UNIVERSITÀ DEGLI STUDI DI PADOVA

Dipartimento di Scienze Cardiologiche, Toraciche e Vascolari

SCUOLA DI DOTTORATO DI RICERCA IN SCIENZE MEDICHE, CLINICHE E SPERIMENTALI

Indirizzo

SCIENZE CARDIOVASCOLARI

XXIV CICLO

TITOLO TESI

PERMANENT ATRIAL PACING

ANATOMICAL STUDY OF THE RIGHT ATRIUM
PACING ATRIAL LEAD TECHNOLOGIES
PROCEDURAL SAFETY

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ABSTRACT

Background and Objectives

The gross anatomy of the right atrial appendage (RAA) and its relationships with the crista terminalis (CT) and the taenia sagittalis (TS) has been poorly described. The RAA is the most common region where leads for the permanent atrial pacing are placed. The atrial leads technology available for lead placement and anchorage is mainly represented by the active or passive fixation. The reliability of active-fixation atrial leads has been compared with passive-fixation ones; straight and J-shaped screw-in lead systems have also been compared. Few data are available on procedural and short-term safety.

The first part of this thesis is a comprehensive review about the modern cardiac pacing, mainly oriented to the atrial permanent pacing clinical aspects, technique and materials. The second part is an original contribution about a brief anatomy overview of right atrial structures involved in the permanent pacing including also a retrospective procedural safety comparison among three different atrial pacing leads technologies.

Patients and Methods

An anatomical study of a consecutive series of human hearts specimens coming from routine autopsies, performed at the Cardiovascular Pathology Unit of the Department of Cardiac, Thoracic and Vascular Sciences of University of Padua, is reported. A total of

100 human hearts have been examined to analyze the macroscopic anatomy of CT and TS. Attention was paid to the anatomic variability of TS in its "entrance" into the RAA. Data were compared with the recent literature.

A retrospective study was then carried out, with the aim to analyze the clinical impact on procedural safety of the main currently available atrial leads technologies for permanent pacing. To this purpose, from January 2004 to January 2010, 1464 patients who underwent to a new pacemaker/implantable cardioverter defibrillator (ICD) implantation, were recruited. Among these, 915 (study population) received a passive or active fixation pre-J-shaped or a straight screw-in atrial lead; the remaining 549 patients, who received only a ventricular lead (VVI pacemakers), were excluded. The 3 study groups were: *Group S-FIX* (165 patients, 18%) receiving a straight screw-in atrial lead (post-shaped in right appendage); *Group J-PASS* (690 patients, 75.4%) receiving a passive-fixation J-shaped atrial lead and *Group J-FIX* (60 patients, 6.6%), receiving an active fixation screw-in J-shaped atrial lead.

Procedural and short-term complication rates have been analyzed up to 3 months post-implantation.

Results

Anatomic review: TS has shown 3 main kinds of anatomic variability related to the presence of a *main trunk* TS (type 1 present in 76% of cases), a *double TS* (type 2 present in 13% of cases) and a fine arborization without a clear TS represented (type 3 present in 10% of cases). A triple morphology of TS was found in one case. The RAA region proximally to TS (or "antral RAA region") is facing the aortic root, without a clear pericardial space in between; the distal region of the RAA, behind TS (or "saccular RAA region") is not facing closely the pulmonary artery infundibulum, due to its "unbound"

nature that better comply the atrial systolic cycles. This could represent a safer region for leads placement, especially for screw-in technology.

Procedural atrial leads technology comparison: One complication occurred in each group as follows: one case of sterile pericarditis in the S-FIX group (0.6%) *vs* one case of sustained atrial fibrillation in the J-PASS group (0.1 %) *vs* one case of pleuro-pericardial atrial lead perforation/migration in the J-FIX group (1.7 %). The *p* values were 0.3, 0.1 and 0.4 respectively for each rates comparison.

The rate of atrial lead dislodgement was higher in the group J-PASS compared with the group S-FIX but not with the group J-FIX, and is distributed as follows: group S-FIX 0 cases *vs* group J-PASS 16 (2.3%) cases *vs* group J-FIX 1 (1.7%) case (p=0.04 and 0.7 respectively).

Conclusions

The "saccular" RAA could be a safer region for atrial leads insertion and anchorage compared with the “antral” RAA, which is quite close to the ascending aorta. However, in our case series the procedural complications of all the 3 available leads technologies were very low. In particular, no aortic perforations occurred.

Straight screw-in atrial leads, “J post-shaped” in the RAA, offer a better stability compared with the passive J pre-shaped fixation and displayed a similar acceptable safety profile compared with both the J pre-shaped systems.

RIASSUNTO

Introduzione e obiettivi

Nella pratica clinica l'auricola atriale destra è la sede preferenziale per il posizionamento e l'ancoraggio dei cateteri atriali per la cardio-stimolazione atriale permanente. L'anatomia macroscopica di questa regione atriale destra e i suoi rapporti con la crista terminalis (CT), la taenia sagittalis (TS), l'aorta e l'infundibolo della arteria polmonare, è scarsamente descritta in letteratura.

La tecnologia a disposizione, riguardante i cateteri stimolatori atriali per pacemakers, ci fornisce modelli con meccanismo di fissaggio endocardico attivo (a vite retrattile) o passivo (con punta catetere circondata da barbe siliconate) e modelli con forma terminale del catetere diritta (da post-formare a J con stiletto dedicato sempre e solo con fissaggio attivo a vite) o pre-formati a J (disponibili con fissaggio attivo o passivo).

La forma J (pre o post-formata) è necessaria per il raggiungimento e la collocazione del catetere nell'auricola destra. In generale i cateteri a fissaggio attivo presentano l'inconveniente teorico di un rischio aumentato di perforazione cardiaca, ma garantirebbero una migliore stabilità, essendo meno esposti alla dislocazione (e necessità di re-intervento). I cateteri a fissaggio passivo, meno esposti al rischio di perforazione, presentano invece una maggiore incidenza di dislocazione a breve e medio termine.

