects with the ordinary ventricular musculature for the first time at the terminal ramifications*" (2). Moreover, in 1893 His was the first to observe the bundle as follow: " *I have succeeded in finding a muscle bundle which unites the auricular and ventricular septal walls…The bundle arises from the posterior wall of the right auricle near the auricular septum*, *in the AV groove*; *attaches itself along the upper margin of the ventricular septal muscle…proceeds on top of this toward the frontal until near the aorta it forks itself into a right and left limb*" (4).

The compact node, approximately 5 mm long, 5 mm wide and 0.8 mm thick in adults, is adjacent to the central fibrous body on the right side but is uninsulated by fibrous tissue on its other sides, allowing contiguity with atrial myocardium (Figure 2). Owing to the lower level of attachment of the tricuspid valve relative to the mitral valve, the AV node 'leans' toward the right atrial side and is a few millimeters far from the endocardium (Figure 2). From the node extends the AV bundle of His that passes through the fibrous core of the central fibrous body (Figure 3 and 4). The bundle veers leftward as it penetrates the central fibrous body, taking it away from the right atrial endocardium and toward the ventricular septum. In majority of hearts it emerges to the left of the ventricular septal crest but is insulated from ventricular myocardium by fibrous tissue and from atrial myocardium by the membranous septum itself (Figure 6). Viewed from the left ventricle, the landmark for the AV bundle is the area of fibrous continuity between aortic and mitral valves that is adjacent to the membranous septum. Viewed from the aorta, the interleaflet fibrous triangle between the right and the non-coronary sinuses adjoins the membranous septum and the AV bundle passes beneath that part of the septum (Figure 7).

Figure 6 Course of the bifurcating bundle on the left side of the ventricular septal crest: note the insulation of the bundle by fibrous tissue and the intramyocardial course of the proximal right bundle branch (4)

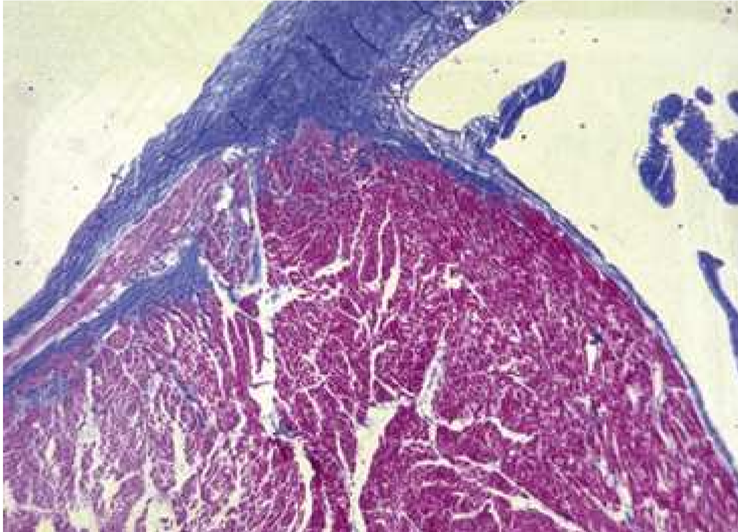
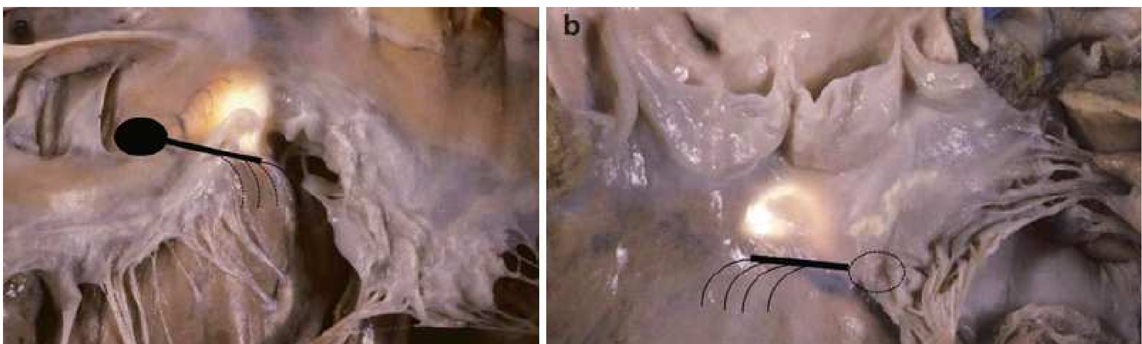


*Figure 7 The "core" of the heart in correspondence of the membranous septum, where the specialised AVJ is located (**a**, right side view; **b**, left side view). The landmark of the AV bundle from the left side is the continuity between the aortic and mitral valve, adjacent to the membranous septum, which is located underneath the interleaflet triangle between the right and posterior non-coronary cusps (4)*



2. AVJ ablation: an overview on indications, technique and results

2.1 Introduction

In patients with atrial fibrillation (AF), the primary end point should be the maintenance of sinus rhythm with antiarrhythmic drugs or, when possible, with pulmonary vein isolation, as suggested by prominent guidelines and working groups. However, in some patients, these strategies are not effective or not indicated. Thus, rate control is considered a reasonable alternative (8-11).

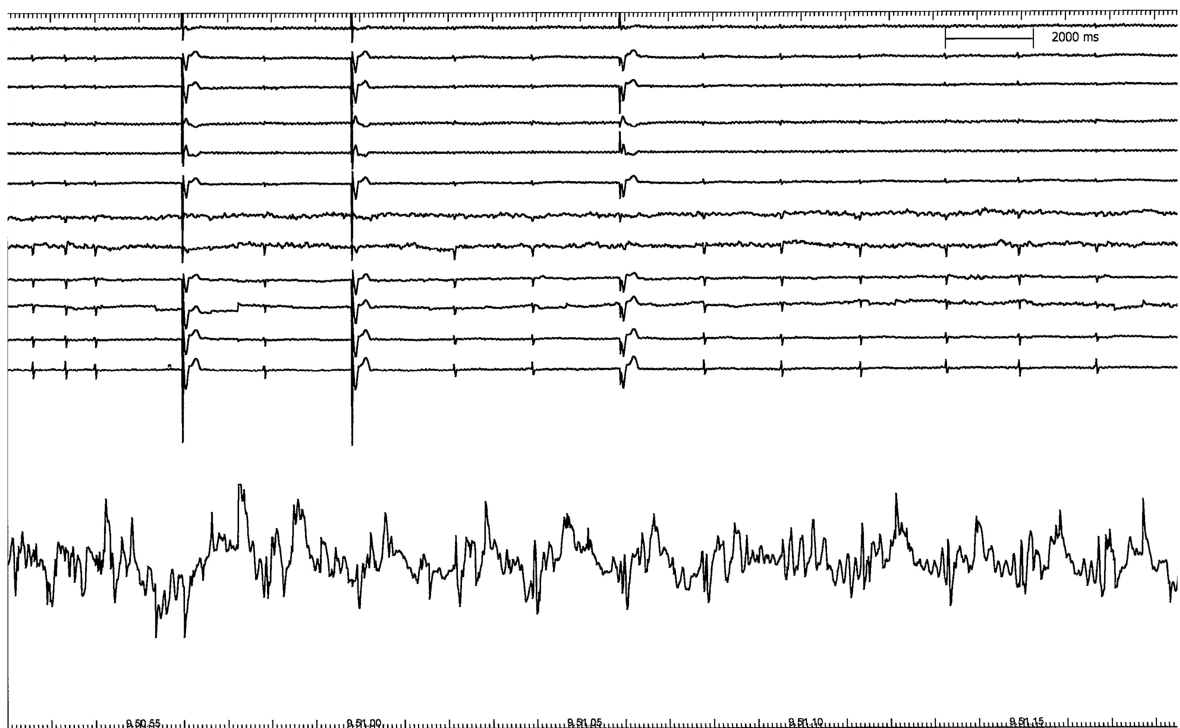
However, pharmacological rate control is never easy to achieve and/or is associated with side effects, leading to poor patient compliance as well as inadequate decrease of ventricular rate. As such, AVJ ablation (producing AV block), followed by implantation of a pacemaker, is a well-established, widely accepted alternative in selected patients. In these patients, evidence exists that, compared with conventional drug therapy, ablation and pacing treatment is able to reduce the specific symptoms of arrhythmia and to improve overall quality of life.

Note, however, that AVJ ablation has several limitations. In contrast with pulmonary vein isolation (in which ablation can be considered curative, AVJ ablation therapy is unable to eliminate the triggers or electrophysiological substrate of the arrhythmias and works only indirectly, by controlling a fast, irregular ventricular rate. Moreover, the procedure is necessarily associated with pacemaker implantation and a small but definite risk of short- and long-term complications. In addition, few data are available on the long-term effects of this treatment on cardiac performance, morbidity, and survival. Finally, a high rate of progression of paroxysmal to permanent AF following ablation and pacing (22% at 1 year, 40% at 2 years) has been described. For these

reasons, the clinical benefit of this powerful therapy must be weighed against the risk of complications and side effects, and a careful risk-benefit evaluation must be performed for each patient who is considered for this procedure, which at present should be a last resort.

In 1982, Scheinmann and colleagues described five patients who underwent successful direct current (DC) ablation, four for atrial fibrillation (AF) and one with nodal tachycardia (12); Gallagher and co-workers (13) reported similar results the same year. However, this technique tended to have a high recurrence rate and a later series in 1990 was reported by Rosenqvist et al. (14) to have a long-term success rate of only 83%. Nine deaths were also reported, one sudden, which were in part ascribed to the rather diffuse damage caused by DC energy. In 1987 Huang and colleagues (15) described the use of radiofrequency (RF) energy for AV node ablation, with a further report from Langberg and collaborators (16) in 1989. However, like other RF applications, this technique only became effective when steerable deflectable 4 mm tip catheters were introduced. In nine series since 1991, 288 patients have been reported (17), in whom the success rate was 84% on the right side, 100% on the left side. The major advantage of the introduction of radiofrequency (RF) energy is the ability to precisely block the AV node and leave a junctional escape pacemaker (Figure 8).

Figure 8 AVJ ablation: the surface ECG (upper signals) and the intracardiac signal of the ablator tip characterized by artifacts created by energy delivery (last signals). At the beginning of the trace, patient has atrial fibrillation, a few seconds after AV block with junctional escape rhythm of 36 bpm and fixed RR interval; also notable are some paced beats (programmed at the lower rate of 30 bpm..



Some investigators have shown interest in the use of intracoronary-delivered ethanol to produce AV block within the AV node. The long-term safety of this procedure is unknown and, moreover, the resumption of AV conduction in 30% of patients has been reported. At this date, we do not believe that catheterization of the AV nodal artery and delivery of ethanol are warranted, because complete AV block can be achieved using RF delivery in almost 100% of patients. In order to avoid permanent pacemaker implantation, attempts have been made to control the heart rate by modifying the

properties of the AV node by means of RF but without inducing block (through AVJ modulation). Although initial non controlled studies yielded encouraging results, two randomized, controlled clinical studies compared “ablate and pace” with heart-rate modulation in patients with congestive heart failure and paroxysmal or permanent AF. Researchers found that ablate and pace was more efficacious than AV node modulation for improving cardiac performance and alleviating symptoms.

To avoid ablation of the AVJ, pacemakers have been developed that are endowed with special algorithms designed to regularize heart rate (ventricular response pacing) with a view to reducing symptoms and improving cardiac performance. While this modality has proved effective for regularizing heart rate in controlled studies, it has not yielded satisfactory results in terms of improving quality of life or functional capacity. Thus, both pacemaker implantation and AVJ ablation seem to be necessary in order to obtain a clinical benefit.

2.2 Indications

The definition of drug-refractory AF requires individually assessing a patient’s symptoms in terms of severity and frequency. “Drug refractoriness” implies that symptoms remain uncontrolled and unacceptable to the patient, even if ventricular rate is within the normal range but remains irregular. AF can be highly symptomatic and may lead to cardiac dysfunction. However, it is important to remember that AVJ ablation is an irreversible process and results in lifelong pacemaker dependence for patients. Table 1 summarizes different of professional groups’ recommendations on AVJ ablation, based on class of recommendation and level of scientific evidence.

Table 1 Comparison of recommendations on AVJ ablation therapy from professional group guidelines.

Class of recommendation	ACC/AHA/ESC 2006[2]	ESC 2010[1]
Class IIa	It is reasonable to use ablation of the AV node or accessory pathway to control heart rate when pharmacological therapy is insufficient or associated with side effects (LOE B).	Ablation of the AV node to control heart rate should be considered when the rate cannot be controlled with pharmacological agents and when AF cannot be prevented by antiarrhythmic therapy or is associated with intolerable side effects, and direct catheter-based or surgical ablation of AF is not indicated, has failed, or is rejected (LOE B). Ablation of the AV node should be considered for patients with permanent AF and an indication for CRT (NYHA functional class III or ambulatory class IV symptoms despite optimal medical therapy, LVEF ≤35%, QRS width ≥130 ms) (LOE B). Ablation of the AV node should be considered for CRT non-responders in whom AF prevents effective biventricular stimulation and amiodarone is ineffective or contraindicated (LOE C). In patients with any type of AF and severely depressed LV function (LVEF ≤35%) and severe heart failure symptoms (NYHA III or IV), CRT should be considered after AV node ablation (LOE C).
Class IIb	When the rate cannot be controlled with pharmacological agents or tachycardia-mediated cardiomyopathy is suspected, catheter-directed ablation of the AV node may be considered in patients with AF to control the heart rate (LOE C).	Ablation of the AV node to control heart rate may be considered when tachycardia-mediated cardiomyopathy is suspected and the rate cannot be controlled with pharmacological agents, and direct ablation of AF is not indicated, has failed, or is rejected (LOE C). Ablation of the AV node with consecutive implantation of a CRT device may be considered in patients with permanent AF, LVEF ≤35%, and NYHA functional class I or II symptoms on optimal medical therapy to control heart rate when pharmacological therapy is insufficient or associated with side effects (LOE C).
Class III	Catheter ablation of the AV node should not be attempted without a prior trial of medication to control the ventricular rate in patients with AF (LOE C).	Catheter ablation of the AV node should not be attempted without a prior trial of medication, or catheter ablation for AF, to control the AF and/or ventricular rate in patients with AF (LOE C).

NYHA = New York Heart Association; ACC/AHA/ESC = American College of Cardiology/American Heart Association/European Society of Cardiology; LOE = level of evidence; AV = atrioventricular; AF = atrial fibrillation; CRT = cardiac resynchronization therapy; LVEF = left ventricular ejection fraction; LV = left ventricular; RV = right ventricular

2.3 Methodology

Patients should be fully clinically assessed and appropriate tests performed before an AVJ ablation procedure. All efforts should be made to stabilize the patient before the intervention. Operators should be experienced in right- and left-sided heart catheterization, and the procedure should be performed in an adequately equipped and staffed cardiac electrophysiology laboratory.

In those patients who have a permanent pacemaker implanted already, this can be used for backup pacing, as long as it is understood that RF energy may inhibit or reprogram the pacemaker. The appropriate programmer should be in the room, and equipment should be set up so that emergency pacing can be commenced through the ablation catheter in the right or left ventricle.

It may be helpful to convert the patient's heart to sinus rhythm before or during the procedure. However, the procedure can be successful in most patients during AF. Choice of catheter and tip design are considered to be personal choices and reflect local practice. AVJ ablation can be accomplished by means of a right- or left-sided approach. The greater experience available with the right-sided approach and the higher prevalence of complications from left-sided catheterization make the right-sided approach the preferred choice. When the right-sided approach fails, however, left-sided ablation can be performed during the same session (the so-called sequential approach) or at another session. Left-sided ablation may be easier to perform and requires fewer RF applications, but it requires arterial catheterization. If AVJ ablation is not achieved after a total of 10 applications of RF energy at the indicated site, right-sided ablation can be considered to have failed and left-sided ablation should be attempted. Ablation can be performed sequentially first in the right and then the left side of the heart if the pacemaker is already implanted. If the pacemaker has not been implanted, and heparin

infusion is given for a left-sided ablation, pacemaker implantation will normally be postponed.

Right-sided approach

The ablation catheter is inserted via the femoral vein and positioned on the AVJ. A two-catheter approach is usually sufficient (one for the right ventricle [RV] to pace the ventricle and one to deliver RF energy), but many prefer placing an additional catheter in the His bundle position (Figure 9). A stable RV position (preferably in the apex) is required, with acceptable pacing thresholds. The goal of the procedure is to ablate the compact AV node rather than interrupt the bundle of His. The compact AV node is positioned in the so called area of "Koch triangle" between septal leaflet of tricuspid valve, His penetrating bundle, coronary sinus ostium and Todaro tendon. AV compact node lies just inferior and posterior to the His bundle (Figure 1). The ideal signal has an atrial-to-ventricular ratio greater than or equal to one, with an early and stable His deflection. The most practical technique consists of looking for the largest His potential, then moving the tip of the steerable catheter a few millimeters into the atrium toward the compact AV node until a large A wave is obtained, having a small or absent His potential (Figure 10). During AF, a smaller atrial signal is acceptable and the His potential is more difficult to identify. In case of failure, successive energy applications are delivered close to this site by moving the tip a few millimeters in different directions. A different catheter curve should be considered if there are difficulties in obtaining stable or adequate signals.

Figure 9 Left anterior oblique projection showing the right-sided approach for AV junctional (AVJ) ablation. (A) Catheter in coronary sinus, (B) catheter in the His bundle position and (C) ablator catheter positioned a few millimeters toward the atrium on the compact AV node.

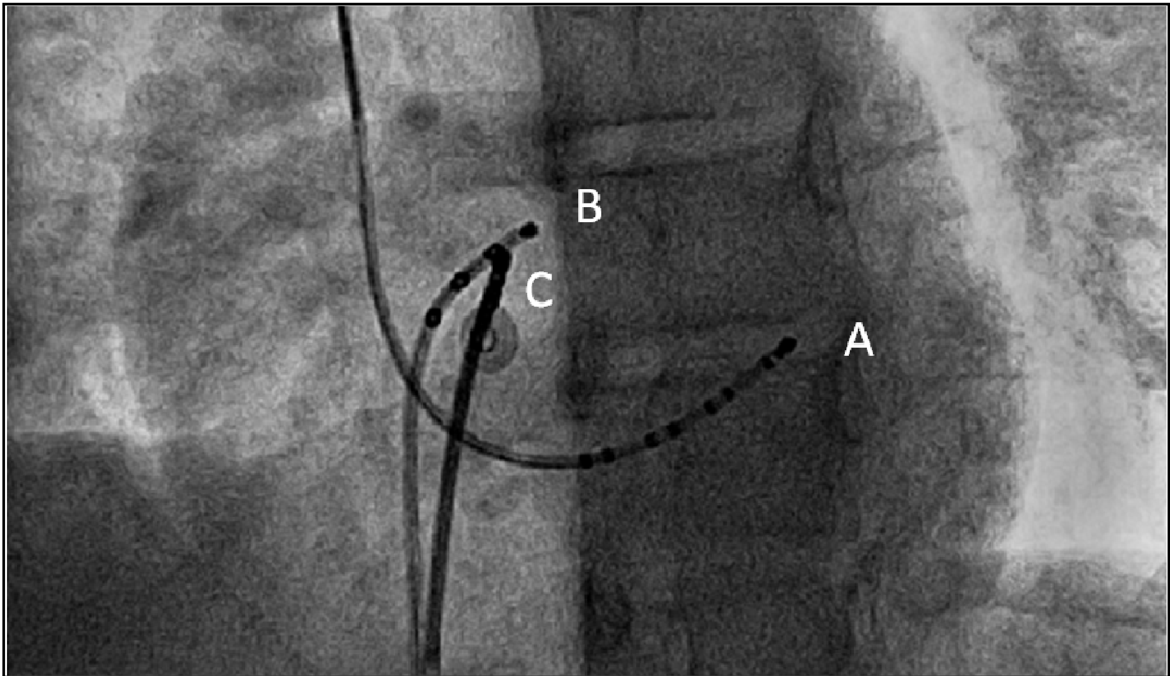
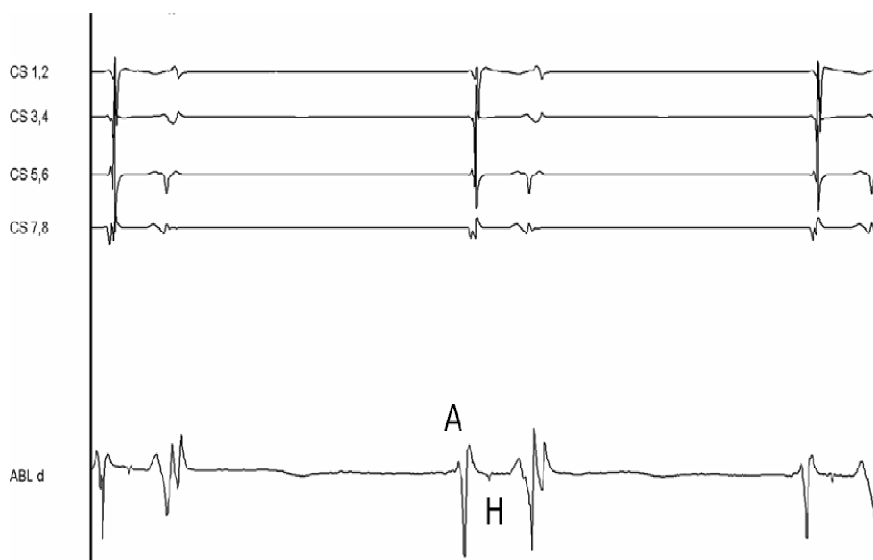


Figure 10 Intracardiac signal recorded by ablator catheter (ABL d) in the site of AVF ablation by the right-sided approach, showing a large A wave (A) with a small or absent His potential (H).