La forma a J è stata ideata per poter raggiungere la sede auricolare destra e mantenere la posizione e perciò potrebbe essere teoricamente la migliore per tale scopo.

In questo ambito, la tecnologia a fissaggio attivo, unica disponibile per i cateteri dritti (da "post-formare" a J), permette un più affidabile aggancio per quest'ultimo tipo di cateteri. Essi infatti, se non ben ancorati, tendono a staccarsi immediatamente durante la procedura (stante la loro natura a ritornare dritti), ma sono immediatamente riposizionabili e pertanto consentono una certa sicurezza nel testare la loro cosiddetta

"stabilità primaria" ovvero intra-operatoria. Il concetto di "stabilità primaria" intra-operatoria è stata l'ipotesi che ha ispirato la seconda parte della presente ricerca, con l'intento di vedere se davvero l'utilizzo di cateteri a fissaggio attivo dritti, post-formati a J in posizione di aggancio auricolare, possa consentire una adeguata affidabilità per la stabilità a medio termine e allo stesso tempo mantenere basso il rischio di eventuali complicanze di tipo perforativo, più caratteristiche dei cateteri a fissaggio attivo.

Metodi

La prima parte di questa analisi è caratterizzata da una revisione della relativamente scarsa letteratura riguardante l'anatomia macroscopica della auricola atriale destra e dei suoi rapporti con la CT e le sue diramazioni muscolari in forma di muscoli pettinati, talora coalescenti in una struttura unica, la TS.

Abbiamo revisionato 100 cuori umani consecutivi provenienti da autopsia eseguita presso il Servizio di Patologia Cardiovascolare del Dipartimento di Scienze Cardiologiche, Toraciche e Vascolari dell'Università-Azienda Ospedaliera di Padova ed esaminato le auricole, la CT, e la presenza, il numero, le dimensioni e il decorso della TS. Abbiamo poi focalizzato la nostra attenzione sui rapporti di contiguità della auricola con le strutture vascolari maggiori cardiache, principalmente la radice aortica e l'arteria polmonare.

La seconda parte della presente ricerca è stata disegnata come valutazione retrospettiva riguardo alla sicurezza procedurale e a breve-medio termine, confrontando la tecnologia di tre tipi di cateteri atriali. Per quest'ultimo obiettivo abbiamo raccolto i dati clinici, anagrafici e tecnici procedurali di 1464 pazienti, sottoposti a impianto di nuovo pacemaker, nel periodo compreso tra il gennaio 2004 e il gennaio 2010 presso l'Unità di Elettrofisiologia della Cardiologia dell'Ospedale di Mirano-Venezia. Tra questi, 915 hanno ricevuto un catetere atriale per indicazioni dunque al pacing cardiaco bicamerale (atriale e ventricolare) e costituiscono la popolazione coorte dello studio, mentre i restanti

549, avendo solo ricevuto un pacemaker monocamerale ventricolare (VVI, pertanto senza catetere atriale), sono stati esclusi dall'analisi.

In base al tipo di catetere atriale utilizzato abbiamo identificato tre gruppi di studio:

1) *gruppo S-FIX* (165 pazienti, 18%) con catetere dritto a fissaggio attivo (J post-formato)

2) *gruppo J-PASS* (690 pazienti, 75.4%) con catetere J preformato a fissaggio passivo

3) *gruppo J-FIX* (60 pazienti, 6.6%) con catetere J preformato a fissaggio attivo

I gruppi sono stati confrontati in base alla comparsa di complicanze peri-procedurali e osservati per questo fino al 3° mese post-procedura.

Risultati

Revisione anatomica

La TS dimostra di avere una certa variabilità anatomica, in relazione alla presenza di: 1) un unico tronco comune (identificata come tipo 1), riportata nel 76% dei casi; 2) una sua duplicazione (identificata come tipo 2), riportata nel 13% dei casi, di rado presentandosi come tenie cosiddette "gemellari", di analoga dimensione e decorso stretto parallelo; 3) di muscoli pettinati finemente arborizzati non coalescenti in una unica struttura definita come TS; pertanto assenza di tenia (pattern identificato come tipo 3) riportato nel 10% dei casi; 4) molto raramente di triplice taenia, riportata solo nell' 1% dei casi.

La nostra osservazione si allinea sostanzialmente con i dati della scarsa letteratura anatomica disponibile. Si conferma che la posizione e il decorso della TS, anche nelle morfologie sovrannumerarie, riescono a farci distinguere una porzione prossimale rispetto a una distale della auricola atriale destra. Tali porzioni in effetti corrispondono alle descrizioni da noi definite come auricola "antrale" e "sacculare". Nella totalità dei reperti la prima porzione si mostra particolarmente adesa alla radice aortica, la seconda è contigua, ma con una certa libertà di rapporti, con la radice della arteria polmonare. Tali

osservazioni suscitano una riflessione riguardo al corretto posizionamento del catetere atriale a fissaggio attivo a vite, distalmente rispetto a posizioni prossimali, le quali ultime potrebbero essere teoricamente pericolose specialmente in pazienti con dilatazione della radice aortica.