Left-sided approach

In left-sided AVJ ablation, in the absence of a permanent pacemaker, it is mandatory to place a temporary pacing catheter in the RV, as for a right-sided approach. The ablation catheter is inserted into the femoral artery and positioned through the aortic valve into the left ventricle (Figure 11). The catheter is withdrawn so that the tip lies against the membranous septum a few millimeters below the aortic valve at the point of recording the largest His deflection with a small A wave (Figure 12). Often, no atrial electrogram may be seen, and in this situation, the best His signal should be sought. The presence of a large A wave suggests that the tip of catheter is close to the left atrium above the aortic valve; ablation must not be attempted at this site. A good radiological reference for the left-sided catheter tip is a right-sided recording catheter placed in a conventional manner over the His bundle.

Left-sided ablation with a retrograde approach is contraindicated if there is an aortic mechanical prosthesis. Complications and technical problems are more common in the presence of disease of the aorta or aortic valve, if the patient is old, or if the patient has peripheral or coronary artery disease. In this circumstance, a further attempt should be considered from the right side on another occasion. The danger of inadvertent placement of the ablation catheter in coronary artery and the potential for damaging the aortic valve during a left-sided approach should be recognized.

Figure 11 Left anterior oblique projection showing the left-sided approach for AVJ ablation. (A) Catheter in coronary sinus, (B) catheter in the His bundle position, and (C) ablator catheter positioned against the membranous septum a few millimeters below the aortic valve.

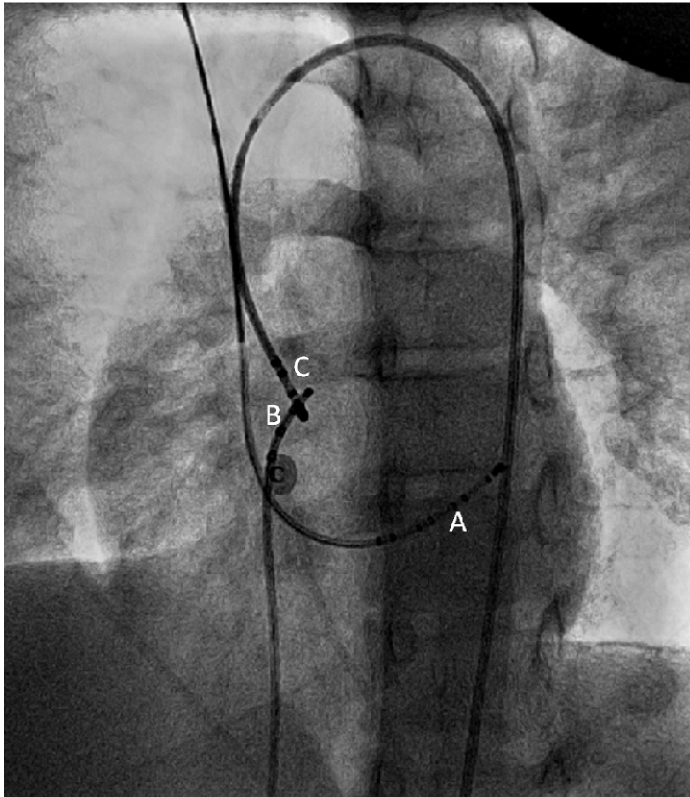
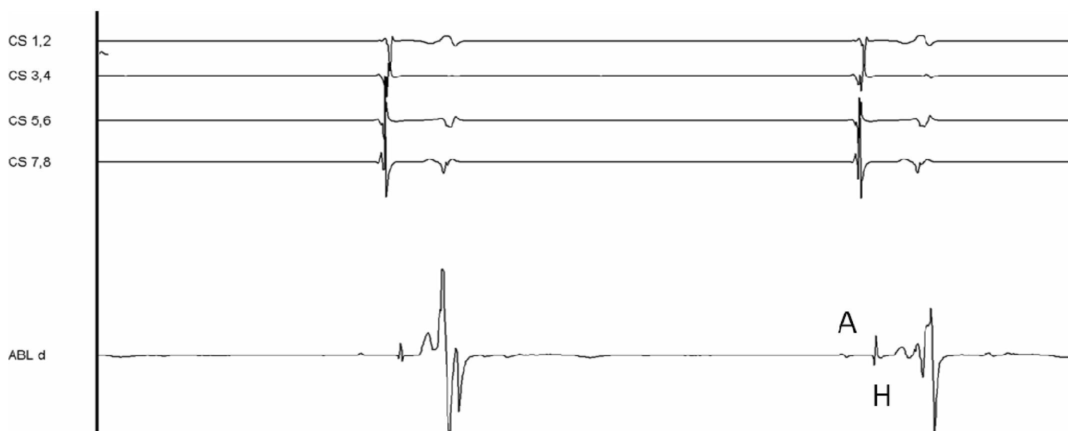


Figure 12 Intracardiac signal recorded by ablator catheter (ABL d) in the site of AVJ ablation by the left-sided approach, showing a large His deflection (H) with a small/absent A wave (A).



Energy and ablators cathethers

DC Ablation

DC electrical energy is delivered through catheter from a standard defibrillator/cardioverter. Most standard defibrillator/cardioverters deliver between 1 and 3 kV to a specific electrode to which the device is connected. Commonly peak voltage is achieved in 1 to 2 msec, which is associated with a peak current flow of 40 to 60 amperes. In most instances, a single electrode, usually the tip of a catheter, is used as the cathode, and an indifferent black plate serves as an anode sink for the discharge. This technique allows the delivery of high-energy shocks in the range of 100 to 400 joules per shock. When DC catheter ablation is performed using a standard defibrillator, a vapor globe is initially formed as a result of electrolysis. This globe subsequently expands and becomes ionized, ultimately resulting in arcing. The arcing is associated with extremely high temperatures and a veritable concussive explosion in the heat. The explosion can be thought of in terms of a compressive shock that is due to the formation of a vapor globe within non compressible blood, followed by rebound shocks with the collapse of the globe. The arcing explosion has led to the widespread use of the term *fulguration* for this type of catheterization. According to Fontaine et al. (25), a shock energy of 40 to 160 joules produces pressure waves of 2.5 to 7.5 atmospheres.

Despite the high temperature associated with the arc, there is insignificant heating of the tissue, suggesting that thermal damage is not the primary mechanism by which the fulguration works. There is still debate as to the relative role of barotrauma and the effects of the high-energy electrical field of the DC shock as the cause of the ultimate pathologic damage and electrophysiologic sequelae. Most investigators believe that it is the direct electrical effect that disrupts myocardial membranes, resulting from either

dielectrical breakdown, change in membrane lipids, or physical compression and mechanical disruption of the membrane (26).

Barotrauma is undesirable, despite the fact that it may play a role disrupting and/or separating myocardial fibers in some types of ablation. Barotrauma associated with fulguration has consistently caused rupture of the coronary sinus when energy is delivered there and has been associated with rupture of other cardiac structures, myocardial dysfunction, and arrhythmias (18,25,26,27,28 and 29). Experimental studies have shown that the extent of damage that is produced by DC shocks is directly related to the amount of energy delivered (23,24 and 25,28,29,30 and 31). The integrity of catheters is frequently disrupted in the caring process, which is due to the transient high temperatures (24,25,32). Arcing not only affects the distal tip but can also result in damage to more proximal electrodes, since a high voltage gradient is formed between the distal electrode and more proximal ring electrodes by the expanding vapor globe. More work is necessary to develop catheters capable of withstanding fulguration-type shocks *if* this technique is going to be used in the future. This is unlikely to occur. In an attempt to avoid barotrauma and arcing, Holt and Boyd (33) developed a new DC energy-delivery system that does not result in arcing and, hence, fulguration This is accomplished by shortening the pulse to 10 to 20 sec, which is too short for the development of the vapor globe and caring to occur. This allows delivery of lower energies but reasonably high voltages (1.8 to 2.8 kV), and up to 25 amperes of current.

Pathologically, fulguration shocks produce a somewhat patchy contraction band necrosis. The volume of damage done generally correlates with the amount of energy delivered and is relegated to the electric field (28,29 and 30). Perhaps it is the patchiness of the damage that apparently makes the tissue more arrhythmogenic than the homogeneous necrosis associated with cryothermal or radiofrequency (RF) injury.

Radiofrequency Energy

Radiofrequency (RF) energy is generated as an alternating current at a frequency of 300–750 kHz (range 100–2000 kHz) delivered between the tip of an ablation catheter and a cutaneous patch (34). The sinusoidal waveform creates a potential difference between the cutaneous patch and the catheter tip, which alternates in polarity. Because of the small surface area of the tip of the catheter relative to the cutaneous patch, the current density will be high at the tip and low at the patch. During RF application electrical energy is converted to thermal energy by resistive heating. The heat that is generated is transferred to the subjacent cardiac tissue primarily by conduction and to a minor extent by radiation, which decreases by the fourth power of the distance from the catheter tip. Heat is simultaneously dissipated by convection into the blood pool. Since the catheter tip-myocardial interface is the major resistor in this AC circuit, current density and heat are greatest at the catheter tip and minimal at the cutaneous patch. Effective heating of the myocardium is critically dependent on catheter contact and stability as well as on the surface area of the catheter tip. Poor contact or stability will lead to heat loss to the blood pool and failure to generate adequate myocardial temperatures despite application of high voltage/power. Although a larger surface area can lead to greater lesion size, it will require delivery of greater power, since the greater surface area will be subjected to greater convective heat loss to the blood pool to which it has greater exposure. Thus maximum lesion size using a 4–5 mm ablation tip can be accomplished using a maximum power of 50 watts while up to 100 watts is required to achieve maximal lesion size using an 8–10 mm catheter tip. Electrodes of 4–5 mm through which the RF energy is delivered provide the best control and most reasonably sized lesion to accomplish the tasks of catheter ablation for most paroxysmal supraventricular arrhythmias (35,36,37 and 38). The size of the lesions produced by radiofrequency are smaller than those associated with fulguration; moreover, scar tissue

limits the ability to transfer thermal energy, making radiofrequency ablation of ventricular arrhythmias associated with scarred endocardium more difficult. A variety of deflectable catheters are available that can have different arcs of curvature, bidirectional deflecting capabilities (with similar or different lengths of deflection), rotational capability, or magnetic sensors that allow for precise localization in 3 dimensions.

Ablation catheters typically have 4–5 mm tips and can be deflected in a variety of different manners. This particular catheter has deflection capabilities in two directions with different curves in each direction. RF ablation results in thermal injury with coagulation necrosis and desiccation when tissue heating exceeds approximately 50°C for at least 10 sec (19, 20, 21 and 22,34,35). Application of RF energy results in a lesion with a volume half-time of »8 sec and maximum volume achieved in 30–40 sec. As heat is produced at the catheter-myocardial interface the impedance drops. A drop of impedance of 5–10 ohms is a sign of conductive heating to the subjacent tissue. The lesion is smaller than that seen with DC ablation and is more homogeneous. If the temperature at the electrode-myocardial interface increases excessively, a rise in impedance develops because of tissue necrosis as well as development of a coagulum on the catheter tip. A drop in current necessarily occurs with an impedance rise. Once a rise in impedance appears, it is mandatory to remove the catheter and wipe off the coagulum, which is a potential source of emboli. If the tissue is heated to >100°C steam will be generated as a consequence of boiling within the myocardium. This often can be detected as an audible popping sound, which will just precede a marked rise in impedance. The steam can produce myocardial rupture and subsequent tamponade. Smaller tears may also occur. Various catheter modifications have been evaluated to optimize the size of and control the lesions produced by radiofrequency. The initial modification of ablation catheters was use of thermocouples or thermistors imbedded near the catheter tip to provide information as to the temperature generated at the tip of

the catheter at any given power. This modification was deemed necessary because of the inability to relate the power used to tissue heating.

These are closed loop-temperature control systems such that the power is automatically adjusted to maintain a desired temperature. Such a system allows for maintenance of electrode temperature despite changes in catheter contact produced by respiration or unstable catheter position. Such control of temperature largely (but not entirely) avoids the formation of coagulum. Unfortunately, the thermistor or thermocouple does not accurately provide information about tissue temperature.

Due to convective heat loss to the blood the temperature recorded at the catheter tip may give a falsely low reading relative to tissue temperatures achieved if inadequate catheter contact is present. This might result in intramyocardial tissue boiling and steam production. Thus, to assure that excessive intramural heating does not take place, target temperatures should be set at 55–65°C. Another modification to increase lesion size has been the development of cool-tip catheters. By cooling the catheter tip more voltage can be applied without a rise in temperature at the catheter-myocardial interface. This results in a greater current density at the catheter-tissue interface, which results in a larger volume (and depth) of tissue heated by conduction. While cool-tip catheters can produce larger lesions, one cannot control the lesion size by assessing catheter tip temperature, since it is constantly being cooled. Excessive tissue heating, steam formation, and myocardial rupture can easily occur if the tip temperature is allowed to get too high. As a result, I recommend using impedance as the main method of assessing lesion formation. A 10-ohm drop in impedance is ideal, and usually occurs at tip temperatures of 35–50°C. The method of cooling varies from an internal counter-current system to catheters in which the saline is flushed through a lumen at the tip of the catheter or through pores at the tip of the catheter. The latter two methods necessarily result in introducing a variable amount of saline into the circulation blood volume

depending on the number of and time over which the lesions are given. Delivery of RF energy in pulses is another method of enlarging lesions. This occurs because of more rapid cooling at the catheter-tissue interface than in deep tissue between pulses. This allows for delivery of greater peak voltage and current (as with cool-tip catheters) while the deeper tissue temperature continues to rise between pulses. The pulsing capability has been built into some generators, although they are not widely available.

The major advantages of RF energy are absence of barotrauma, lack of requirement of general anesthesia, lack of muscle stimulation, and the ability to control very focal injury. It is because of these factors that RF ablation has supplanted fulguration as the method of ablation in most centers. Another advantage of RF ablation is the fact that intracardiac electrograms may still be recorded throughout the procedure; and following delivery of RF energy, the catheter electrodes function perfectly to record and stimulate. Nevertheless, RF techniques remain limited by the requirement of good contact to achieve appropriate damage and by the fact that the extent of tissue damage is not predictable.

Laser Ablation

Lasers have been used in surgery for many years. In the past decade, there has been interest in using lasers intraoperatively for the management of ventricular arrhythmias or the creation of A–V block (39,40,41,42 and 43). There has also been an interest, however, in the development of catheter delivery of laser light (44). The mechanism by which laser ablation works is based on heat generation within tissue by the conversion of light energy into thermal energy. Depending on the laser used, the distribution of light within the tissue and the degree and site of destruction are quite variable and highly dependent on the wavelength. The two major laser systems used are argon laser light, which has a wavelength of 500 nM, and the ND:YAG laser, which has a wavelength of 1060 nM. With the argon laser, the light energy is absorbed rapidly in the

first few millimeters of tissue, resulting in surface vaporization with crater formation. In contrast, the ND:YAG laser is associated with significant scatter in tissue, causing more diffuse and deeper tissue injury resulting in photocoagulation necrosis. Lee et al. (45) compared the electrophysiologic effects of the ND:YAG laser with DC shock in normal canine left ventricular endocardium. While the pathologic responses were similar qualitatively, the laser lesions were associated with less ventricular arrhythmias. The gross lesions produced by 40 to 80 joules of laser energy were comparable to lesions produced by 100 to 200 joules of DC shock in volume; however, lesions produced by the ND:YAG laser are homogeneous and well circumscribed. The advantages of laser-delivered energy are that it takes a short period of time to deliver and the amount of energy delivered can be easily controlled. However, if catheter delivery systems are to be developed, contact issues with the endocardium the site in the heart at which ablation is to take place (e.g., venous and arterial blood absorb laser energy to different degrees), and the ability to focus the laser on the specific target are issues that need further resolution. In addition, laser-delivery systems are the most expensive form of ablation, and as such, I believe will be the least widely employed.

Cryoablation

Cryoablation has been used in the surgical treatment of a variety of arrhythmias for 25 years. Well demarcated, homogeneous lesions produced by endocardial or epicardial application are similar to those produced by the ND:YAG laser. The lesions produced preserve the underlying fibrous structure, so they are inherently stronger and less likely to rupture than RF lesions. They were also apparently nonthrombogenic (e.g., no emboli in the absence of anticoagulation). While near transmural lesions can be produced intraoperatively using temperatures of –60°C in the presence of cold cardioplegia, achievement of such lesions with a catheter-based delivery system has not been definitively established at this time. However, several companies are developing

catheter-based cryodelivery systems. The blood pool is a major impediment to achieving temperatures necessary to create permanent lesions that are adequate in size using cryothermia. At least two catheter systems are currently under investigation. The ability to reversibly cool tissue makes cryothermia a means to map sites for permanent ablation.

Ultrasound

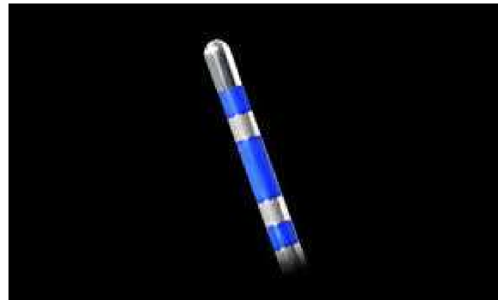
Ultrasound energy converts mechanical energy to heat. The frequency required to produce destructive lesions ranges from 4–9 MHz. Ultrasound can be focused, and therefore has the unique property of not requiring tissue contact. Preliminary studies have applied ultrasound to the ablation of focal triggers by isolating the pulmonary vein from the atrial myocardium using ultrasound delivered via a balloon placed in a pulmonary vein (46). There are also trials under way to assess its use in ablation of ventricular tachycardia. Theoretically, one could design catheters that have transducers that can both deliver energy and characterize the tissue response to the delivered energy. While this technique is exciting, the lack of electrophysiologic information associated with it makes its major use for anatomically based ablation.

For AV ablation are usually used radiofrequency delivered trough a deflectable ablator catheter. The by far most used tip size are: 4mm tip or 8 mm tip (Figure 13 A, B and C). Eight mm tip is able to provoke a larger lesion in comparison with 4 mm tip. Temperature-controlled ablation is preferred, for which a temperature of 60° to 70°C should be set, with a maximum power output of 40 to 50 Watts. Energy is applied for 10 to 30 seconds. When AV block or accelerated junctional rhythm occurs, energy delivery may be continued for a further 30 seconds, up to a total of 60 seconds.

Figure 13

A: deflectable ablator catheter

B: 4 mm tip



C: 8 mm tip

Confirmation of AV block

After successful ablation, temporary pacing must be commenced immediately if the escape rhythm is unstable or absent, or if there is a hemodynamic compromise. The regularity and width of the escape rhythm (if present) should be recorded by reducing the rate of pacing at regular intervals during the observation period. The target of ablation is a stable, third-degree AV block for at least 10 minutes despite giving 1 mg intravenous atropine.

Pacemaker implantation

There are four strategies for AVJ ablation and pacing:

A single procedure in which ablation of the AVJ is followed by pacemaker implantation.

If the right-sided ablation fails, then the pacemaker is implanted at the session and the patients returns at a later date for a left-sided approach to AVJ ablation.

The pacemaker is implanted initially and the patients is then readmitted approximately 1 to 3 months later (i.e., when the pacemaker system is considered stable and wounds have healed) in order to review the need to proceed to AVJ ablation, with sequential right-sided and then left-sided approaches as necessary.

As for point 1, but with delay between ablation and permanent pacing of up to 24 hours. This is the least favored approach and should be performed only when local factors demand it. The patient must be carefully monitored during the intervening period owing to dependency on the temporary pacemaker.

Due to some malignant arrhythmias (polymorphic VT, torsade de pointes and VF) and QT interval modifications observed immediately after AVJ ablation (with probably different mechanisms: bradycardia and sympathetic tone increase) is important to reduce this risk by routine reprogramming the pacemaker to pace at 80-90 bpm for some weeks after the procedure. After this first period is safe slowly reduce the lower pacing rate.