Comparazione sicurezza procedurale tra i gruppi dello studio

Una complicanza è stata rilevata in ognuno dei gruppi di studio con la seguente distribuzione: un caso di pericardite "sterile" senza sequele, nel gruppo S-FIX (0.5%) *vs* un caso di fibrillazione atriale sostenuta, indotta meccanicamente durante il posizionamento del catetere atriale, nel gruppo J-PASS (0.1%) *vs* un caso di perforazione e migrazione nello spazio pleurico del catetere atriale, nel gruppo J-FIX (1.7 %), con valori di *p* non statisticamente significativi, pari a 0.3, 0.1, 0.4 per ognuno dei confronti. Per quanto riguarda le dislocazioni dei cateteri abbiamo documentato che non si sono registrate dislocazioni nel gruppo S-FIX mentre abbiamo rilevato 16 (2.3%) casi di dislocazioni nel gruppo J-PASS e 1 (1.7%) caso nel gruppo J-FIX, con valori di significatività statistica per il confronto tra gruppo S-FIX *vs* J-PASS (p=0.04) e solo un trend per il confronto J-PASS *vs* J-FIX (p=0.7).

Conclusioni

La regione auricolare distale definita come "sacculare" sembra essere la regione più sicura per l'impianto di catetere atriale per la cardiostimolazione permanente, a prescindere dalla tecnologia di fissaggio utilizzata, rispetto a regioni auricolari più prossimali, definite come "antrali".

Nella nostra casistica l'incidenza di complicanze riguardo all'utilizzo delle tre tecnologie di cateteri utilizzate è stata comunque molto bassa. In particolare, tra i pazienti portatori di catetere a fissaggio attivo, abbiamo registrato un solo caso di versamento pericardico

lieve (gruppo di studio con catetere dritto) ed un solo caso di perforazione e migrazione tardiva del catetere atriale in spazio pleuro-pericardico (gruppo di studio con catetere J-preformato). Non si sono registrati casi di perforazione dell'aorta ascendente.

I cateteri atriali dritti (post-formati a J) a fissaggio attivo offrono una migliore stabilità in confronto ai cateteri a fissaggio passivo (J pre-formati) e un analogo profilo di sicurezza in confronto a entrambi i sistemi J pre-formati (a fissaggio attivo e passivo).

PART 1

OVERVIEW ON THE ATRIAL PERMANENT PACING

1 - ATRIAL PACING: A HISTORICAL, CLINICAL AND TECHNICAL PERSPECTIVE

1.1 - Brief history of permanent cardiac pacing

A permanent cardiac pacemaker is an implantable device used to maintain a sufficient heart rate when the natural mechanisms fail, either as a result of a deficiency with the natural pacemaker or the atrio-ventricular conduction system in the heart.

With an increasing older population is inevitable that we will face with this kind of cardiologic problem. The normal atrial impulse starts at the sino-atrial node and then propagates through the atrial conduction specialized fibers to reach the atrio-ventricular node and then, through the His bundle, the ventricular final activation is made. Depending of which part of the entire conduction system is functionally or structurally damaged, the cardiac pacing can supply the natural pacing and conduction system in a specific way which means that for patients without a preserved atrial function, such as in permanent atrial fibrillation, a solely ventricular pacing could be enough for restoring the cardiac chronotropic function, while for the majority of patients with a preserved atrial function, a contemporary atrial and ventricular pacing should be provided, to restore the physiologic chronotropic activity.

Cardiac permanent pacing has been used in the treatment of brady-arrhythmias for more than 50 years and during that time an impressive body of research has objectively proved its effectiveness, in terms of parameters that include the patients' quality of life, morbidity

and mortality. There is also no doubt that the related technology has made great strides over the same period. (1-5)

Today, thanks to the microelectronics' development, the pacemaker are smaller, the programming options wider and the pacing leads are thinner and long-lasting than before. All these hardware and software engineering have aimed to provide an appropriate correction of pulse and conduction defects, in such way to simulate the physiological activity and natural electrical behavior as closely as possible.

The first epicardial pacing system has been implanted by Senning in 1958 subsequently followed by a complete trans-venous system, soon in the years later. (6,7)

The further sophistication of the sensing circuit made possible to improve the pace maker software with a sensing function and not only pacing capabilities, which was followed, in 1963 by the first ventricular pacemaker implantation with the so called "on demand" function. (6) Although atrial synchronous systems and dual chambers systems have been described during the 1950s, the routine clinical use of an atrial permanent pacing added to a ventricular one in a dual chamber technology did not occur for many years.(6)

The 1970s were significant for the introduction of lithium battery accumulators and for the multi-programmable capable devices (6-10)

The milestone of the 1980s was the introduction and the wide acceptance of the dual chamber pacemakers, incorporating a double (atrial and ventricular) lead technology. This new developing pacing techniques have therefore followed the previous studies about the use, safety and performance of the atrial leads, added to the well known and little bit "older" ventricular leads technology.

One of the first study regarding the atrial leads technology and clinical performance, has been published in the 1977, followed by other studies until the first 1980s. Among these latter, one of the largest retrospective studies regarding the endocardial anchorage lead technology (active screw-in leads and passively tined leads) has been performed by

Perrins et al, who compared the above anchorage system in 315 atrial and ventricular leads.(11) They concluded that the active fixed screw-in atrial leads and short tined passive fixed ventricular lead might be the preferable choice, which could provide the virtual elimination of lead displacement and a very low incidence of lead related complications (11-15)

The further years over the 1990s have witnessed the continuing sophistication of sensor and automaticity of the devices' software.

The traditional position for the lead insertion for the atrial and ventricular pacing since the beginning of cardiac pacing, have been the RAA and the right ventricle apex.