2.4 Results and Complications of Ablation

As discussed, ablation of the AVJ is easy to perform and can be carried out through either a right-sided or left-sided approach (47). Extensive experience of ablation through the right-sided approach and the higher complication rates associated with left-sided catheterization make the right-sided approach preferable. If this fails, the left-sided approach can be undertaken during the same procedure; while this requires fewer RF deliveries, it involves arterial catheterization. Complete AV block is achieved by means of such a sequential approach in more than 95% of cases; late regression of AV block occurs in 0% to 7% of cases. Periprocedural complications are <2% and procedure-related mortality is 0.1%, almost exclusively involving patients with severe heart failure (47).

In view of the results of open studies, meta-analyses, and randomized controlled trials, the clinical efficacy of "ablate and pace" can be regarded as well established (see tables in the following 2 pages).

Study author	Year	Study type	Nr patients	AF type	Average follow-up	End points	Results	Comments
Kay[6]	1988	Prospective, not controlled	12 AVJAP	Paroxysmal	8 ± 2 months	QoL and exercise capacity before and 6 weeks after ablation	Ablate and pace significantly improved QoL and exercise capacity	
Rosenqvist[7]	1990	Observational prospective single center	47 AVJAP	59% AF/AFL, 26% AVNRT, 12.5% AVRT, 2.5% AT	41 ± 23 months	Early complication and long-term outcome	4 early complications and 1 sudden death at 2 weeks. Improved activity level in 83% of patients with successful ablation. Significant decreased hospital admissions/year. Most patients with low LVEF showed a significant increase. New onset of CHF occurred after ablation in 4 patients (2 without SHD). Total mortality rate 17%, higher among patients with underlying SHD.	Direct current ablation tecnique
Rodriguez[8]	1993	Observational retrospective	30 AVJAP : group I LVEF <50% (N=12) , group II LVEF >50% (N=18)	Lone AF: 90% Paroxysmal	14 ± 20 months	Left heart chambers dimension and function	LVEF increased significantly and LVESV, LVEDV and LA dimensions decreased in group I. No changes in group II.	Group I had a longer history of AF (deterioration of LV function, maybe related to duration)
Marshall[9]	1999	Prospective single-center, randomized controlled trial	37 AVJAP (DDDR/MS pacing mode with slow- or fast-switch algorithm or VVIR); 19 drugs	Paroxysmal	18 weeks	Primary: QoL and symptoms Secondary:(1) comparison of QoL intrapatient and intergroups (2) exercise capacity and LVEF (3) complications, development of permanent AF	AVJAP is significantly better for controlling symptoms (−41%), palpitations (−58%), and breathlessness (−37%). DDDR/MS pacing improve QoL and all symptoms, except chest pain, compared with baseline (no changes with drug). VVIR pacing improved only palpitations. Permanent AF had a more frequent trend of prevalence in AVJAP group and develops faster compared with drug treatments.	Exercise tolerance and LV systolic function were not significantly affected by ablation and pacing or medical therapy.
Brignole[5]	1999	Controlled prospective multicenter randomized trial in severely symptomatic patients	22 AVJAP ; 21 drugs	Paroxysmal	6 months	Primary: QoL and specific symptoms. Secondary:(1) intrapatient comparison of QoL and specific symptoms (2) major clinical events (complications, development of permanent AF, number of hospitalizations and/or CVE)	Ablate and pace is highly effective and superior to drug therapy for controlling symptoms and improving QoL.	
Wood[10]	2000	Meta-analysis of all published outcome studies	1,181 patients (21studies)	97% AF: Paroxysmal and Permanent	—	QoL, cardiac function, exercise duration, healthcare use	Ablate and pace significantly reduces symptoms and health care use and improves exercise duration and cardiac function (except fractional shortening). 1-year total mortality 6.3%; sudden death mortality 2.0%.	

Study author	Year	Study type	Nr patients	AF type	Average follow-up	End points	Results	Comments
Ozcan[11]	2001	Observational retrospective case-control study	350 AVJAP ; 229 drugs	45% paroxysmal 50% chronic 5% AFL (7% lone AF)	36 ± 26 months	Long-term survival	Similar survival for patients with AF, whether they received ablation or drug therapy. AVJAP did not adversely affect long-term survival.	IMA, history of CHF, and treatment with cardiac drugs after ablation- independent predictors of death.
Ozcan[12]	2003	Retrospective case-control comparison between pt with FE> or ≤40%	56 AVJAP; 56 controls	Paroxysmal and permanent	40 ± 23 months	Long-term survival in patients with EFE_=40%	End FU: Mortality: 41%, 61% for cardiac causes. Normal survival in patients with reversible LV dysfunction. Poor survival in patients with persistent LV dysfunction.	LVEF increase in 68%; normalization of LVEF occurred in 29% of patients.
Weerasooriya[13]	2003	Controlled prospective randomized multicentre trial	59 AVJAP ; 50 controls	Permanent	12 months	Primary: cardiac function (echocardiographic data and exercise tolerance). Secondary: ventricular rate control and QoL.	No significant difference in LVEF or exercise duration. Peak ventricular rate lower in the AVJAP group during exercise and activities of daily life. Better QoL and symptoms in the AVJAP group.	
Brignole[14]	2005	Prospective randomized, single-blind, 3-month crossover comparison between RV vs LV pacing and RV vs BiV pacing	56 AVJAP (3 different pacing modalities (RV/LV/BvV)	Permanent	12 months (6-month phase 1; 6-month phase 2)	Primary: QoL and exercise capacity. Secondary: effect of AVJAP on QoL and exercise capacity in subgroups: (1) patients with ≤40% and LBBB or not and (2) different pacing modalities.	QoL and exercise capacity improved little with LV and BiV versus RV pacing. BiV pacing, but not LV pacing, was slightly better than RV in patients with LVEF >40% and no LBBB. Compared with preablation baseline, clinically significant improvement in all pacing modalities (better in BiV group).	
Gasparini[15]	2008	Observational multicentre longitudinal on patients undergoing CRT	118 AVJAP (CRT); 125 drugs + CRT	Permanent	34 (10–40) months	Overall, cardiac, and HF survival	Total mortality 4.6%/ year; cardiac mortality 4.1%/year. AVJAP group had less overall and cardiac mortality and HF	
Dong[16]	2010	Observational single-center study on patients undergoing CRT	49 AVJAP (CRT); 109 drugs + CRT	88% Permanent	2.1 (1.4–3.0) years	Clinical and survival outcomes in AF and heart failure population	AVJAP and CRT provides greater improvement in NYHA class and survival benefit (96.0% vs 76.5%)	

Paroxysmal AF

One non-controlled study (48) and two randomized controlled trials (51, 59) demonstrated that ablate and pace was superior to drug therapy for improving the quality of life of patients with drug-refractory, symptomatic paroxysmal AF. After ablation, palpitations were eliminated in 80% of patients, and specific symptom scores (effort dyspnea, effort intolerance, easy tiring) improved by 30% to 80%.

Permanent AF

Observational studies comparing designated patient end points with baseline measures (49,56) have suggested that ablation is effective for improving quality of life during long-term follow-up. In comparison with pre-ablation baseline values, quality of life and exercise capacity increased by 30% to 60% (although in one controlled study (60), about 40% of this improvement was attributed to the placebo effect). These results were partially confirmed by two randomized controlled trials (61) in which ablate and pace was compared with drug treatment during long-term follow-up. Ablate and pace proved more effective for controlling specific symptoms; however, it was less effective than observed in the intra-patient comparisons. Moreover, symptoms improved to a greater degree than quality-of-life indexes (Minnesota Living with Heart Failure Questionnaire [LHFQ], NYHA class, and activity scale).

In non-controlled studies, ablation has been seen to reduce left ventricular diameters, as measured by echocardiography. It did so especially in patients with depressed functional capacity, leading to an improvement in indexes of systolic function, ie, ejection fraction and fractional shortening (49, 50, 60, 62, 63). Exercise capacity was also reported to improve after ablation (48, 50. 51). In one controlled randomized parallel study,

however, no substantial changes in echocardiographic parameters or exercise capacity were observed (51).

2.5 Pacing Mode

The aim of permanent cardiac pacing is to restore AV synchrony during sinus rhythm and to provide an adequate increase in heart rate in response to physical activity during AF. These criteria are met by pacing in the DDDR mode. The VVIR mode, which is adequate during AF, is inadequate during sinus rhythm because it does not maintain AV synchrony and may cause pacemaker syndrome (47). Therefore, the VVIR mode is preferred in patients with permanent AF or with persistent AF who are at high risk for progressing to permanent AF after AVJ ablation (ie, patients aged >75 years or those who have previously undergone electrical cardioversion) (64,65).

2.6 Long-Term Follow-Up

Some data on the long-term effects of ablation suggest that initially paroxysmal or persistent forms of AF frequently progress to permanent AF following ablate and pace therapy (approximately 20% per year) (66). However, to date, ablate and pace does not seem to increase thromboembolic risk in patients with AF (67). Anticoagulant therapy should therefore be prescribed in accordance with the current guidelines. Finally, the results of randomized controlled studies (49, 51, 59) do not indicate an increased risk of death. Indeed, a meta-analysis carried out on 1,073 patients from 16 peer-reviewed studies revealed a one-year total mortality rate of 6.3% (95% CI; 5.5%–7.2%) and a one-year sudden death rate of 2% (95% CI; 1.5%–2.6 %). These Figures are very similar to the 6.7% total mortality rate and the 2.4% sudden death rate observed in 1,330 AF patients followed up for 1.3 years in the Stroke Prevention in Atrial Fibrillation Trial

(53). Thus, it is more likely that the long-term outcome is attributable to the natural course of the underlying disease than to an adverse effect of ablate and pace.

Ozcan et al (53) concluded that: A) in the absence of heart disease, survival among AF patients after undergoing ablate and pace is similar to that of the general population; B) long-term survival is similar both in patients who undergo ablation and in those on drug therapy; and C) ablate and pace does not impact long-term mortality. A recent subanalysis was conducted of the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) trial. In it, the authors showed how non-pharmacological therapy, even in more symptomatic patients with more frequent AF and faster ventricular rates during AF, led to increased time to cardiovascular hospitalization and reduced total length of stay compared with drug therapy (68).

In contrast with its usually excellent results, ablate and pace is ineffective in a minority of patients. With regard to paroxysmal AF, inefficacy was reported in 14% of patients in a study by Rosenqvist et al (49) and in 7% of patients in a study by Kamalvand et al (69). There are various possible explanations for this. Careful analysis of the follow-up of these patients has suggested that AF relapses were only partly responsible for their symptoms. Indeed, it is possible that their symptoms were linked to any of several factors: from DDDR pacing, to inappropriate programming, to the unfavorable hemodynamic effect of electrical stimulation from the RV apex. Moreover, Weber et al (34) found that palpitations are caused by a psychiatric illness in almost one third of all patients. In patients with congestive heart failure, early hemodynamic deterioration was observed by Vanderheiden (71) in 7% of cases and by Twidale (72) in (9%) of cases; mitral regurgitation and a very low ejection fraction were predictors of this adverse event. Although a randomized study (51) did not confirm this result, other studies have

found that pacing from the RV apex is not optimal because it determines a non-physiological asynchronous contraction (73).

2.7 AVJ Ablation and Cardiac Resynchronization Therapy (CRT)

We now consider two other clinical situations: cardiac resynchronization therapy (CRT) in patients who are candidates for AVJ ablation, and AVJ ablation in patients who are candidates for CRT (Figure 8)

CRT in candidates for AVJ ablation

In patients who require ventricular response control through AVJ ablation (see previous section), adding CRT ("upstream") is justified by the fact that the hemodynamic benefits of regularizing cardiac rhythm may be partially offset by the adverse effects of non-physiological stimulation of the right ventricle (25,38). Indeed, during RV stimulation, the ventricular activation sequence resembles that of left bundle branch block, ie, the RV is activated before the left ventricle (so-called interventricular dyssynchrony) and the interventricular septum is activated before the free wall of the left ventricle (intraventricular dyssynchrony). Both acute (75) and chronic(76) pacing, studies have shown that stimulating the RV induces dyssynchrony of the left ventricle in about 50% of cases. Moreover, some small studies (64,77) have suggested that biventricular pacing can exert a beneficial hemodynamic effect additive to that of the regularizing the ventricular rhythm by means of AVJ ablation. In sum, the abovementioned studies reveal that AVJ ablation associated to RV pacing is able to increase ejection fraction and reduce mitral regurgitation, and that biventricular pacing is able to double these effects.

Three randomized studies (56, 78, 79) involving a total of 347 patients, compared the short-term clinical results of biventricular pacing with those of RV pacing. Individually, these trials were unable to demonstrate a statistically significant improvement in terms of survival, stroke, hospitalizations, or cost reduction. In two of the studies, biventricular pacing achieved a significant improvement in ejection fraction and exercise capacity. On the other hand, in non-controlled observational studies (80, 81), upgrading to biventricular pacing in patients who developed heart failure months or years after AVJ ablation and RV pacing was seen to produce a great clinical benefit. For example, in 20 patients who had become severely symptomatic 17 months after AVJ ablation, Leon et al (80) added biventricular pacing; this led to a 29% improvement in NYHA class, a 33% improvement in Minnesota LHFQ scores, and an 81% reduction in hospitalizations. Similar results were obtained by Valls-Bertault et al (81).

The last ESC Guidelines on cardiac pacing and cardiac resynchronization therapy published in 2013 (89) conclude that "There is evidence, from small randomized trials, of an additional benefit of performing CRT pacing in patients with reduced EF, who are candidates for AVJ ablation for rate control, in order to reduce hospitalization and improve quality of life. However, the quality of evidence is moderate and discordance of opinion exists among experts. RCTs are warranted". On the other hand "There is weak evidence that CRT is superior to RV pacing in patients with preserved systolic function" (Figure 14).

AVJ ablation in candidates for CRT

In patients with heart failure in whom CRT is indicated, regularizing the ventricular rhythm by means of AVJ ablation enables biventricular pacing to be optimized.

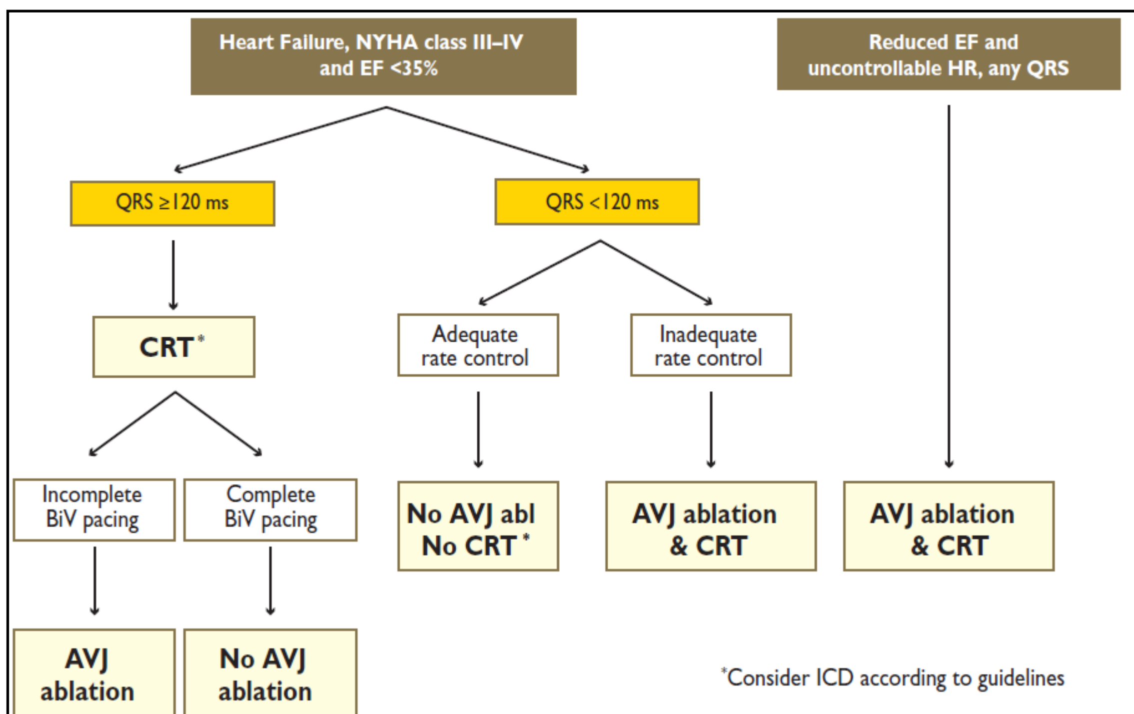
The large trials conducted on CRT have not included patients with AF. A possible

explanation for this omission lies in the fact that AF potentially reduces the advantages offered by CRT. First of all, the possibility of AV resynchronization is lost, and with it, the benefits that can be obtained from lengthening the phase of diastolic filling (since only intra- and interventricular dyssynchrony can be corrected). Second, the efficacy of CRT may be impaired by the presence of a high intrinsic heart rate that renders biventricular pacing incomplete. In a small Holter-controlled study (82) only 47% of patients had complete biventricular pacing in more than 90% of beats, while the others had fusion beats (60% of beats) and pseudo-fusion beats (24% of beats); the patients with complete capture displayed a better clinical response to CRT (responders: 86% vs 67%; $P = 0.03$). AV node ablation is the best way of completely controlling the heart rate and, at the same time, obtaining a regular ventricular rhythm. Moreover, this procedure offers the even greater advantage of ensuring effective CRT by means of constant biventricular pacing.

Gasparini et al (83) compared the efficacy of biventricular pacing in 48 patients with permanent AF who had not undergone AVJ ablation because their ventricular rate was apparently well-controlled by drug treatment (>85% of beats were placed in the biventricular mode) and 114 patients who had undergone biventricular pacing after AVJ ablation. During 4 years of follow-up, they observed an improvement in ejection fraction, inverse ventricular remodeling, and an increase in exercise capacity only in those patients who had undergone ablation. The improvement observed was of similar magnitude to that seen in patients in sinus rhythm. Similarly, in a study by Ferreira et al (84) the percentage of responders (52%) was significantly lower in AF patients who had not undergone AVJ ablation than in those who had (85%) or in those in sinus rhythm (79%). Indeed, Koplan et al (85) demonstrated that the clinical efficacy of CRT is proportional to the percentage of biventricular pacing achieved; in patients who had

93% to 100% of their beats paced in the biventricular mode, the risk of events during follow-up was 44% lower than in patients who had 0% to 92% of biventricular pacing ($P < 0.001$). Patients with a history of tachyarrhythmia were more likely to have had fewer than 92% of their beats paced in the biventricular mode. In some studies, however, the favorable effects of CRT have been documented even in the absence of AVJ ablation. Some authors (86,87) have reported similar results in terms of mortality and functional capacity in AF patients and patients in sinus rhythm who have not undergone AVJ ablation. In one multicenter study, (88) no differences in functional capacity or ventricular remodeling emerged between patients who had undergone AVJ ablation during CRT and those who had not. The last ESC Guidelines on cardiac pacing and cardiac resynchronization therapy published in 2013 (89) conclude that "AVJ ablation should be added to CRT in case of incomplete BIV pacing" (Figure 14).

Figure 14 from "2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy"



3. Review of literature on histologic findings after AVJ ablation

While several studies have been published reporting histologic effect of ablation on AV conduction system in dogs (90-97), only few case reports are available on histologic effect of ablation of AV conduction system in humans.

In 1984 Ward (98) published the first case report about the histological effect AVJ ablation in a patients treated with direct current shock for refractory atrial tachycardia associated with severe left ventricular impairment. A standard bipolar pacing electrode was used to deliver one shock of approximately 275 watt on the region of the His bundle-AV node resulting in immediate AV block. Author reported that there were no signs of ablations at gross examination. At histological examination, the endocardium overlying the node was normal, and no inflammatory cells were present. The fibrous stroma of the node was condensed rather than increased in amount with morphologically normal nodal artery. There were no surviving AV nodal myocardial tissue. On the contrary, the penetrating AV bundle as well as the bifurcating AV bundle were present and contained the normal numbers of conduction fibers. Therefore morphological features were those of selective loss of AV nodal conduction fibres not associated with any evidence of damage of fibrous stroma, vascular system or endocardium in the vicinity. Author conclude that: "….the technique may be used with minimal damage to the heart provided that the number of shocks is small".

The same year Critelli (99) report a similar case in which histologic studies of the AVJ tissue that underwent ablation demonstrated severe damage to the nearby AV node and penetrating His bundle, while no damage to the branching His bundle or either bundle branch was observed.

In 1992 Bharati and Sheinman (100) published a detailed pathological examination of the heart including the conduction system from the world's first human who had catheter ablation of the AVJ who survived 3 years and 8 months, and later died of congestive heart failure. Two DC shocks of 300 and 400 joules were administered from throw a quadripolar electrode catheter positioned on the AVJ region to record the largest His-bundle potential.

Sequelae of the ablation procedures consisted histologically of chronic inflammatory cells, marked fatty metamorphosis with fibrosis of the atria, the approaches to the AV node, and the AV node, with almost isolation of the node from the atria, and considerable fibrosis of the bundle and bundle branches. In addition, there was fibrosis of the summit of the ventricular septum with chronic inflammatory cells.

In summary, author conclude that DC shock produce great damage and extensive lesions beyond the targeted area.