Late in the last century, the further most important changes in the technical development were proposed mostly by French authors, who were starting to insert ventricular lead in different positions. The different positions proposed as first were the inter-ventricular septum pacing, in the higher part (therefore the right ventricle outflow tract below the pulmonary artery) and the lower part of the septum. Soon after the exploring of the left ventricle epicardially, by means of coronary sinus navigation, a new dedicated leads technology was launched in the pacing market, with special features to ensure the stable displacement into the coronary sinus branches. This technology and implant technique, been proposed for simultaneous pacing of right ventricle (via the ventricle apex pacing) and left ventricle (via an epicardial left ventricle pacing) was, and is currently, the only reliable and safely available one for the so called cardiac resynchronization therapy (CRT). The following fast advance of this multisite pacing was then the established worldwide development of the CRT, by means of biventricular pacemakers. Thus, these years were witnessing for the first time the pacing indications not only proposed for bradycardia correction but also for left ventricular systolic "dissynchrony" and failure correction. The CRT was indeed proposed for resynchronize the "failing left ventricle", especially when this was related to the electrical right-to-left ventricle dissynchrony, due

to the enlargement of the QRS duration on the ECG due to left bundle branch block, or to right ventricular pacing (in so called upgrading procedures from dual chambers pacemakers to CRT pacing). Soon the CRT technique showed, by means of several randomized controlled trials, to be striking for all the strong endpoints in heart failure for functional, clinical and mortality outcomes.

As well as in the ventricular pacing research field, also for atrial pacing new indications were proposed by the beginning of the 2000s, not only for bradycardia correction but also aiming to the atrial electrophysiology electrical synchronization, especially for atrial fibrillation prevention. The alternative atrial pacing sites, mainly interatrial septal, were then proposed alternatively to the RAA pacing. The two conventional site of atrial septal pacing were the high interatrial septum (the so called Bachmann bundle atrial pacing) and the low interatrial septum (the so called Koch triangle pacing). Both techniques have been developed to ensure a better biatrial electrical synchronization with the aim to prevent the atrial fragmentation of the impulse propagation and the dispersion of atrial activation and refractoriness. Both mechanism are believed as critical for atrial fibrillation development. (16-21).

In the following Fig 1 (A, B and C panel) is displayed the main technical pacemaker technologic development in the last 50 years

Fig 1 A: First external pacemaker implantation, with the lead anchoring on the cardiac epicardial surface by means of sewing and external lead connection with the battery generator (during the 1950s)

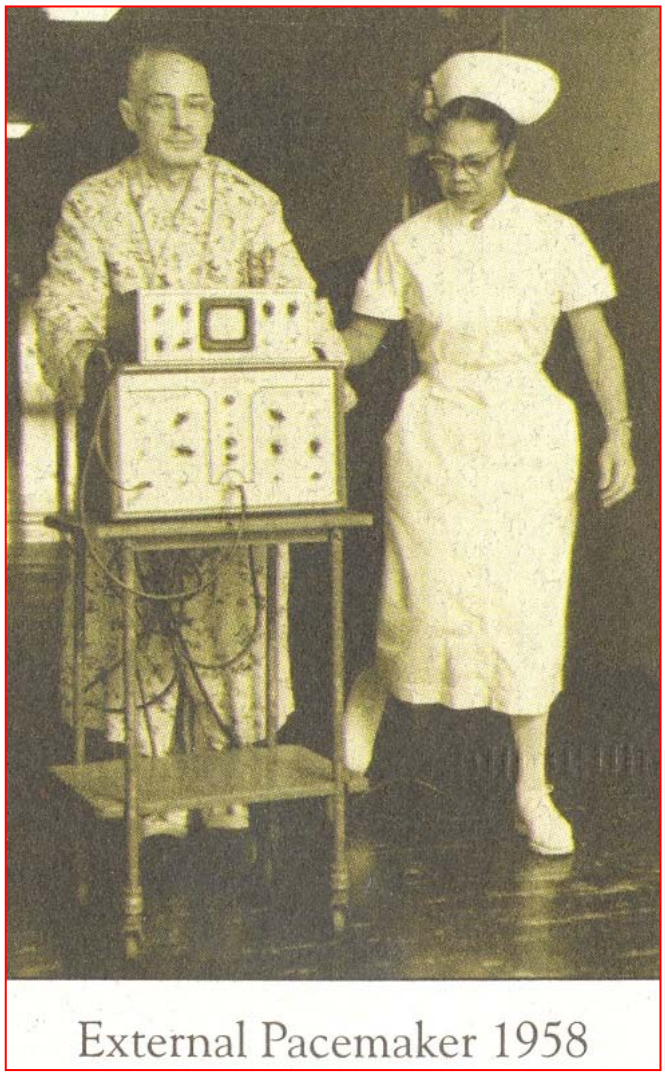
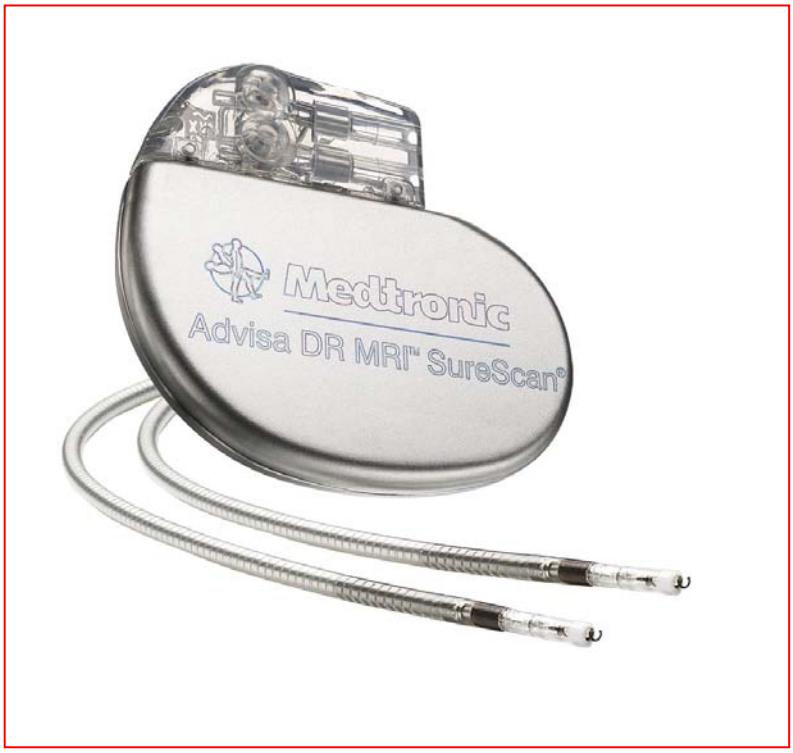