In 1991 Jackman (101) published a study on efficacy of AVJ ablation using radiofrequency energy in 17 patients. One patient died 13 days after ablation with acute heart failure and another patient underwent heart transplantation 10 months after ablation. In the first patient examination of the right heart showed a 1.0 x 0,5 cm area of flat hemorrhagic discoloration in the region of the AV node. Microscopic examination of the lesion showed atrial necrosis extending to a depth of 2 mm posteriorly involving the outer third of the AV node and to a depth of 5 mm anteriorly including the full thickness of the proximal His bundle. The distal His bundle was free of necrosis. Examination of the heart of the second patient showed an area of smooth endocardial fibrosis, measuring 1.5 x 1.3 cm, overlying the region of the AV node. Microscopically, there was nearly transmural fibrosis, completely replacing the AV node and extending into the proximal His bundle; the distal His bundle was spared. In summary, pathological examination of the heart in both showed necrosis of the AV node and origin

of the His bundle, without injury to the middle or distal His bundle. Therefore, radiofrequency energy produces more distinct and more localized areas of fibrotic changes with less impressive changes in the bundle, in comparison with DC shock.

Moreover to note, that each patient had, after successful ablation, a junctional escape rhythm therefore author conclude that the pathological examination of the heart in these two patients suggests that the presence of a junctional escape rhythm is dependent on avoidance of injury to much of the His bundle. Limiting the extent of injury may be easier to accomplish with radiofrequency current than with DC shocks.

Cesario in 2005 (102) reported the histology effect of a left side procedure of AVJ ablation. AV node was only partially replaced by collagen deposition at the site of first attempts of ablation from the right side. Also the His bundle showed only mild fatty infiltration. On the contrary, penetrating His bundle appeared completely replaced by the collagenous scar tissue.

Original contribution

1. Atrio-Ventricular Junction Ablation experience at the Cardiovascular Department , “All’Angelo” Hospital, Mestre, Venice.

1.1 Study population

The present study was conducted as a retrospective analysis of data collected in a single high-procedural volume center (EP Section of Cardiovascular Department, “Ospedale all’Angelo”, Mestre, Venice, Italy). From January 2005 to December 2014, we analyzed data from 62 consecutive patients who underwent AVJ ablation. Patients underwent ablation according with guidelines indications already presented in part 1 of the manuscript. The characteristics of study population are summarized in Table 3. Briefly, the mean age was > 70 years, more than 80% of patients had a chronic ischemic heart disease and they were largely affected by permanent atrial fibrillation. Most of the patients were in NYHA class III and the mean EF was <30%. At the time of AVJ ablation an ICD or a CRT–ICD device was already implanted in most of the study population.

Table 3

Baseline Characteristics of the Study Population	
Patients, n	62
Age, y	71± 5
Gender, m/f	34/28
AF duration (years)	6.2 ± 3.6
Type of AF	
- Paroxysmal, n (%)	58 (94)
- Permanent, n (%)	4 (6)
DM, *n* (%)	9 (15)
Hypertension, *n* (%)	58 (89)
Valvular heart disease, *n* (%)	7 (11)
Ischemic heart disease, n (%)	51 (82)
Left atrial diameter (mm)	46± 12
LVEDD (mm)	70,3 ±5,8
LVESD (mm)	55,1 ± 4,4
Left ventricular ejection fraction, %	29 ± 12
NYHA Class	
- II, n (%)	5 (9)
- III, n (%)	48 (77)
- IV, n (%)	9 (14)
Ca-antagonist *n* (%)	55 (89)
β-blockers, *n* (%)	57 (92)
ACEI/ARB, *n* (%)	60 (97)
Statins, *n* (%)	52 (84)
Previous PVI, n (%)	2 (3)
ICD or CRTD, n (%)	47 (76)

1.2 Material and methods

Written informed consent for AVJ ablation was obtained from all the study patients. Following light sedation, two punctures were made in the patients' right femoral vein. In patients without? a previous pacemaker, ICD or CRT-ICD implantation an electrode was passed to the right ventricle to allow rescue pacing. In patients that had a previous PM ICD or CRT-ICD implantation, the device was programmed in VOO at 30/bpm to obtain a pacemaker stimulation not susceptible to suppression by RF delivery and to allow rescue pacing. A second steerable, 4-mm tip catheter was placed across the superior tricuspid valve annulus (Cordis or Medtronic "Cournard"). Initially a His signal was sought and the catheter then withdrawn into the atrium until, ideally, the atrial signal was the same size as the ventricular signal, the His recording was early and the signal stable. This is the usual anatomical site of the compact node and is the target tissue. Energy was delivered for 30–60 s at a temperature of 60–70) C (using thermistor control) to a maximum of 60 Watts (8 mm EPT ablator). Two positive signs were sought as indicators of a successful ablation site: initial nodal acceleration and subsequent AV block (a sudden AV block without a preceding nodal rhythm suggests His bundle rather than compact AV node ablation). In absence of previous device a pacemaker a ICD or an ICD-CRT vas implanted. In permanent AF, a VVIR device was implanted, while patients with PAF received a mode-switching DDD system.

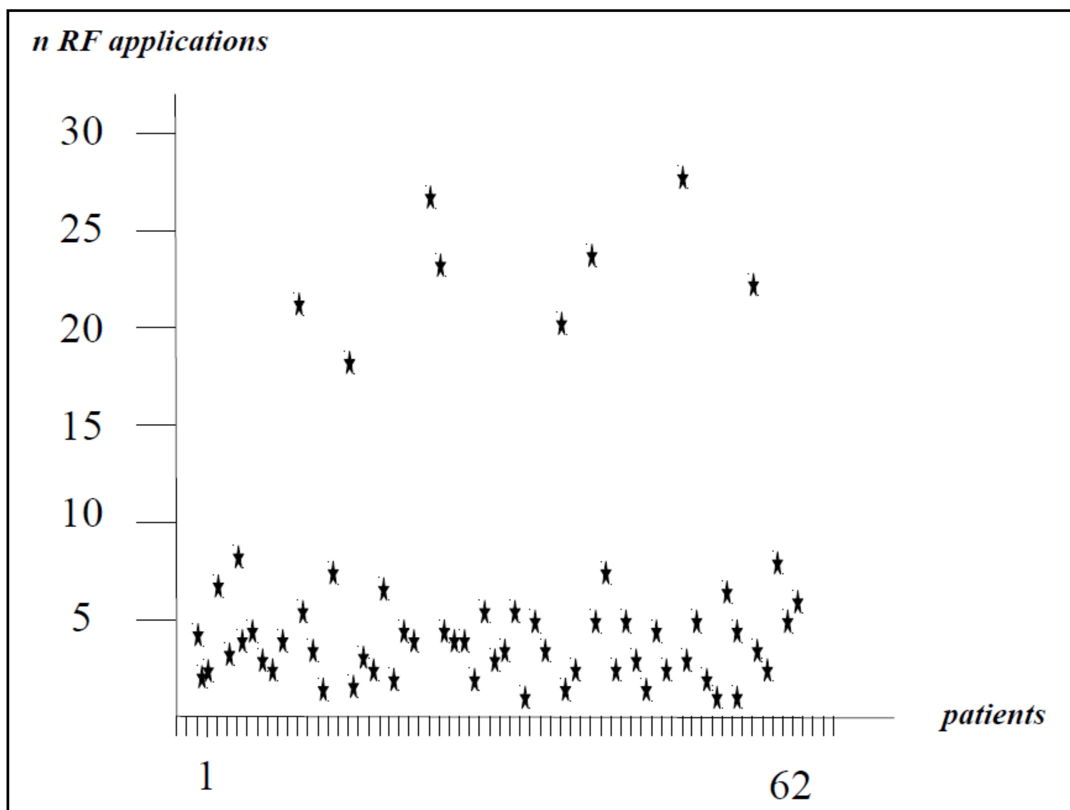
Statistical analysis

Continuous variables with normal distribution are expressed as mean $\pm$ standard deviation. Discrete variables are presented as percentages. Univariate comparisons between variables were made by means of Fisher's exact test. A p value < 0.05 was considered statistically significant. For analyses, commercially available computer software (SPSS version 12.0) was used.

1.3 Results

Success was achieved in all the patients population from the right side (62/62; 100%) with a mean procedural time of 21,4±18,1 min. The range of energy applications was 1 to 27 attempts (mean 6,7±5,2). Of these patients, 8 (13%) needed more than 15 energy applications (Figure 15). This group had a statistically significant increase of procedural time in comparison with the other patients (18,8±10,5 min vs 41,3±9,8 min = $p < 0,001$). We have experienced no major complications of this procedure related to the ablation and in particular there have been no subsequent sudden deaths. Only 3 (5%) experienced minor vascular complications, that were 3 groin hematomas likely related to the needs of a bridge with heparin i.v. to oral anticoagulation therapy. The long-term success rate was 100%.

Figure 15



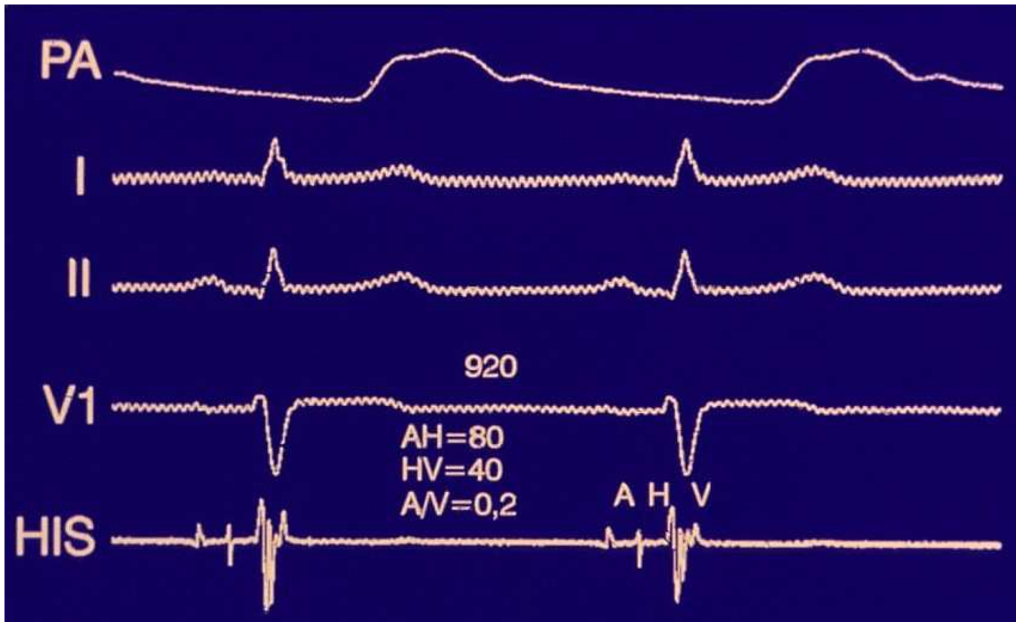
2. Clinico-pathologic correlation in four cases with "in vivo" AVJ ablation

2.1 Clinical history

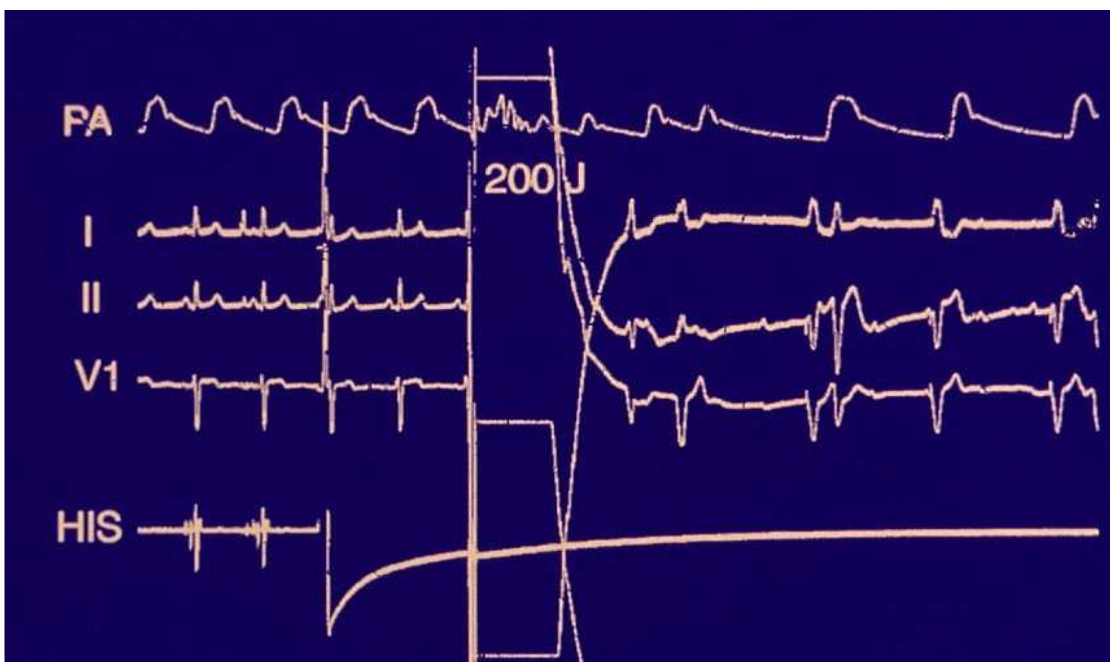
Case 1. Patient male, 65 years old admitted to the Cardiology Unit of Vicenza Hospital for palpitation and chest pain due to fast heart rate paroxysmal atrial fibrillation. Patient had a history of smoke and of peripheral arterial occlusive disease treated with left aorto-iliac bypass. Echocardiographic examination showed presence of bicuspid aortic valve and normal ejection fraction. Patient was discharged with prophylactic antiarrhythmic treatment (Propafenone 750 mg/day), but about two months later patient was re-admitted with the same symptomatology. At least patient underwent trans-catheter AVJ ablation. Procedure was efficient after two deliveries of DC shock (200J): the first on AV node region that was not efficient and the second on distal His bundle region resulting in AV complete block (Figure 16). After the procedure a DDDR pacemaker was implanted. Two weeks after ablation, the patient died suddenly and autopsy showed a massive pulmonary thromboembolism likely related to a previous right leg deep venous thrombosis.

Figure16

A) *Case 1- Intracardiac signal recorded by ablator catheter (HIS) in the site of second and efficient AVJ ablation (distal His bundle) showing a large His (H) and ventricular potentials (V) with a smaller atrial potential (A).*



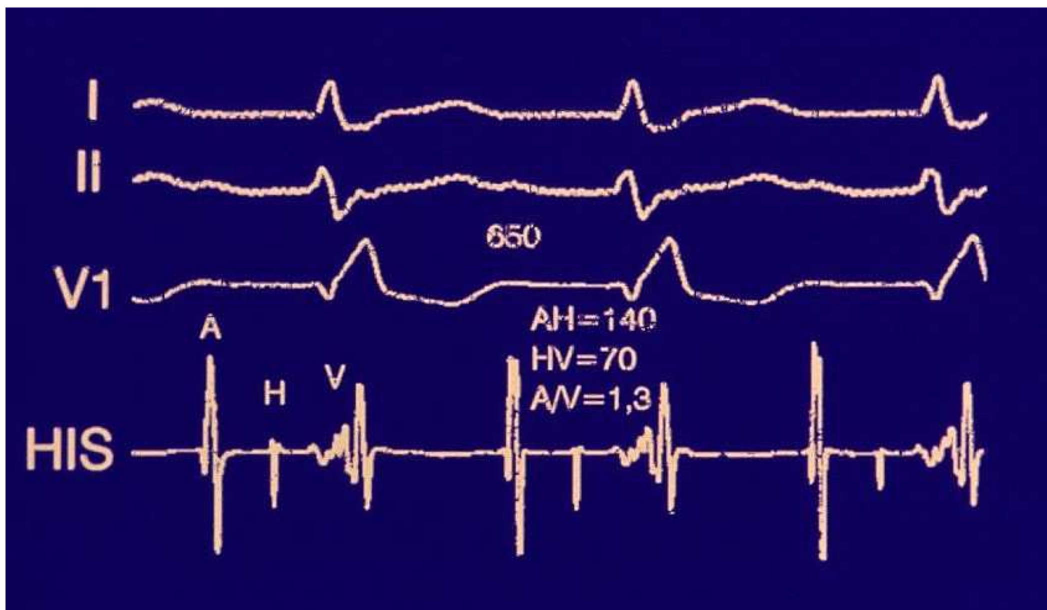
B) *Case 1- Complete AV block after 200 Joule DC-Shock*



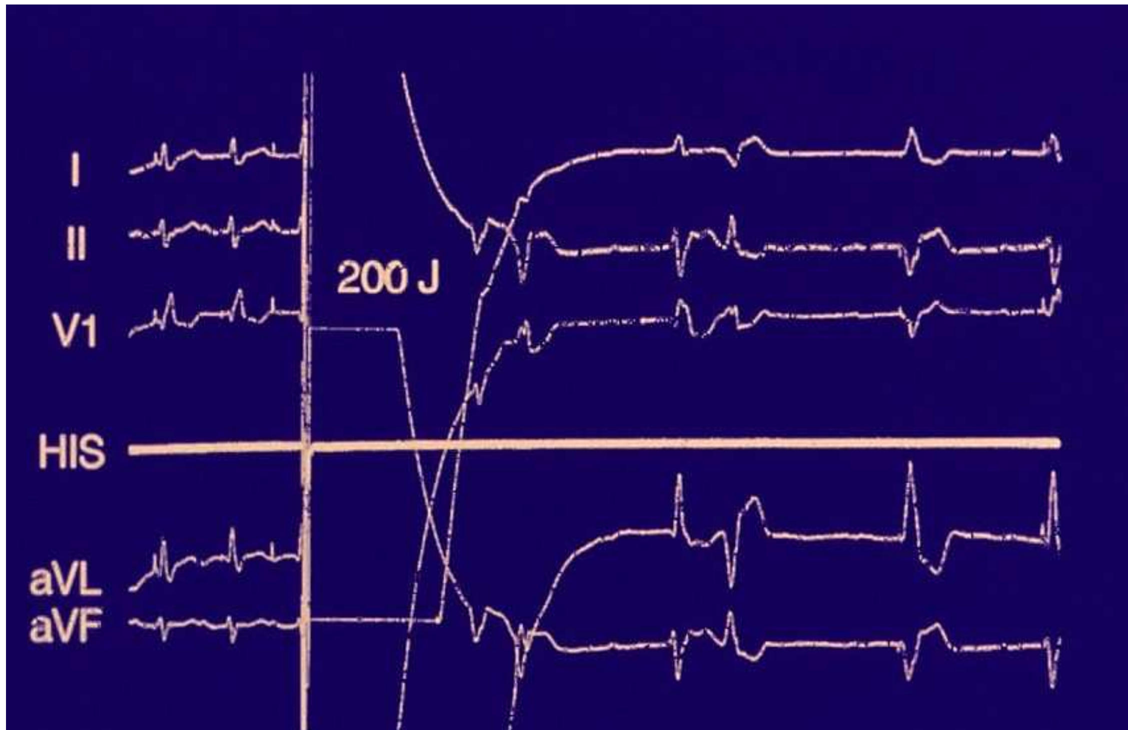
Case 2. Patient male, 67 years old admitted to the Cardiology Unit of Vicenza Hospital for palpitation and effort dyspnea due to fast heart rate paroxysmal atypical atrial flutter. Patient had an history of “potus”. Echocardiographic examination showed the presence of hypertrophic cardiomyopathy. Patient was initially treated with Verapamil but therapy was not able to control heart rate during episodes of atrial flutter and at least underwent AVJ ablation. Ablation was efficient after delivery of DC shock on AV node obtaining complete AV block (Figure 17). After the procedure a DDDR pacemaker was implanted. About one month later, the patient was readmitted for heart failure that became quickly refractory to any treatment and eventually died.

Figure 17

A) *Case 2- Intracardiac signal recorded by ablator catheter (HIS) in the site of efficient AVJ ablation (AV node) showing a large atrial (A) and His potentials (H) with a smaller ventricular potential (V).*



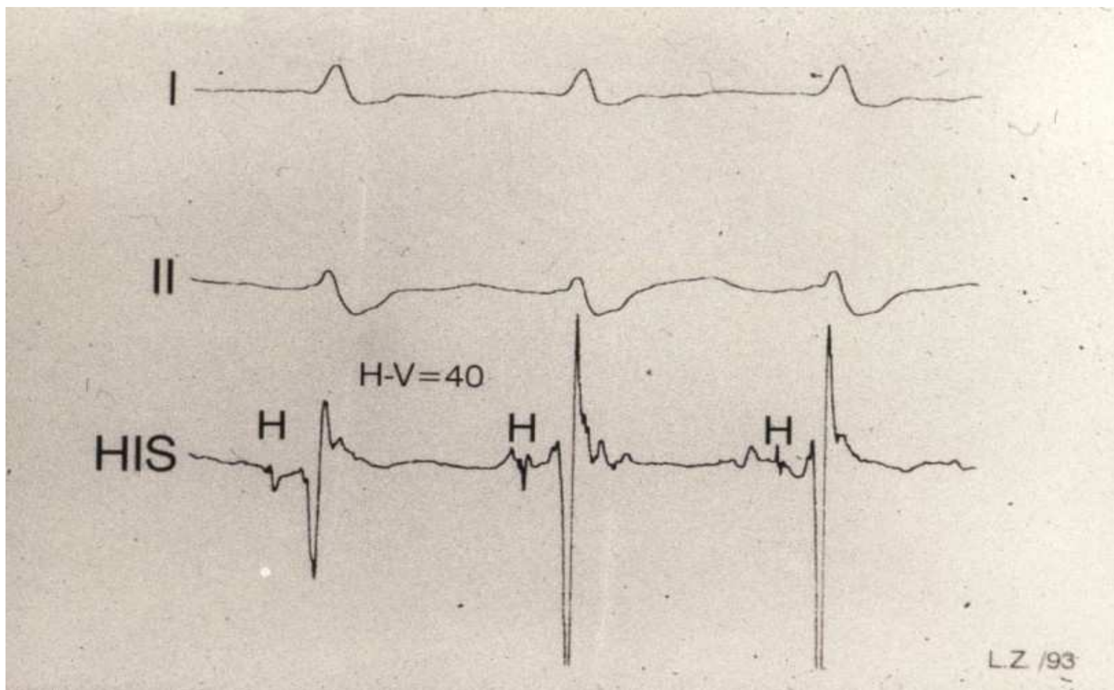
B) Case 2 - Complete AV block after 200 Joule DC-Shock



<u>Case 3</u>- Patient female, 75 years old admitted to the Cardiology Unit of Cittadella Hospital, Padova for palpitation and effort dyspnea due to fast heart rate permanent atrial fibrillation uncontrolled with drugs. Patient had history of malignant non-Hodking lymphoma. Echocardiographic examination showed normal ejection fraction with mild mitral and tricuspid regurgitation. Patient underwent AVJ ablation. After some non-efficient deliveries of DC shock from right side, at last AV complete block was obtained from left retroaortic approach (Figure 18). After the procedure, a VVIR pacemaker was implanted. About one month later patient died due to the progression of her malignant lymphoma

Figure 18

Case 3- Intracardiac signal recorded by ablator catheter (HIS) in the site of AVJ ablation by the left retroartic approach, showing a large ventricular potential with a small His potential (H).

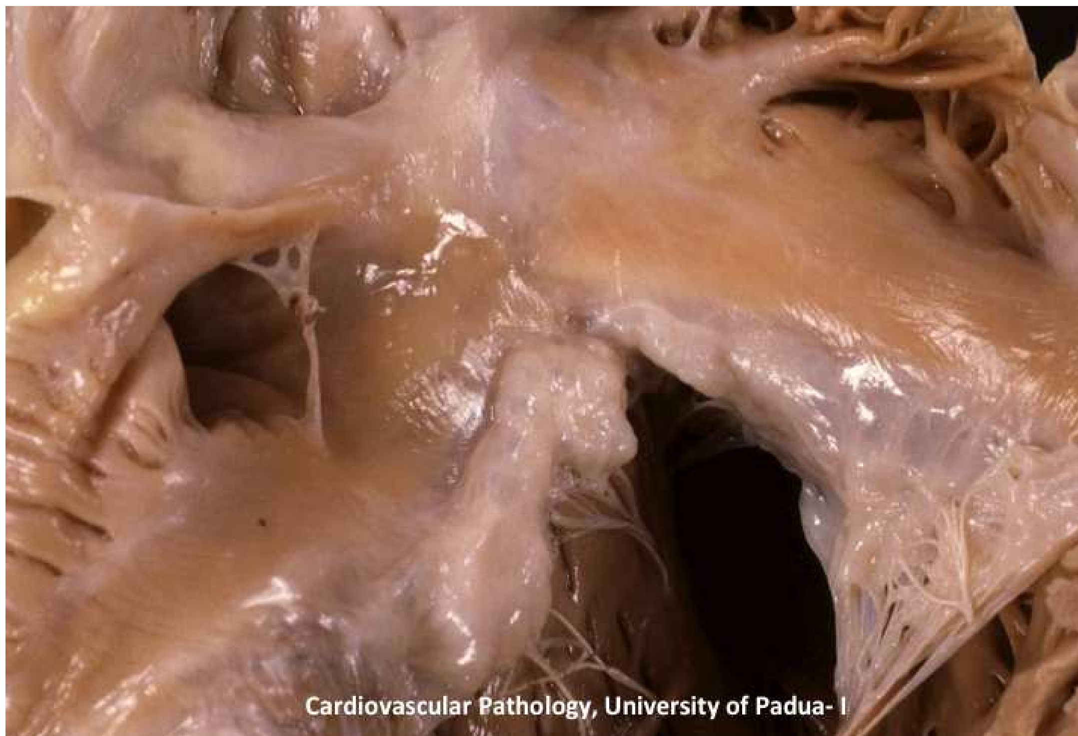


Case 4. Patient male, 53 years old admitted to the Cardiology Unit of Camposampiero Hospital, Padova due to several inappropriate ICD shock due to fast heart rate permanent atrial fibrillation. Patient had a history of ischemic heart disease (three previous myocardial infarction and surgical coronary artery bypass grafts). Echocardiographic examination showed a moderate dilatation of left ventricle with a severe reduction of ejection fraction (EF 34%), moderate mitral and trivial tricuspid regurgitation. The patient underwent AVJ ablation using radiofrequency energy. Ablation was efficacient from the right approach, obtaining complete AV block (intracardiac signals registration is not available). About one year later, the patient underwent heart transplantation due to severe symptoms of refractory heart failure.

2.2 Macroscopic anatomical examination

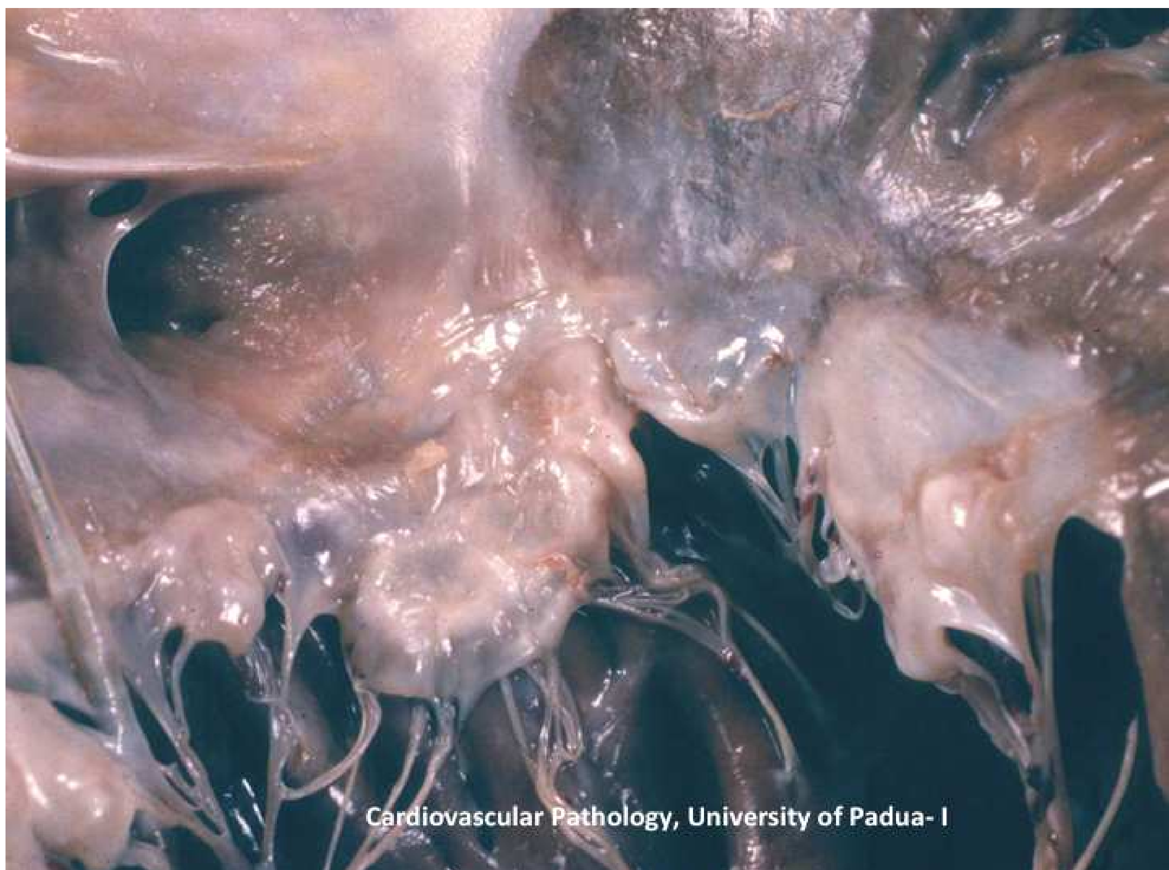
Case 1. The heart had a weight of 500 gr, a transverse diameter of 12 mm and a longitudinal diameter of 9 mm. The thickness of the left ventricle free wall was 12 mm and of the right ventricle 4 mm. There was a bicuspid aortic valve and a non-obstructive atherosclerotic coronary artery disease. In terms of interventional anatomy of the tricuspid valve, the septal leaflet was separated from the anterior leaflet (Figure 19).

Figure 19



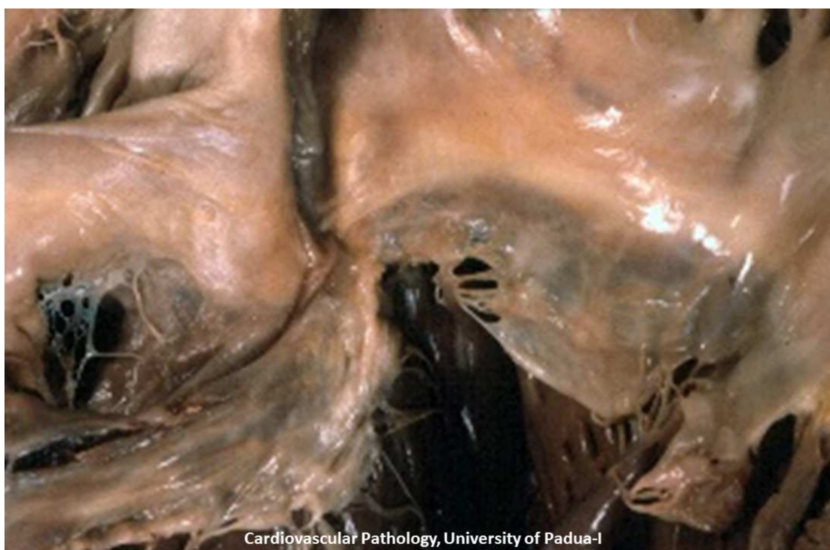
Case 2. The heart weight was 700 gr, with a transverse diameter of 12 mm and a longitudinal diameter of 9,5 mm. The thickness of the left ventricle free wall was 15 mm, of the septum 17 mm and of the right ventricle 5 mm. There was a bi-atrial dilatation with left atrial appendage thrombosis. The cardiac walls were stiff, particularly the left atrial wall, looking like a "stone heart" in keeping with "amyloid heart disease". In terms of interventional anatomy, there was continuity between the septal and the anterior tricuspid valve leaflets (Figure 20).

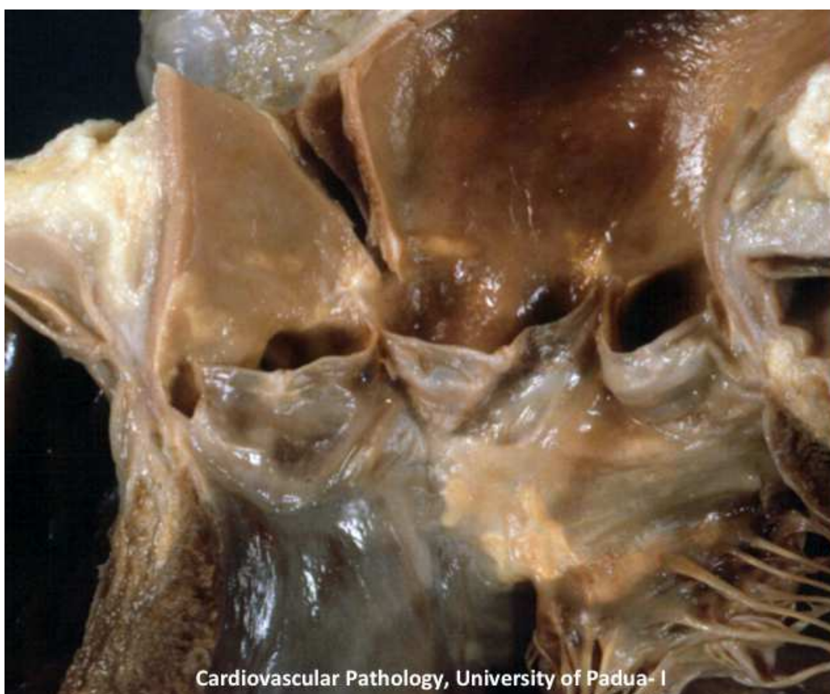
Figure 20



Case 3. The heart weight was 700 gr, with a transverse diameter of 10,5 mm and a longitudinal diameter of 13 mm. The thickness of the left ventricle free wall was 10 mm, of the septum 10mm and of the right ventricle 6 mm. A severe bi-atrial dilatation was observed. There was continuity between the septal and the anterior tricuspid valve leaflets (Figure 21a) and the ablation was eventually successful with a left-sided approach (Figure b)

Figure 18 a,b





Case 4. The explanted native heart at the time of heart transplantation had a weight of 520 gr, a transverse diameter of 9,5 mm and a longitudinal diameter of 11,5 mm. Chronic ischemic heart disease with posterolateral left ventricle aneurysm was evident, due to multi-vessel obstructive coronary artery atherosclerosis and with the sequelae of previous coronary artery by-pass grafts (i.e. left internal mammary artery anastomosed to left anterior descending and three saphenous veins anastomosed to diagonal and marginal branches of the left coronary artery and to the right coronary artery). The septal tricuspid valve leaflet was separate from the anterior leaflet.

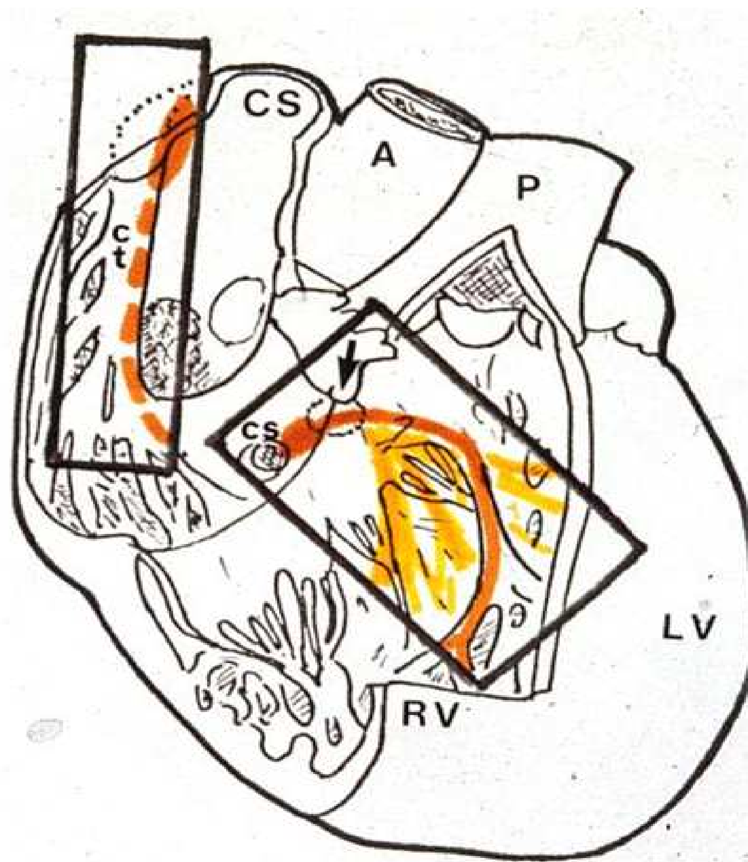
2.3 Pathology examination with serial sections histologic investigation of the conduction system

For the study of the cardiac conduction system, 2 comprehensive blocks of the sinoatrial junction and the AV specialized junction (including AV node, His bundle, and bundle branches) were removed according to a previously described method (103). Block 1 consisted of a portion of the right atrial wall including the lateral half of the funnel of the superior vena cava, sulcus and crista terminalis. This first block includes the sinoatrial node, its atrial approaches, the crista terminalis (with the upper 2/3 of the posterior internodal tract, the proximal part of the middle and anterior tracts) and the sinoatrial node ganglionated plexus. Block 2 consisted of the lower portion of the atrial septum, the trigonum fibrous, the anterior contour of the coronary sinus and the upper 2/3 of the ventricular septum. This second block contains the AV node, His bundle, bifurcation and bundle branches (Figure 22)

Entire blocks were fixed in 10% buffered formalin, embedded in paraffin, and serially sectioned at 7-µm intervals. At every tenth section, 1 section was stained with

hematoxylin-eosin and the next consecutive section with Heidenhain trichrome. The remaining sections were studied, when necessary, after examination of the initially mounted series. For each heart, the average number of histologic sections stained and examined is about 200.

Figure 22: study of the cardiac conduction system (103)



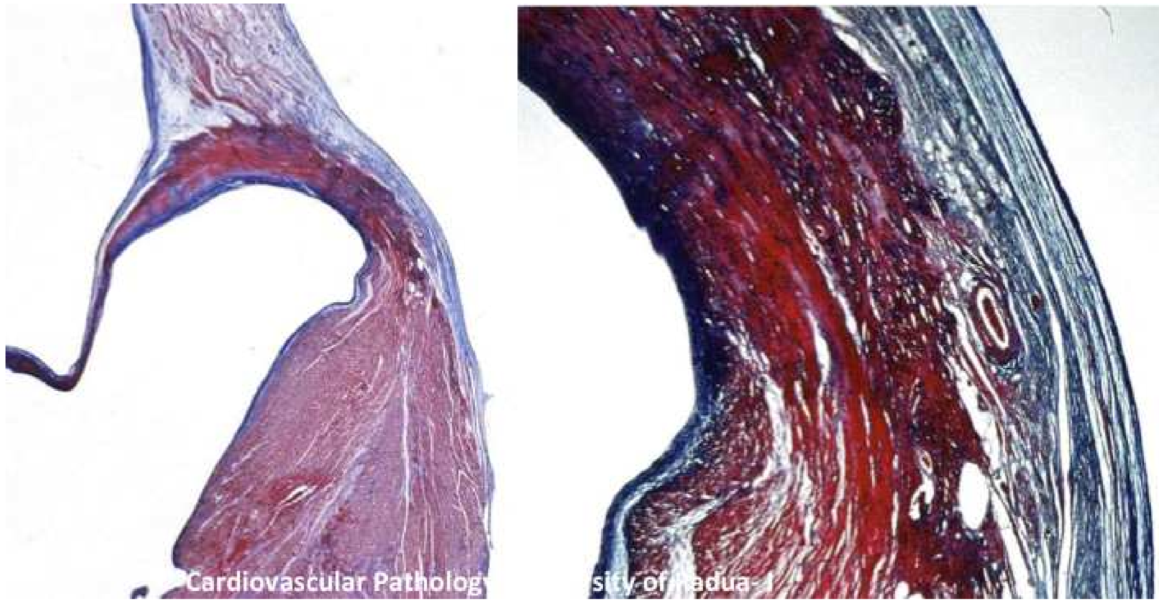
Case 1

At the gross examination the septal tricuspid valve leaflet was separate from anterior leaflet at the antero septal commissure and the membranous septum was well visible. On the right side of membranous septum, a small thrombotic formation was visible. The AV node was, as usual, on the right side of central fibrous body, immediately under the right atrial endocardium over the insertion of septal tricuspid valve leaflet, in front of the coronary sinus. The AV nodal artery was intact. The AV node appeared almost completely replaced by fibrous tissue, only few fibers around the AV artery in the compact region appeared preserved. Even the penetrating bundle appeared completely replaced by fibrous tissue, while the first tract of the common bundle was intact. The branching bundle was almost completely replaced by fibrous tissue with neovessels formation. The crista of interventricular septum showed a large region of necrosis, myocytolysis and repair fibrosis. In the distal region of branching bundle, immediately under the anteroseptal commissure, a mural thrombus 1,5 mm of diameter, likely the site of the second ablation, was visible. In the same section, over the insertion of septal tricuspid valve leaflet on the right side of membranous septum, a small thrombotic formation was also visible likely at the site of the first ablation. Here the branching bundle appeared replaced by fibro-fatty tissue. The origin of left and right bundle branches appeared completely replaced by fibrous tissue, and right bundle branch merged into an area of necrosis and reparative tissue on the right side of septal myocardium.