Fig 1 B: First miniaturized subcutaneous implantable epicardial pacemaker (Dr. Senning, Karolinska Institute, Stockholm Sweden, October 1958)

Fig 1 C: Last generation transvenous pacemaker: first implantable pacemaker with MRI exposition compatible technology



1.2 - Pacemakers international nomenclature code

A three letter code describing the basic function of the various pacing system was proposed in the 1974. Since that time, responsibility for periodical updating the code has been assumed by the North American Society of Pacing and Electrophysiology (NASPE) and the British Pacing and Electrophysiology group. The code has been designed in 5 positions, but the fifth is rarely used.

1. the first position reflects the chamber or the chambers in which the pacing occurs (A= atrial, V= ventricular, 0= none, D= dual, atrial and ventricular).

Some manufacturers also use the letter S to indicate the single chamber of either pacing or sensing function.

2. the second position refers to the chamber or chambers of sensing function (the same letter meaning as described above)

3. the third position refers to the mode of sensing, or how the pacemaker respond to a "sensed" event (I= inhibition, which indicates that a sensed event inhibits the pacing output pulse, T= triggered, which indicates that an output pacing pulse is triggered by a sensed event, D= dual, i.e. I and T response may occur).

4. the fourth position reflects both programmability and rate responsive modulation (R= rate-responsive) and means that the device incorporates a rate-accelerating sensor, which can increase the pacing rate, independently of intrinsic cardiac chronotropic activity.

The fifth position describes multisite pacing functionality. Atrial multisite pacing is being investigated as way to prevent atrial fibrillation. Ventricular multisite pacing is a treatment for pacing a patient with dilated cardiomyopathy. It is used very rarely.

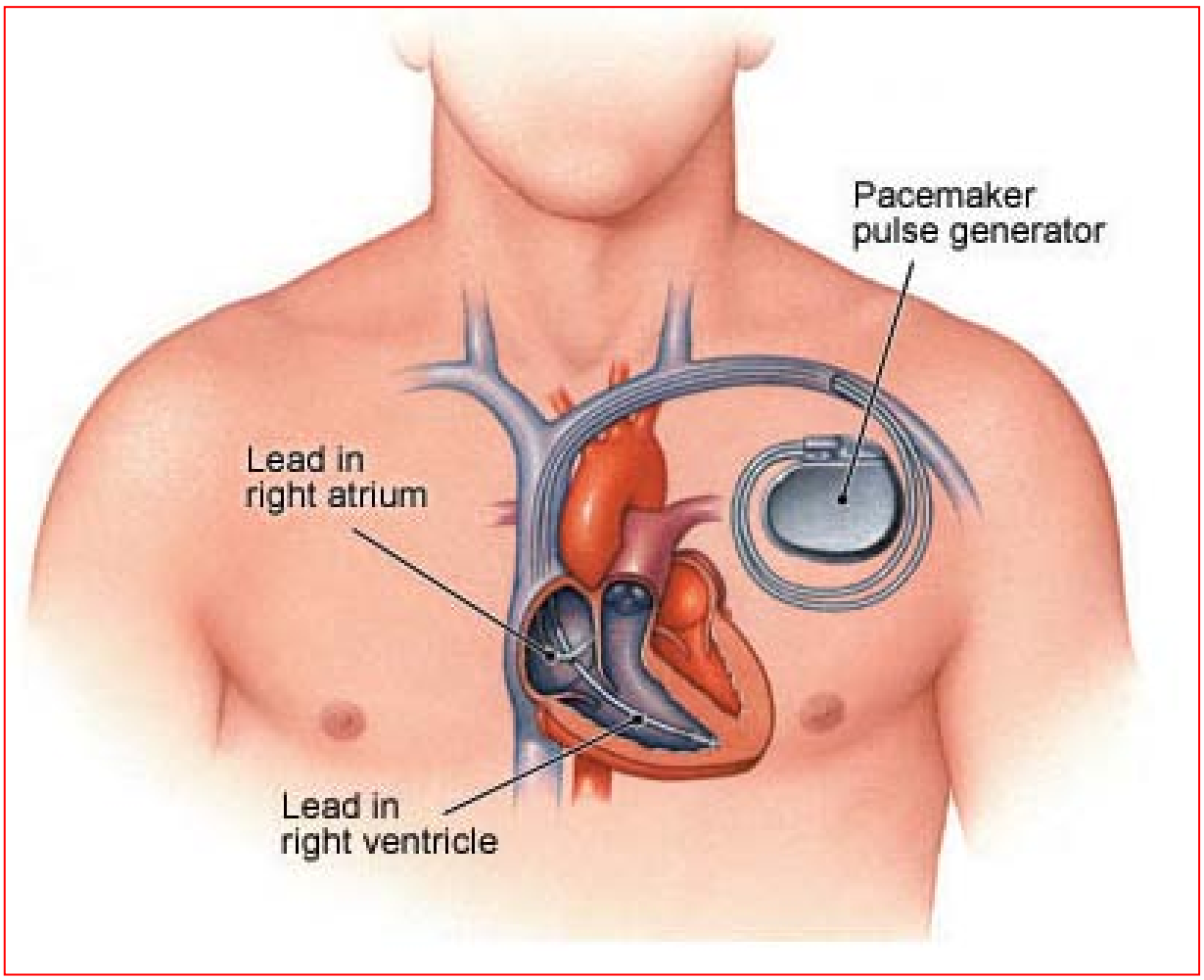
The following schematical table 1, displays the current updated code nomenclature.