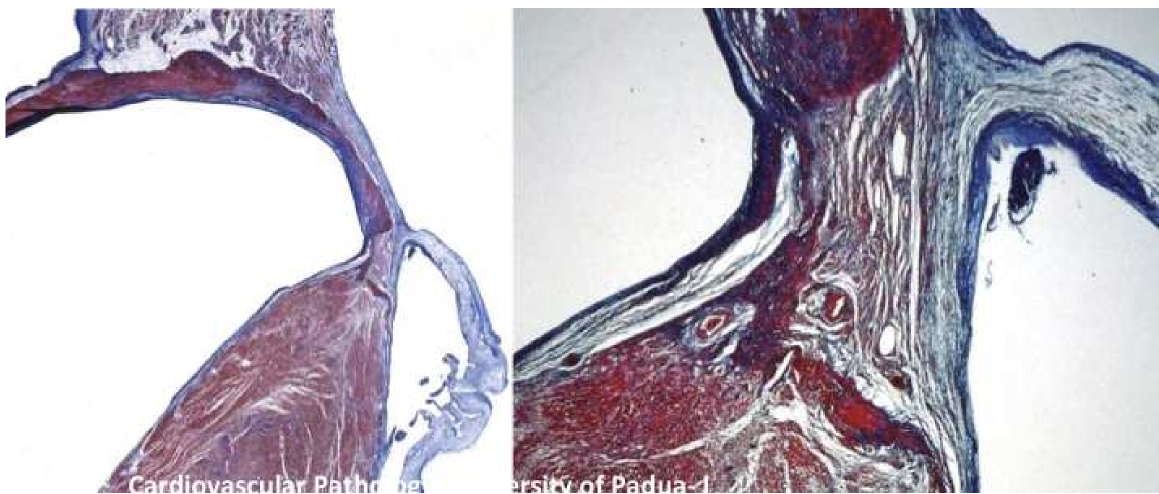
In conclusion, the AV conduction system resulted interrupted at two level: 1) AV node and penetrating bundle, while common bundle appeared preserved; 2) branching bundle and proximal tract of both bundle branches. Two mural thrombus were consistent with the sites of ablation (Figure 23).

Figure 23, Case 1

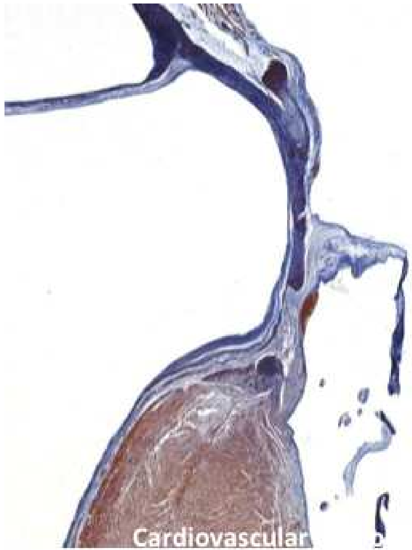
A) AV node. The AV node appears totally fibrotic as the result of ablation (on the right close-up)

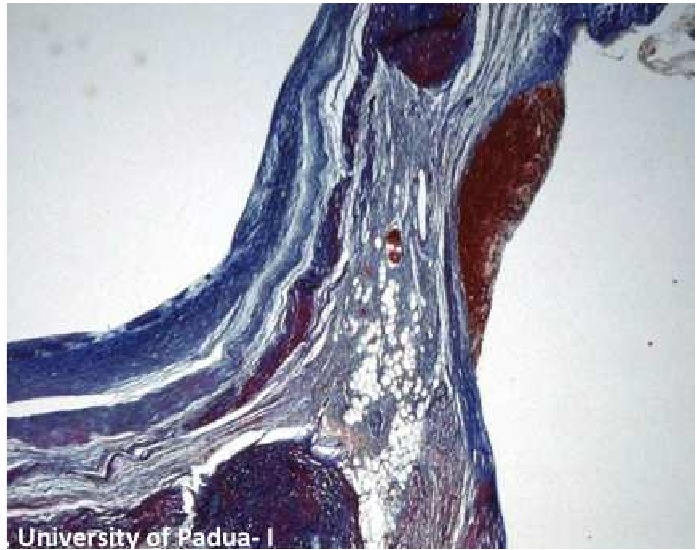


B) Common bundle. The common bundle is intact (on the right close-up)



C) Branching Bundle. The specialized fibers disappear and are replaced by fibro-fatty tissue (on the right close-up)





Case 2

There was continuity between the septal and anterior tricuspid valve leaflets at the antero septal commissure, so that only the AV portion of membranous septum was visible, while the interventricular portion resulted covered by the anteroseptal tricuspid valve leaflet continuity at the commissural level.

Histologic examination of myocardium showed massive amyloid deposits, both in the interstitium and in the vessel wall, with large regions of myocytolysis. The AV node was, as usually, on the right side of central fibrous body over the insertion of septal tricuspid valve leaflet and was almost completely replaced by fibrous tissue with only few fibers in the compact region that appeared preserved. Also the penetrating bundle appeared completely replaced by fibrous tissue with neovessels formation, as well as the first tract of the common bundle. While the distal tract of common bundle as well as the branching bundle and the right and left bundle branches appeared perfectly preserved.

In conclusion AV conduction system resulted interrupted at level of AV node, penetrating bundle and first tract of the common bundle, while the distal part of common as well as branching bundle and both bundle branches were preserved. The peculiar anatomy of anteroseptal commissure did not allow ablation of common bundle covered by anteroseptal continuity of tricuspid leaflets. (Figure 24).

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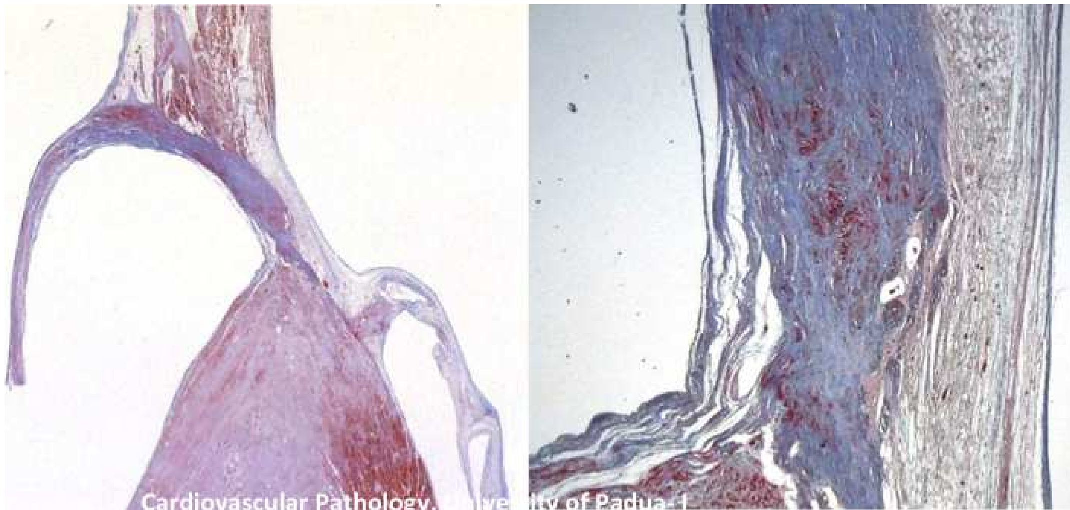
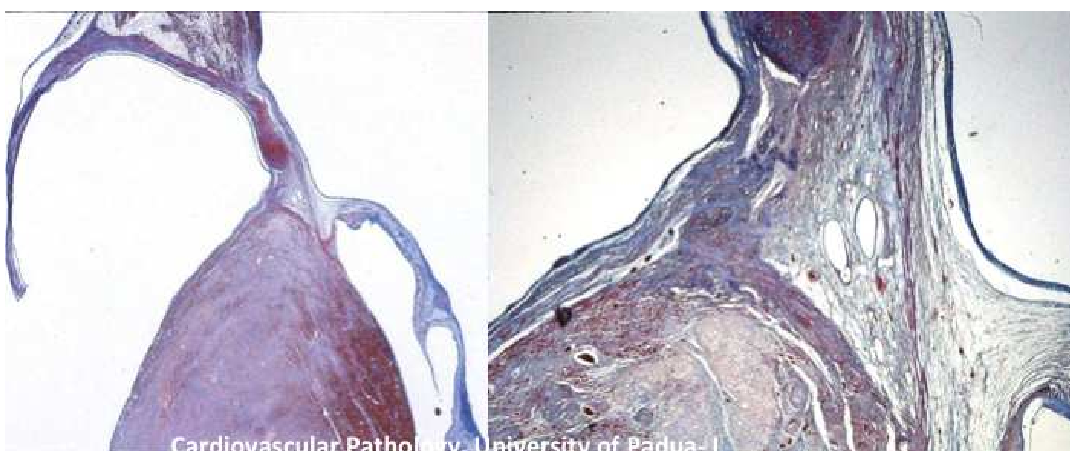
Figure 24, Case 2

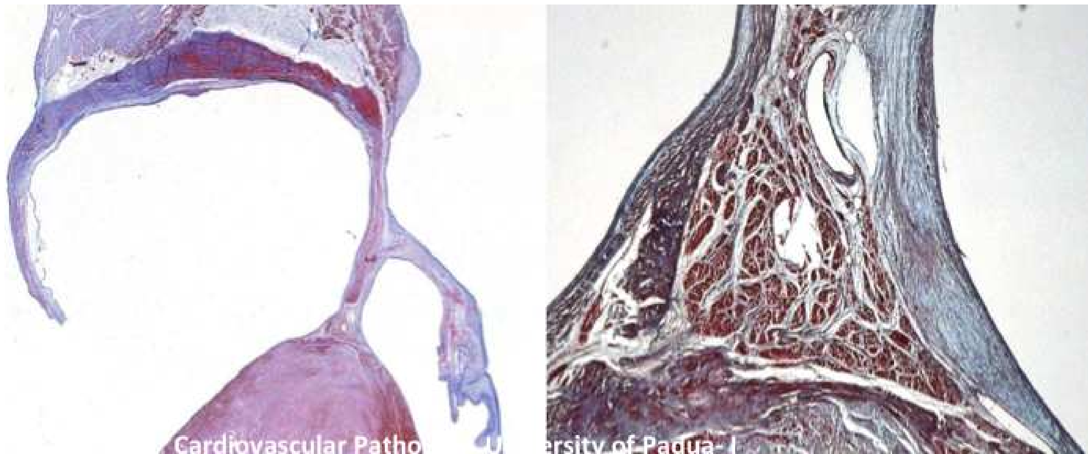
A) AV node: the specialized fibers totally disappeared and are replaced by loose connective tissue (on the right close-up)



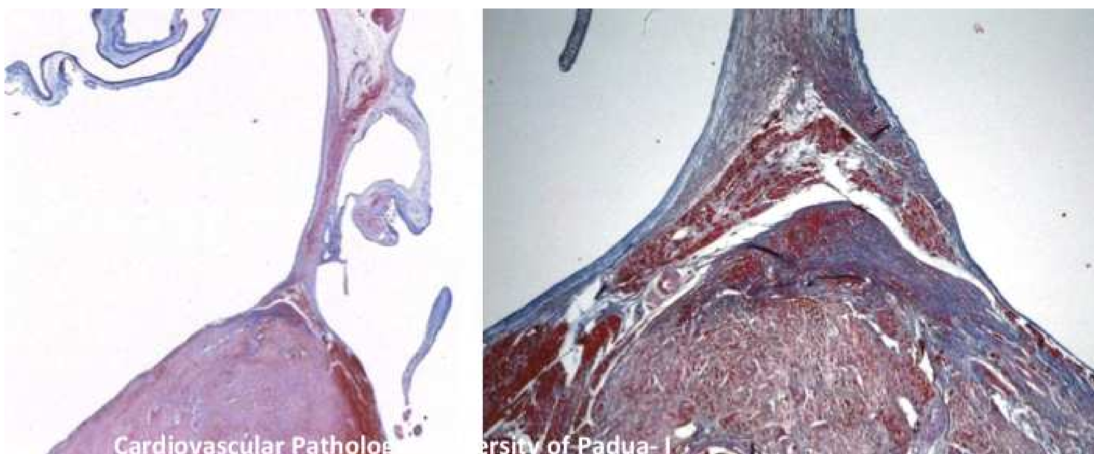
B) Proximal common bundle: the specialized fibers also disappear and are replaced by loose connective tissue with neovessels (on the right close-up)



C) Distal common bundle: it appears intact (on the right close-up)



D) Bifurcating bundle: preserved specialized fibers both on left and right bundle branches (on the right close-up, mirror image)



Case 3

There was continuity between the septal and anterior tricuspid valve leaflets, and the ablation was eventually successful with a left-sided approach.

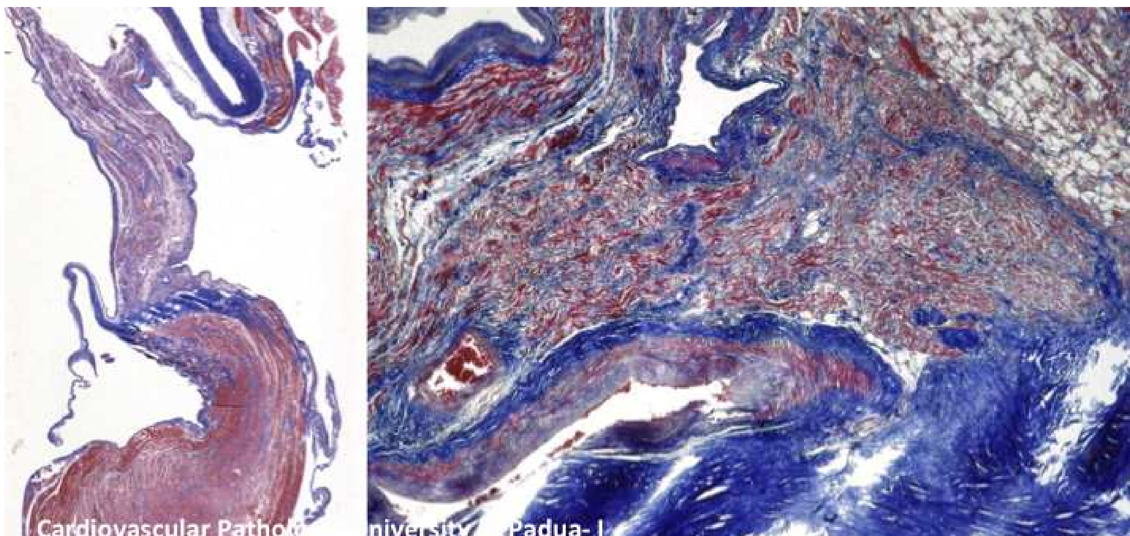
By serial section histologic examination, the AV node was, as usually, on the right side of central fibrous body over the insertion of septal tricuspid valve leaflet and was intact, with preserved specialized fibers. The penetrating bundle appeared almost intact and perfectly preserved the distal tract of common bundle.

Extensive endocardial and replacement-type fibrosis was visible on the crest of the ventricular septum in subaortic position with selective interruption of the branching bundle and bundle branches.

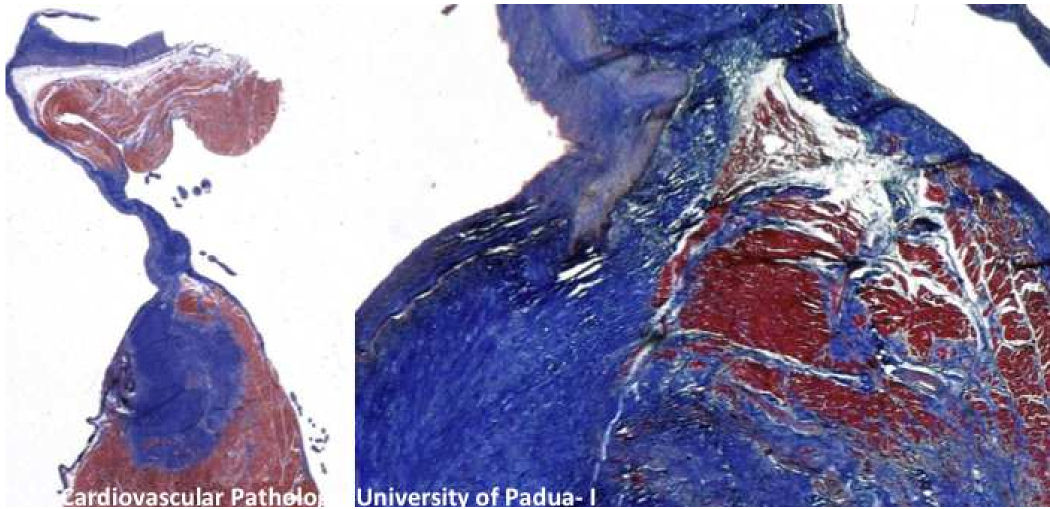
In conclusion, the AV conduction system resulted interrupted at level of the distal part of branching bundle and bundle branches (Figure 25). The extensive fibrosis on the left sided endocardium and subaortic myocardium was in keeping with the left approach for catheter ablation.

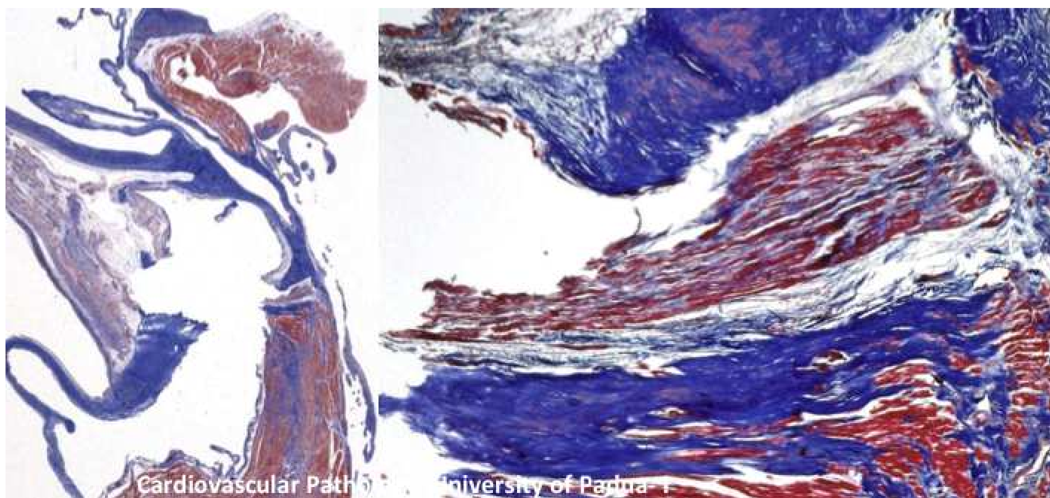
Figure 25, Case 3

A) AV node. Preserved specialized fibers (close-up on the right)



B, C*) Common Bundle: extensive scarring of the crest of the ventricular septum with mostly preserved specialized fibers (close-up on the right)*





Case 4

The septal tricuspid valve leaflet was separate from the anterior leaflet. The AV node was, as usual, on the right side of central fibrous body immediately under the right atrial endocardium and over the insertion of septal tricuspid valve leaflet, in front of the coronary sinus. The AV nodal artery was still visible. The AV node appeared intact, with preserved specialized fibers around the AV artery in the compact region. Even the common and penetrating bundle appeared almost intact. The distal common His bundle shows a moderate degree of replacement-type fibrosis, particularly evident at the origin of the left bundle branch.

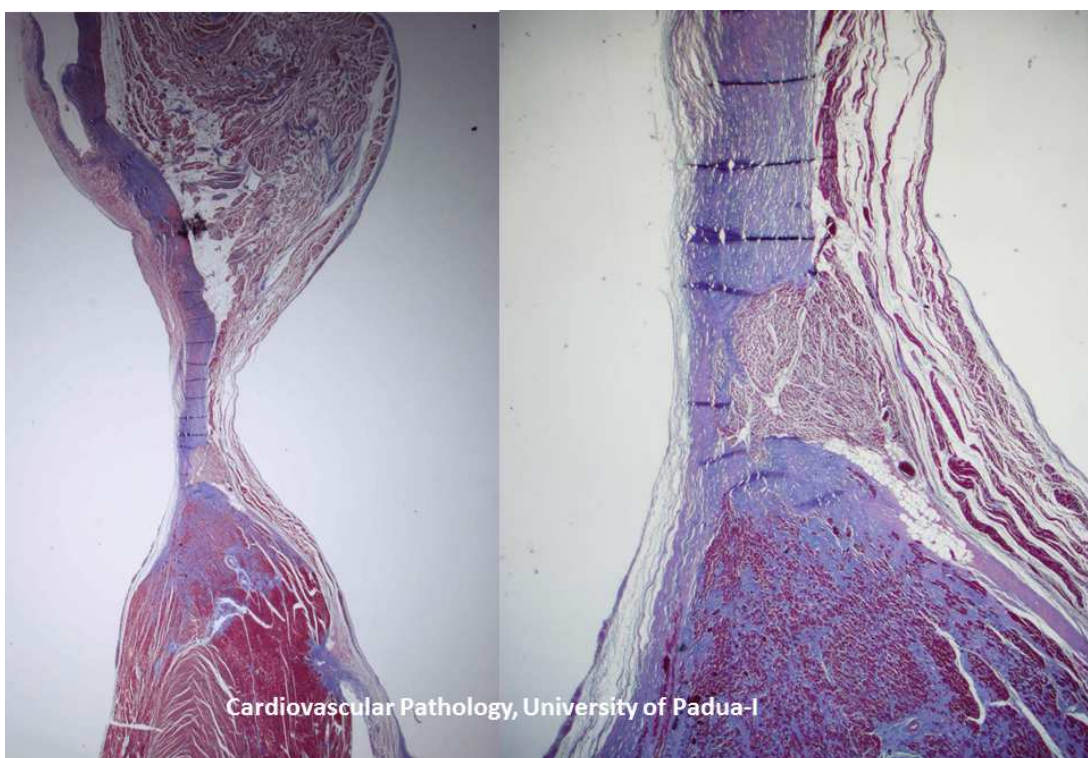
The crista of interventricular septum showed some areas of repair fibrosis. Under the insertion of the non-coronary aortic cusp, a fibro-myxoid tissue proliferation superimposed to a partial injury of the membranous septum is visible. Over the insertion of septal tricuspid valve leaflet on the right side of membranous septum, fibro-myxoid proliferations, involving also the spongiosa, are also visible, representing the possible site of the ablation procedure.

In conclusion, the AV conduction system resulted partially interrupted at the level of the distal common His bundle and of the origin of the left bundle branch (Figure 26).

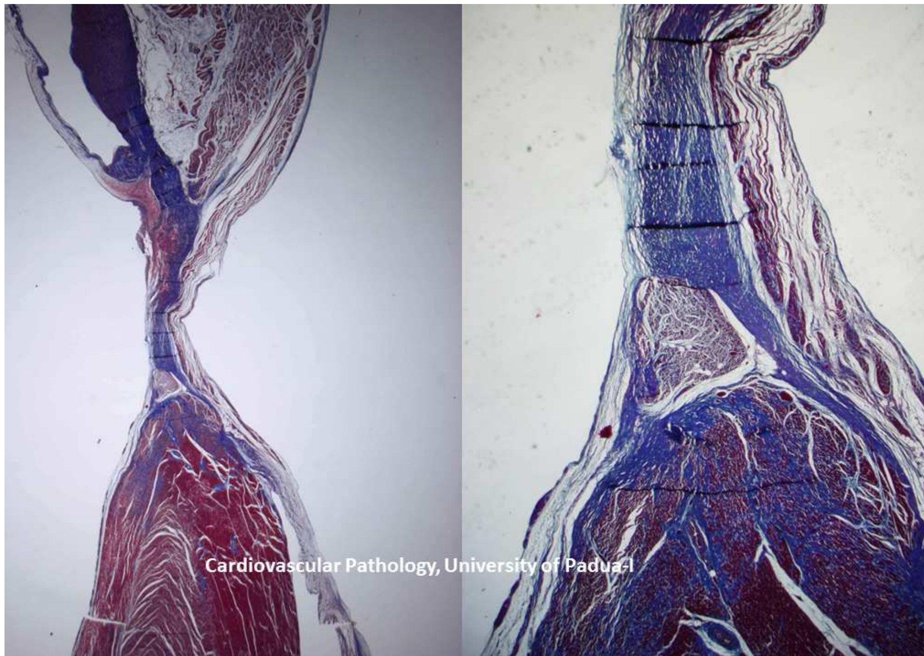
Fibro-myxoid proliferation on both the membranous septum (mostly on the left side) and the septal leaflet of the tricuspid valve, consistent with the iatrogenic injury from previous radiofrequency ablation extended also to the left side of the membranous septum.

Figure 26 A) AV node; B) common His bundle; C,D) bifurcating bundle with origin of the left bundle branch.

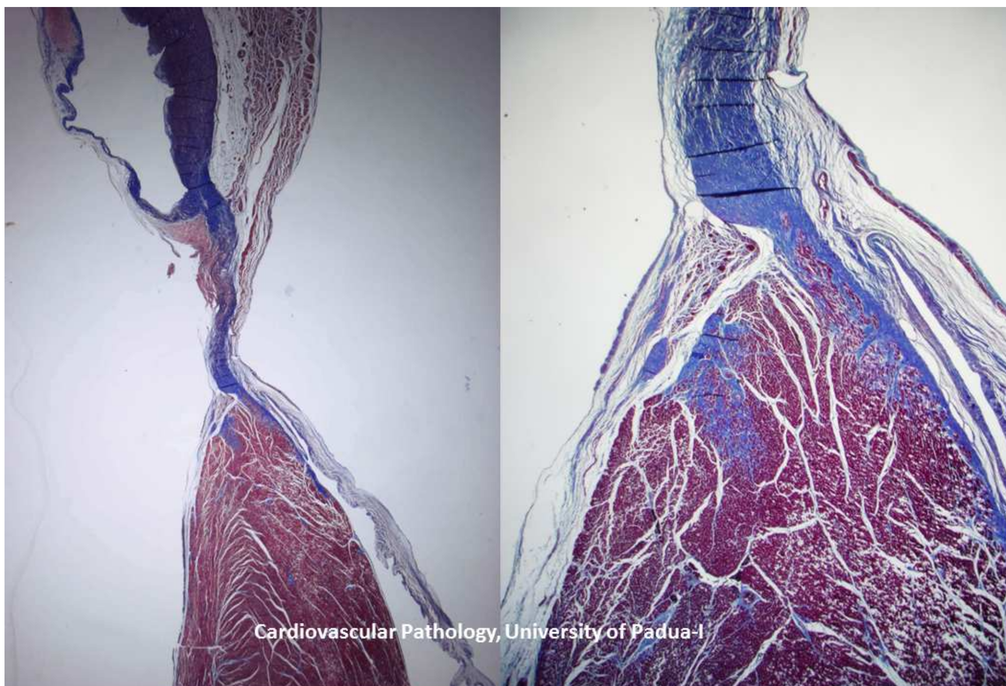
A) *AV node and penetrating bundle: well preserved specialized fibers (close-up on the right)*



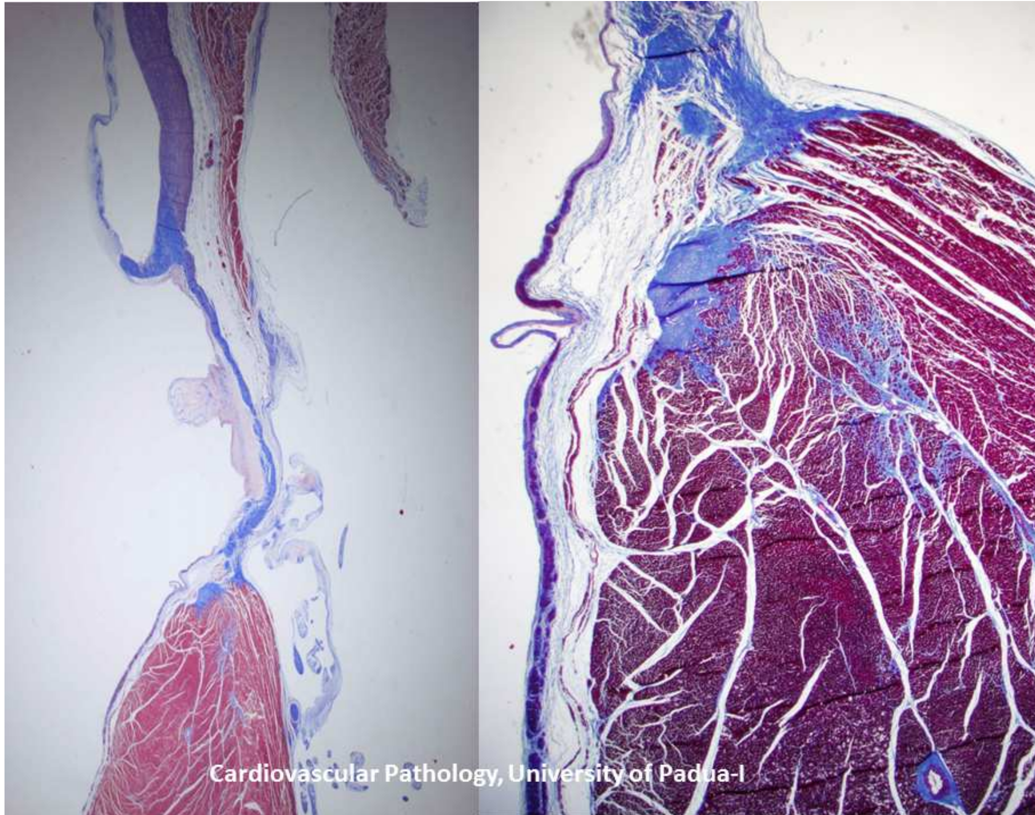
B) *Common bundle: well preserved specialized fibers (close-up on the right). Note an injury at the top of the membranous septum and on the base of the non-coronary cusp .*



C) Bifurcating bundle: mild fibrosis more remarkable at the origin of the left bundle branch (close-up on the right).



D) Origin of the left bundle branch from the bifurcating bundle with severe atrophy of specialized fibers (close-up on the right). On the left side of the membranous septum there is a proliferating tissue indicating the site of injury.



3. Anatomic study of the interventional anatomy of the tricuspid valve for AV ablation: the antero-septal commissure morphology (Cardiac Registry, Cardiovascular Pathology Unit, Department of Cardiac, Thoracic and Vascular Sciences of Padua University)

3.1 Material and Methods

A consecutive series of 100 human hearts coming from autopsies performed at the Cardiovascular Pathology Unit of the Department of Cardiac, Thoracic and Vascular Sciences of Padua University, Padua, Italy have been examined, to analyze the macroscopic anatomy of tricuspid valve leaflets. Hearts with previous surgery at the level of right heart chambers were not included in the study. Attention was paid to the anatomic variability of antero-septal commissure, in order to assess the presence of a continuity between the anterior and the septal tricuspid valve leaflets, and if present, to measure its length All hearts were preserved in a 10% formalin solution. In order to correct inter-individual variability among examiners, measurement of the antero-septal commissure was performed by three co-investigators, independently. After the right atrial wall opening, starting at the entrance of the inferior vena cava towards the right atrial appendage, the RAA was opened obliquely to expose the tricuspid valve. Pictures were obtained form each specimen, data were digitally analyzed and stored by means of anonymous pre-specified related codes, never including the patient anagraphic data.

3.2 Results

A continuity of antero-septal commissure was found in 98 of 100 (98%) of the examined heart specimens. The mean value of the continuity was 3,8±2,9 mm, ranging from 0 mm to 12 mm (Fig 1). More in details, the antero-septal continuity was ≥ 1 mm in 98% of hearts, ≥ 2 mm in 93% of hearts, ≥ 3 mm in 79% of hearts, ≥ 4 mm in 66% of hearts, ≥ 5 mm in 36% of hearts, ≥ 6 mm in 26% of hearts, ≥ 7 mm in 17% of hearts, ≥ 8 mm in 12% of hearts and ≥ 9 mm in 6% of hearts (Figure 27and 28).

Figure 27

A) distribution of antero-septal commissure values

Continuity between the anterior and septal leaflets of TV 98/100 (98%)

Mean value 3,8±2,9 mm

≥ 1 mm	98%
≥ 2 mm	93%
≥ 3 mm	79%
≥ 4 mm	66%
≥ 5 mm	36%
≥ 6 mm	26%
≥ 7 mm	17%
≥ 8 mm	12%
≥ 9 mm	6%

B) distribution of antero-septal commissure values

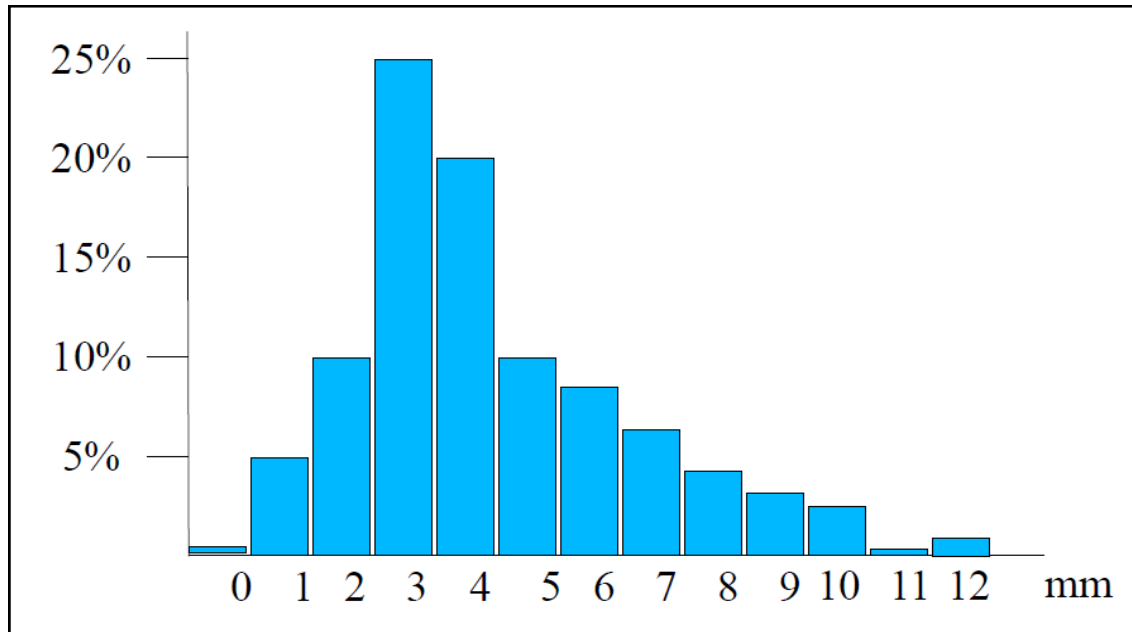
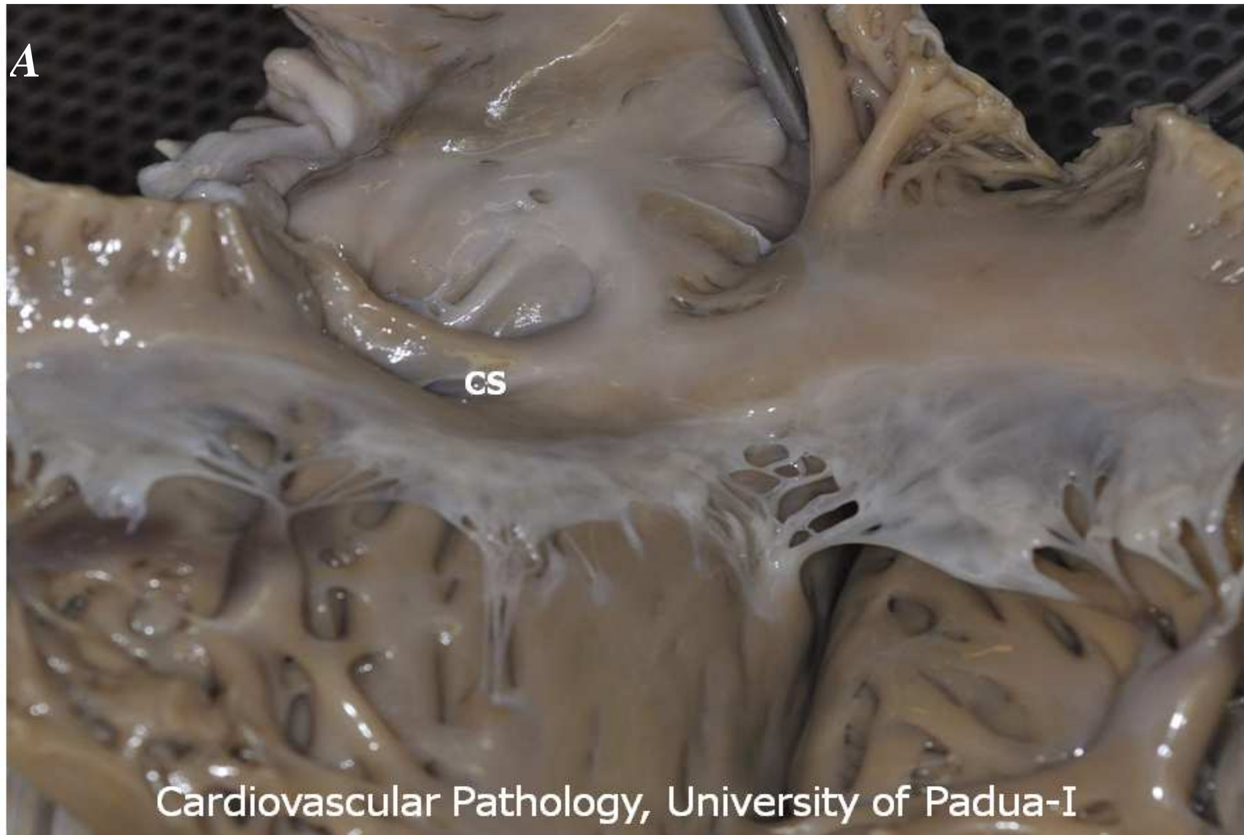
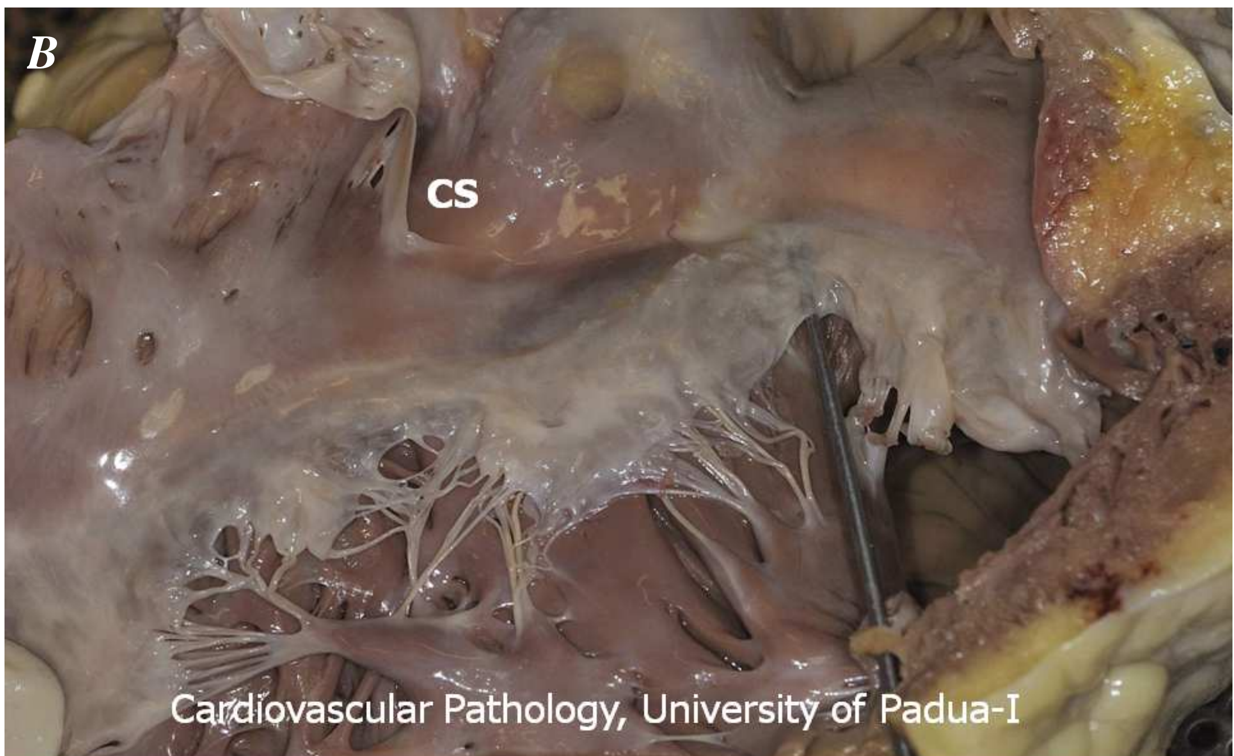


Figure 28 : example of short (A) and long (B) continuity of the antero-septal leaflets commissure of tricuspid valve





5- Discussion

As previously described, the first AVJ ablation in humans was performed in 1981, using high-energy direct current shock delivered over standard electrode catheters from a portable defibrillator (12).

Early experience with direct current energy was soon surpassed by radiofrequency energy, in 1987, when Huang and colleagues described that the use of this energy for AVJ ablation resulted more effective and associated with lower complication rates (15).