The further Fig 2 displays the traditional anatomical scheme of pacemaker and leads locations.

Table 1: pacemaker nomenclature international code

Position I	Position II	Position III	Position IV	Position V
(Chamber Paced)	(Chamber Sensed)	(Response to Sensed Event)	(Programmability,	(Multisite Pacing)
O = none	O = none	O = none	Rate Modulation)	O = none
A = atrium	A = atrium	I = inhibited		A = atrium
V = ventricle	V = ventricle	T = triggered	O = none	V = ventricle
D = dual (A + V)	D = dual (A + V)	D = dual (T + I)	R = rate moduation	D = dual (A + V)

Fig 2: Schematic anatomy of pacemaker position and right atrium and ventricle leads placement



1.3 - Bradycardia indications principles for permanent pacing

Although some indications for permanent pacing are relatively certain or unambiguous, other may require a considerable expertise and judgment and an individualized approach. In case of presence and therefore recruitable atrial activity (such as patients without a permanent atrial fibrillation), the patients may require always an atrial lead incorporated in a dual chamber pacemaker (DDD), if the sino-atrial pulse generation is failing. These conditions are related to the sinus bradycardia, the so called chronotropic incompetence and the sick-sinus syndrome. The DDD pacing choice, instead of a simple single chamber and single lead atrial pacing (AAI), is made on the basis of a possible future development of atrio-ventricular block, following the sino-atrial electrical disease. In very rare cases of young patients a AAI system could be implanted in these cases.

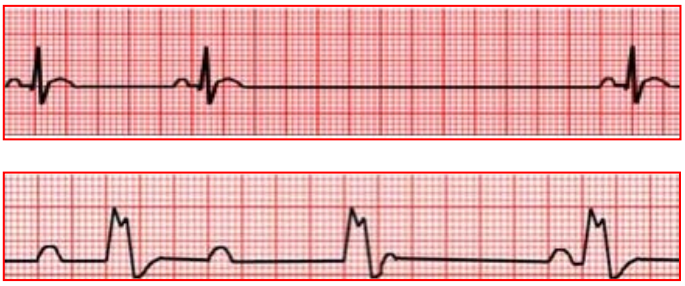
The choice of the rate-responsive sensors, that are specialized sensors incorporated in the pacemaker hardware (which can recognize the patient activity and increase the paced heart rate as needed), can add a considerable cost over the pacemaker system expenses and should be individualized on the basis of the patient age, physical and daily activity, life expectancy and kind of the underling bradycardia disease.

In the two table below is displayed a schematic flow chart for the cardiac pacing mode suggested in case of sinus-node and in case of atrio-ventricular (His and infra-Hisian conduction system) conduction disease.

In the following Fig. 3 are displayed two typical ECG diagnosis of sinus node and atrio-ventricular conduction disease.

Fig 3 - <u>upper ECG</u>: sinus node dysfunction with preserved atrio-ventricular conduction;

- <u>lower ECG</u>: complete atrio-ventricular block with atrio-ventricular dissociation



The following Fig. 4 (A and B panels), shows a flow chart decisional schemes for pacemaker implantation indications for sinus node and atrioventricular conduction diseases.

Fig 4 A - Decisional flow-chart scheme for bradycardia pacing indication in sino-atrial dysfunction

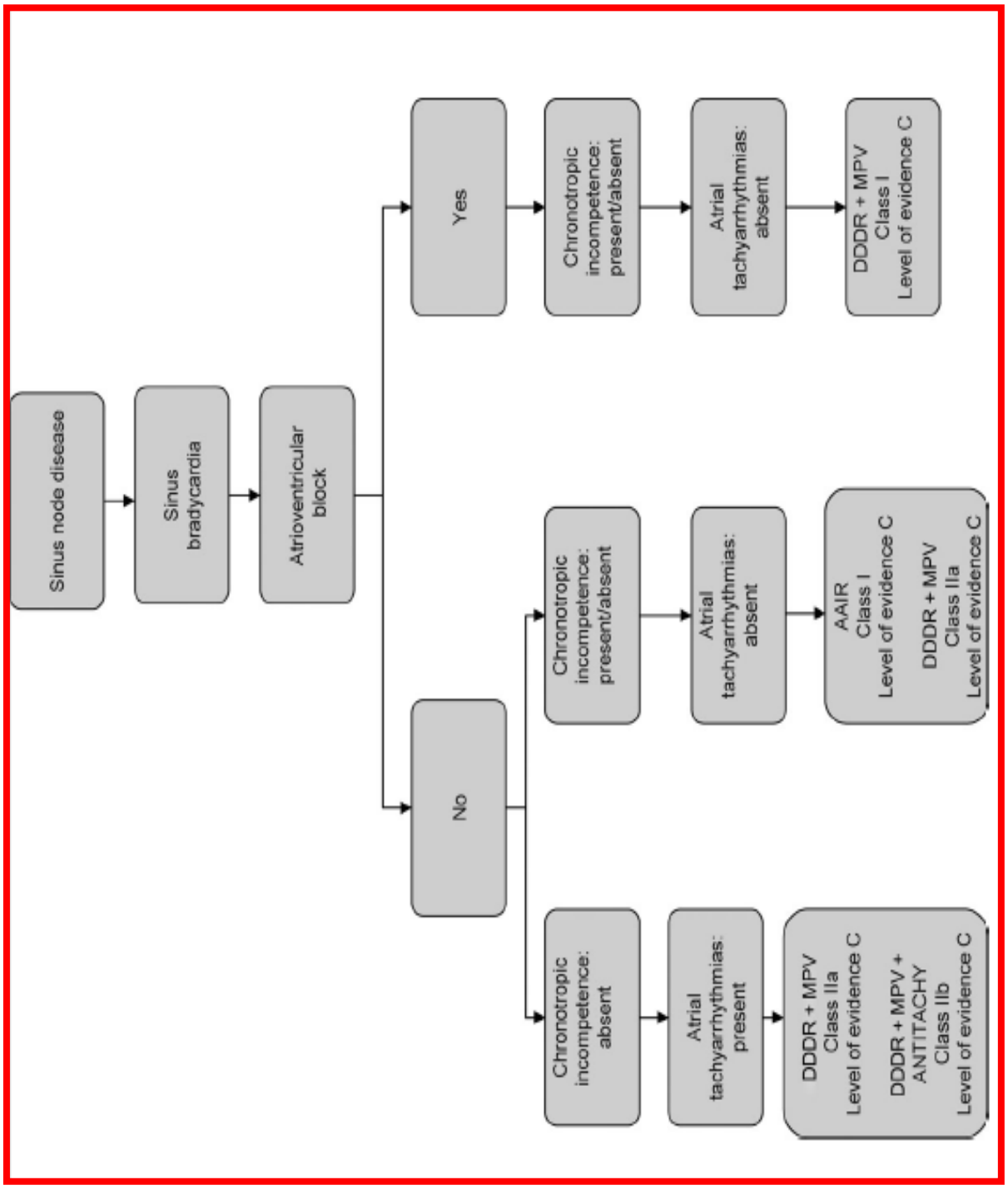
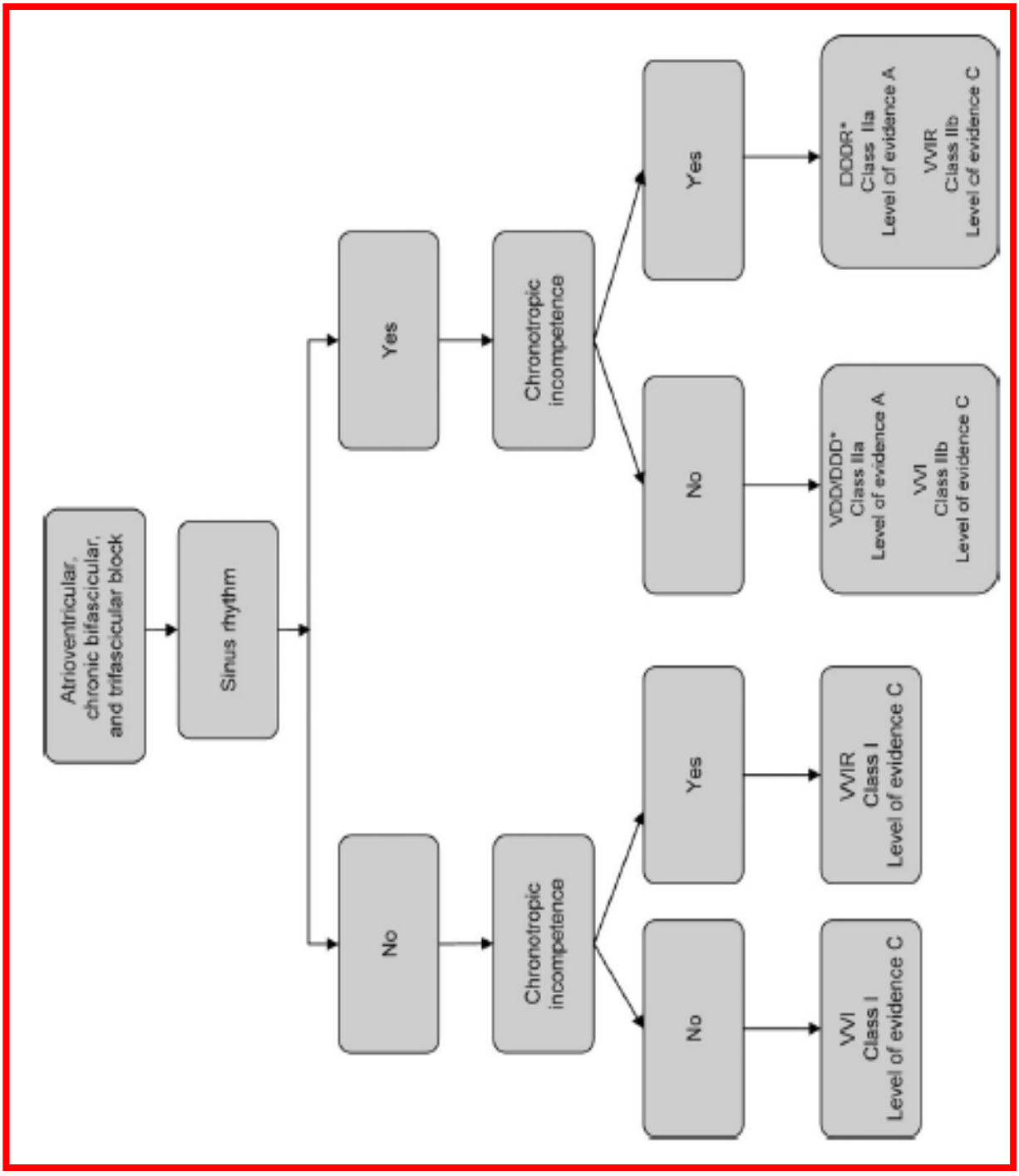


Fig. 4 B - Decisional flow-chart scheme for bradycardia pacing indications in atrio-ventricular conduction dysfunction



Legend: **MVP**= pacemaker software algorithm to minimize the unnecessary ventricular pacing thus resulting in improving and promoting the spontaneous ventricular activity. **Class and Level of evidence:** international guidelines code for appropriateness application of any therapy (subdivided in three Class I, II or III and three levels of evidence, a, b or c)

1.4 - Pacing leads technology

The pacing lead is a relatively fragile insulated conductor wire implanted in the "hostile" human body. In comparison with the market advances with regard of sensors, software and other device capabilities, concomitant advances in pacing leads have occurred slowly.