After the introduction in 1998 by Haissaguerre of pulmonary vein isolation for the treatment of atrial fibrillation (104), AVJ ablation remains indicated only for patients in which PVI was ineffective or not recommended such as elderly patients, patients with a long history of permanent atrial fibrillation and patients with a severe enlargement of the left atrium. On the other hand, due to the increasing number of patients with heart failure treated with cardiac resynchronization therapy (CRT), AVJ ablation has found a new indication. Infact it is actually recommended for patients affected by atrial fibrillation treated with CRT to ensure a high degree of biventricular pacing (89).

According with these indications, our study population was characterized by patients with a mean age over than 70 years and largely affected by permanent atrial fibrillation with an enlargement of left atrium. Few of them had a previous non effective PVI, most of them, at the time of AVJ, were already implanted with a CRT or CRTD for a cardiomyopathy with a severe reduction of mean EF and NYHA class of III or IV.

According with literature data, reporting a very high rate of success of AVJ ablation with a very low rate of complications, in our series of patients we had 100% of success rate with 5% rate of only minor vascular complications.

To note that in all patients AV block has been achieved from the right side, while in the literature in 5 to 10% of patients AV block failed from right side access and required left side access.

This difference is likely due to the fact that we have used, since to 2005, a 8 mm ablator catheter, while data of literature are referred to the use of 4 mm ablator catheter. A Tip of 8 mm instead of 4 mm means a better performance because a larger surface of delivering RF that is able to generate larger lesions.

Moreover in the literature, it is suggested to switch from the right side to the left side approach after 10 non efficacy attempts, while our strategy was to continue (even over 15 attempts) from the right side, in order to avoid any possible complication related to left side approach (vascular complications, cerebrovascular embolism, etc.)

According with this strategy, our results showed that in a quite small group of patients (13%) more than 15 attempts have been necessary to obtain AV complete block, while in the other groups less than 10 attempts were enough to obtain AV block.

The meaning is that in a not specified number of patients same variables make very difficult (or not allow) ablation from the right side. Some authors suggested that right side approach could be difficult (or may fail) for a number of reasons, including anatomic variations, such as increased distance of the AV node from the right-sided septal endocardium and a small AV node and His bundle, RF application within the central fibrous body, or the presence of accessory connections of the AV node from atrial tissue (14). Other reasons include coagulum formation on the catheter tip and fibrosis overlying the conduction system, effectively insulating it from the thermal effects of ablation. In case of failure of the right side approach some electophysiologic characteristics have been reported such as: instability of the His-bundle potential, low

amplitude of the his bundle potential, un-correct ratio between the atrial, His bundle and ventricular potentials (15).

Interestingly, our four cases that underwent “in vivo” AVJ ablation the available postmortem conduction system serial histologic examination suggest a crucial role of the anatomic variability of antero-septal tricuspid valve leaflets commissure on the efficacy of AVJ ablation. In fact, in the first case, in which the septal tricuspid valve leaflet was separated from the anterior leaflet, a first DC shock partially damaged the AV compact node without obtaining the AV complete block and the second shock damaged the His bundle thus leading at that time to the complete AV block. On the contrary, in the second case, complete AV block was obtained at the level of AV compact node, while His bundle was preserved probably becouse protected from the continuity between septal and anterior tricuspid valve leaflet. On the contrary in the fourth case the discontinuity between anterior and septal leaflets of tricuspid valve allowed a distal ablation (on the distal common His bundle) even from the right approach. Finally, more explicative is the third case, in which attempts to obtain the AV block on the AV compact node failed as well as attempts on His bundle, because it was protected by the continuity between the septal and the anterior tricuspid valve leaflet. In this case, a subsequent left side approach was necessary to obtain complete AV block. Moreover, these findings are consistent with the reported electrophysiologic characteristics of unsuccessful ablation from right side described before. In fact, the discontinuity between the anterior and the septal leaflets creates a ravine very helpful for the efficacy of ablation allowing at the same time: 1) a very good stability of the catheter tip between the two leaflets, 2) an easy reachable His-bundle with a recordable high amplitude His bundle potential and correct ratio between atrial, His and ventricle potentials. On the contrary, the continuity between the two leaflets covers and protects

the His bundle, creating an anatomical condition for catheter instability, low amplitude of His potential and incorrect ratio between atrial, His and ventricular potentials.

The preferred site of ablation should be the compact AV node. In fact, a more proximal ablation of the conduction system (at the level of AV node instead of His bundle) preserve the automaticity distal to the site of interruption and resulting escape rhythm prevent pacemaker dependence. On the contrary, ablation of His bundle more often results in complete heart block without an escape rhythm.

However, the AV node is a quite large region to be disrupted because of many atrium nodal connections. On the contrary, interruption at the level of the His bundle is easier because the latter, surrounded and isolated by the central fibrous body, is really a "pathway". These consideration explain why sometimes, even after many attempts, ablation of AV node could be ineffective and operators have to shift towards the ablation of the His bundle to obtain the AV block. Finally, if the His bundle is protected by the continuity of the antero-septal commissure of the tricuspid valve, the procedure may results in an ineffective ablation from the right side.

In the last part of the study, we reviewed 100 normal hearts to evaluate and measure the anteroseptal commissure of tricuspid valve leaflets. Relative small data are reported about this commissure. In the study of Restivo is reported a large variability of the commissure (105) and Rosenquist reported a high rate of absence of continuity in the Down's syndrome (106).

We found that a continuity between anteroseptal leaflets of tricuspid valve is almost ever present (98% of examined hearts) with a men value of 3,8 ± 2,9 mm. Even it is very difficult to make any correlation, considering: A) dimensions of surface of the ablator catheter tip delivering ablation of 4-8 mm x 2-3 of diameter, B) dimension of Koch's triangle, C) data reported by literature of failure from the right side ranging

between 5 and 10 % (and our series 13%) we can conclude that a value of continuity of ≥ 8 - 9 mm (12 - 6%) could be enough to cover and protect the His bundle from the ablation lesions.

6- Conclusions

AVJ ablation has still a relevant role in the treatment of patients with atrial fibrillation either to control the rate in highly symptomatic patients either to optimize pacing in patients affected by heart failure implanted with a CRT device.

Technique has an efficacy of about 100% with a very low rate of complications (generally minor complications).

The anatomic variability of the commissure between anterior and septal leaflets of tricuspid valve seems to have a crucial importance on the ablation procedure. A continuity between the two leaflet is almost ever present and, when remarkable, could cover and protect His bundle from attempts of ablation. Therefore when, as usual, AVJ ablation is approaching from the right atrium this anatomic variability could explain the cases in which procedures result more difficult, longer or inefficacy. In these last cases became necessary to switch to left side retroaortic approach to obtain the complete AV block.

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FORMATO EUROPEO PER IL CURRICULUM VITAE

INFORMAZIONI PERSONALI

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E-mail	andreacorrado2003@yahoo.it
Nazionalità	italiana
Data di nascita	23/07/1968

ESPERIENZA LAVORATIVA

Dal 2000 Dirigente Medico di I livello nell' Unità Operativa di Cardiologia dell' Ospedale Umberto I di Mestre-Venezia diretta dal Dr A. Raviele con incarico in elettrofisiologia ed elettrostimolazione (attualmente Unità Operativa di Cardiologia, Ospedale dell'Angelo, diretta dal Dr F. Rigo).

Nel 2010 consulente per l'elettrofisiologia e l'elettrostimolazione all'OC di Portogruaro.

Dal 2011 responsabile della Syncope Unit, dell'ambulatorio Holter ed event recorder

ISTRUZIONE E FORMAZIONE

Nel 1994 Laurea in Medicina e Chirurgia, Università degli Studi di Padova. Tesi di laurea: "Correlazioni elettro-anatomiche nell'ablazione transcatetere della giunzione atrioventricolare".

Nel 1995 Borsista CNR sul tema "Cardiomiopatie Aritmogene" sotto la direzione del Prof G Thiene.

Nel 1999 Specializzazione in Cardiologia presso la I Scuola di Cardiologia dell'Università degli Studi Padova. Tesi di specializzazione: "Trattamento mediante ablazione transcatetere con radiofrequenza della tachicardia da rientro intranodale".

Da ottobre 2006 ad aprile 2007: "fellow" presso il laboratorio di elettrofisiologia interventistica della Cleveland Clinic (Ohio, USA), sotto la direzione del Dr A. Natale.

Dal 2010 "Dottorando in Scienze Cardiovascolari" presso l'Università degli studi di Padova sotto la direzione del Prof G. Thiene e della Prof.ssa C. Basso,

PRIMA LINGUA — **ITALIANO**

ALTRE LINGUE

INGLESE

- Capacità di lettura: buono
- Capacità di scrittura: buono
- Capacità di espressione orale: buono

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ATTIVITA' SCIENTIFICA

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Dal 2007 revisore per il giornale europeo di Elettrofisiologia ed Elettrostimolazione: "Europace

Dal 2007 membro del comitato organizzatore del congresso "Venice Arrhythmias"

Dal 2008 al 2010 membro del consiglio regionale Veneto dell'AIAC (Associazione Italiana Aritmologia e Cardiostimolazione).

Nel 2009 vincitore del premio "Morgagni" assegnato dal "Collegio dei Primari di Cardiologia Veneti" per la pubblica-zione: Efficacy, safety, and outcome of atrial fibrillation ablation in septuagenarians. J Cardiovasc Electrophysiol. 2008 Aug;19(8):807-11.

CAMPI DI INTERESSE ED EXPERTISE

Aritmologia clinica e cardiomiopatie aritmogene

Più di 1500 impianti di pacemaker, CRT e/o ICD

Più di 500 ablazioni transcatetere di aritmie atriali e ventricolari

Ottima conoscenza dei sistemi di mappaggio elettroanatomico

Particolare esperienza nell'utilizzo dell' eco-intracardiaco applicato alle procedure di ablazione

PUBBLICAZIONI PRESENTI IN PUBMED

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Morphology of right atrial appendage for permanent atrial pacing and risk of iatrogenic perforation of the aorta by active fixation lead. Zoppo F, Rizzo S, Corrado A, Thiene G, Basso C. Heart Rhythm. 2014 Dec 20 [Epub ahead of print]

Interventional Cardiac Elecrophysiology. A Multidisciplinary Approach; Chapter: Atrioventricular Junction Ablation. Saksena, Marchlinski, Este and Damiano, edited by Wiley-Blackwell in press

Impact of systematic isolation of superior vena cava in addition to pulmonary vein antrum isolation on the outcome of paroxysmal, persistent and permanent atrial fibrillation ablation: results from a randomized study. Corrado A, Bonso A, Madalosso M, Rossillo A, Themistoclakis S, Di Biase L, Natale A, Raviele A. *J* Cardiovasc Electrophysiol. 2010 Jan;21(1):1-5

Lead malfunctions in implantable cardioverter defibrillators: where are we and where should we go? Corrado A, Gasparini G, Raviele A. Europace. 2009 Mar;11(3):276-7.

Efficacy, safety, and outcome of atrial fibrillation ablation in septuagenarians. Corrado A, Patel D, Riedlbauchova L, Fahmy TS, Themistoclakis S, Bonso A, Rossillo A, Hao S, Schweikert RA, Cummings JE, Bhargava M, Burkhardt D, Saliba W, Raviele A, Natale A. J Cardiovasc Electrophysiol. 2008 Aug;19(8):807-11.

Results from a single-blind, randomized study comparing the impact of different ablation approaches on long-term procedure outcome in coexistent atrial fibrillation and flutter (APPROVAL). Mohanty S, Mohanty P, Di Biase L, Bai R, Santangeli P, Casella M, Dello Russo A, Tondo C, Themistoclakis S, Raviele A, Rossillo A, Corrado A, Pelargonio G, Forleo G, Natale A. Circulation. 2013 May 7;127(18):1853-60.

Introductory Guide to Electrophysiology; Corrado A, Rossillo A, China P, Raviele A. Chapter: Bradycardia Steinberg, edited by Wiley-Blackwell, 2011

Left atrial appendage: an underrecognized trigger site of atrial fibrillation. Di Biase L, Burkhardt JD, Mohanty P, Sanchez J, Mohanty S, Horton R, Gallinghouse GJ, Bailey SM, Zagrodzky JD, Santangeli P, Hao S, Hongo R, Beheiry S, Themistoclakis S, Bonso A, Rossillo A, Corrado A, Raviele A, Al-Ahmad A, Wang P, Cummings JE, Schweikert RA, Pelargonio G, Dello Russo A, Casella M, Santarelli P, Lewis WR, Natale A. Circulation. 2010 Jul 13;122(2):109-18.

Periprocedural stroke and management of major bleeding complications in patients undergoing catheter ablation of atrial fibrillation: the impact of periprocedural therapeutic international normalized ratio. Di Biase L, Burkhardt JD, Mohanty P, Sanchez J, Horton R, Gallinghouse GJ, Lakkireddy D, Verma A, Khaykin Y, Hongo R, Hao S, Beheiry S, Pelargonio G, Dello Russo A, Casella M, Santarelli P, Santangeli P, Wang P, Al-Ahmad A, Patel D, Themistoclakis S, Bonso A, Rossillo A, Corrado A, Raviele A, Cummings JE, Schweikert RA, Lewis WR, Natale A. Circulation. 2010 Jun 15;121(23):2550-6

Venice Chart International Consensus document on ventricular tachycardia/ventricular fibrillation ablation. Natale A, Raviele A, Al-Ahmad A, Alfieri O, Aliot E, Almendral J, Breithardt G, Brugada J, Calkins H, Callans D, Cappato R, Camm JA, Della Bella P, Guiraudon GM, Haïssaguerre M, Hindricks G, Ho SY, Kuck KH, Marchlinski F, Packer DL, Prystowsky EN, Reddy VY, Ruskin JN, Scanavacca M, Shivkumar K, Soejima K, Stevenson WJ, Themistoclakis S, Verma A, Wilber D; Venice Chart members. J Cardiovasc Electrophysiol. 2010 Mar;21(3):339-79.

The risk of thromboembolism and need for oral anticoagulation after successful atrial fibrillation ablation. Themistoclakis S, Corrado A, Marchlinski FE, Jais P, Zado E, Rossillo A, Di Biase L, Schweikert RA, Saliba WI, Horton R, Mohanty P, Patel D, Burkhardt DJ, Wazni OM, Bonso A, Callans DJ, Haissaguerre M, Raviele A, Natale A. J Am Coll Cardiol. 2010 Feb 23;55(8):735-43.

Integration of positron emission tomography/computed tomography with electroanatomical mapping: a novel approach for ablation of scar-related ventricular tachycardia. Fahmy TS, Wazni OM, Jaber WA, Walimbe V, Di Biase L, Elayi CS, DiFilippo FP, Young RB, Patel D, Riedlbauchova L, Corrado A, Burkhardt JD, Schweikert RA, Arruda M, Natale A. Heart Rhythm. 2008 Nov;5(11):1538-45. Novel ICE-Guided

Registration Strategy for Integration of Electroanatomical Mapping with Three-Dimensional CT/MR Images to Guide Catheter Ablation of Atrial Fibrillation. Rossillo A, Indiani S, Bonso A, Themistoclakis S, Corrado A, Raviele A. J Cardiovasc Electrophysiol. 2009 Apr;20(4):374-8.

Role of transoesophageal echocardiography in evaluating the effect of catheter ablation of atrial fibrillation on anatomy and function of the pulmonary veins. De Piccoli B, Rossillo A, Zanella C, Bonso A, Themistoclakis S, Corrado A, Raviele A. Europace. 2008 Sep;10(9):1079-84.

Role of anticoagulation therapy after pulmonary vein antrum isolation for atrial fibrillation treatment. Rossillo A, Bonso A, Themistoclakis S, Riccio G, Madalosso M, Corrado A, De Piccoli B, Raviele A. J Cardiovasc Med (Hagerstown). 2008 Jan;9(1):51-5

Sports physicians and prescription of sports therapy, Giada F, Guiducci U, D'Andrea L, Corrado A, Raviele A. G Ital Cardiol (Rome). 2008 Oct;9 (10 Suppl 1):90S-93S.

Atrial fibrillation in patients with a dual defibrillator: characteristics of spontaneous and induced episodes and effect of ventricular tachyarrhythmia induction. Boriani G, Raviele A, Biffi M, Gasparini G, Martignani C, Valzania C, Diemberger I, Corrado A, Raciti G, Branzi A. J Cardiovasc Electrophysiol. 2005 Sep;16(9):974-80

Rate-responsive pacing regulated by cardiac haemodynamics. Gasparini G, Curnis A, Gulizia M, Occhetta E, Corrado A, Bontempi L, Mascioli G, Maura Francese G, Bortnik M, Magnani A, Di Gregorio F, Barbetta A, Raviele A. Europace. 2005 May;7(3):234-41.

Impact of coronary sinus lead position on biventricular pacing: mortality and echocardiographic evaluation during long-term follow-up. Rossillo A, Verma A, Saad EB, Corrado A, Gasparini G, Marrouche NF, Golshayan AR, McCurdy R, Bhargava M, Khaykin Y, Burkhardt JD, Martin DO, Wilkoff BL, Saliba WI, Schweikert RA, Raviele A, Natale A. J Cardiovasc Electrophysiol. 2004 Oct;15(10):1120-5

Attività svolta nel periodo di dottorato

Dopo aver definito con il Coordinatore d'indirizzo (Prof Thiene) ed il Supervisore (Prof.ssa Basso) l'argomento della tesi (ablazione transcatetere della giunzione atrioventricolare) ho iniziato l'attività di ricerca con una ampia revisione della letteratura sul tema della: 1) anatomia della giunzione atrioventricolare (AV), 2) istologia del tessuto di conduzione a livello della giunzione AV, 3) indicazioni, tecniche e risultati dell'ablazione transcatetere della giunzione AV.

Durante gli anni di dottorato ho condotto parte della ricerca presso l'ospedale dove lavoro in qualità di dirigente medico dedicato all'attività di elettrofisiologia interventistica (Ospedale Civile di Mestre), raccogliendo i dati relativi ai pazienti sottoposti ad ablazione della giunzione AV dal 2005 al 2014, valutando in particolare le indicazioni, le caratteristiche cliniche dei pazienti e i risultati in acuto della procedura.

Sotto la supervisone della Prof.ssa Basso e del Prof Thiene abbiamo analizzato la commisssura anterosettale della valvola tricuspide in 100 cuori appartenenti alla collezione anatomica dell'Istituto di Anatomia Patologica dell'Università di Padova ed abbiamo infine revisionato l'isto-patologia del tessuto di conduzione in 4 casi sottoposti in vita ad ablazione della giunzione AV.

Durante il corso di dottorato ho esposto di anno in anno i risultati della ricerca: nel 2012 al Palazzo del Bo e nel 2013 e nel 2014 in occasione della "Spring School" a Bressanone.

Durante gli anni di dottorato ho partecipato inoltre a numerosi corsi e seminari organizzati dalla scuola di dottorato tra cui: la settimana di scienze di base denominata "Summer School" nel 2011, i corsi di "anatomia per l'aritmologo" nel 2011, 2012, 2013 e 2014, il Simposio Internazionale "ARVC: from Genes to Therapy" nel 2011, il XVI

congresso nazionale "SIC Sport" nel 2013, il corso "Update in ARVC and SCD in the young" nel 2014 e il "Forum triveneto di elettrofisiologia" nel 2014.

Durante gli anni di dottorato ho inoltre partecipato ai seguenti congressi:

- Congressi Nazionali AIAC: Catania 2011, Pisa 2012, Bologna 2013, Bologna 2014
- Congressi Internazionali: EHRA, Cardiostim, Nizza 2012 e 2014
- "Venice Arrhythmias" nel 2011 e nel 2013 (in qualità di membro del comitato organizzatore del congresso)

Durante il dottorato ho inoltre contribuito alle stesura delle seguenti pubblicazioni:

- Morphology of right atrial appendage for permanent atrial pacing and risk of iatrogenic perforation of the aorta by active fixation lead. Zoppo F, Rizzo S, Corrado A, Bertaglia E, Buja G, Thiene G, Basso C. Heart Rhythm. 2014 Dec 20 [Epub ahead of print]

- Atrioventricular Junction Ablation. Corrado A, Rossillo A, China P, Raviele A Chapter 38 in "Interventional Cardiac Elecrophysiology. A Multidisciplinary Approach" Saksena S, Marchlinski FE, Estes NAM, Damiano R eds, Cardiotext in press

- Results from a single-blind, randomized study comparing the impact of different ablation approaches on long-term procedure outcome in coexistent atrial fibrillation and flutter (APPROVAL). Mohanty S, Mohanty P, Di Biase L, Bai R, Santangeli P, Casella M, Dello Russo A, Tondo C, Themistoclakis S, Raviele A, Rossillo A, Corrado A, Pelargonio G, Forleo G, Natale A. Circulation. 2013 May 7;127(18):1853-60.

- Anticoagulation issues in patients with AF, Rossillo A, Corrado A, China P, Madalosso M, Themistoclakis S, Cardiac Electrophysiology Clinics Sept 2012: 4 (3): 363-373

- Bradycardia. Corrado A, Gasparini G, Rossillo A, Raviele A. Chapter 1 in "Introductory Guide to Electrophysiology" Steinberg S eds, Wiley-Blackwel 2011