The main following features are important for the lead performance in safety and function:

- Lead polarity

The pacing impulse may be delivered by an unipolar or bipolar energy. The former technology may require a simpler lead wire technology, therefore a thinner and less fragile lead. After a 30 years of controversy about which polarity design should be the best choice, unlike the early bipolar leads, the modern ones are very well resembling the unipolar leads as lead size and ease of insertion. The main concerns about the bipolar lead are related to the lead structure reliability, owing a more complex lead design and the more components used. Despite this, excellent long term survival and performances have been documented about the modern silicon insulated bipolar leads, and since reliability is now comparable, the bipolar leads should be preferable for almost all aspects.

- Lead shape (atrial leads)

The ventricular leads are all represented by just straight leads, regardless the position of the destination pacing site. The anatomy of the right atrium require at least two kind of lead shaping to ensure the main atrial pacing sites.

The two atrial lead available shapes are currently represented by the *straight* ones, which means that they have a default straight shape which must be modified by dedicated shaped stylets and by the *J pre-shaped* ones, which shape is pre-engineered in a J fashion and are made only for RAA pacing.

The former should be advanced in the right atrium and subsequently anchored by shaping in a "J" fashion (so called post-J-shaping) to reach the RAA or, alternatively a in "L" shaping to reach the atrial septum; the second must be forced to be straight (with an inner straight styilet) to advanced in the right atrium and then can be positioned in the RAA by withdrawing the straight stylet, to reach their natural shape.

(see the following Fig 4 and 5)

Fig 4: - <u>upper panel</u>: active fixation straight atrial lead tip (screw-in system)

- <u>lower panel</u>: J pre-shaped atrial lead tip

Fig 5: Straight atrial lead (right) and J pre-shaped stylet (left) which should be inserted in the lead body to ensure the final positions, and then withdrawn, after a successful screwing and anchorage.

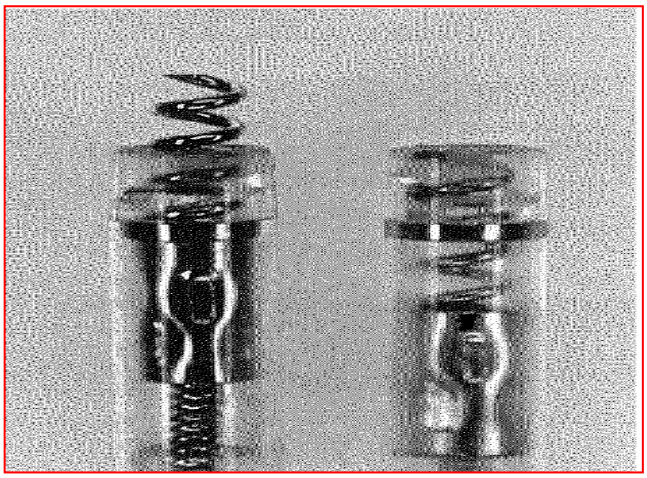
- Lead fixation

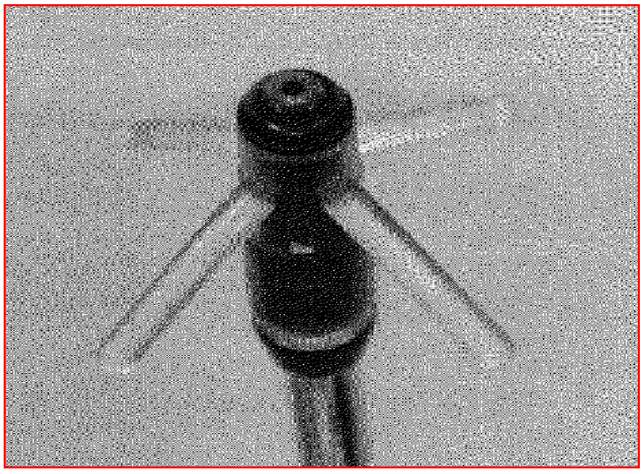
The mechanism of fixation is mainly divided in two technologies: the active fixed leads, which use a screw-in system, that in the vast majority of cases is represented by a retractable screw and rarely by an exposed, non retractable screw. This feature allows the implanters physicians to re-position the lead (especially for straight leads) after a failed anchorage or after a failed performance, during the same procedures or along the follow up during a "redo" procedure, in different positions. The retractable screw mechanism is made possible by means of a dedicated tweezer which should be rotated clock or

counterclockwise, for screwing or unscrewing. The second system is the passive fixed technology which allows the lead placement by means of tines that surround the lead tip. They chronically may generates endocardial fibrosis at the lead-endocardium interface and therefore a reliable long term anchorage (see the following Fig. 6)

Fig 6: - ***<u>upper panel</u>: active fixed atrial lead tip with a retractable screw-in system***

- <u>lower panel</u>: passive fixation silicone tined atrial lead tip





- Lead size

The matter of lead size is related to the pacing polarity and components incorporated in the lead. The modern technology has made possible to reach low profile leads, which can display excellent performance and thus are comparable with the previous narrower unipolar leads, today very rarely used. The current atrial lead sizes in diameter vary among 5 to 7 French.

- Lead conductor and insulation

Two separated and insulated conductor wire are located inside the lead, the former dedicated to the pacing circuit and the latter to the sensing circuit. Insulation integrity between them (each wire is insulated) and the main further external insulation of both, is the weakest part of this technology. The biophysical parameters monitoring of leads, by means of electronic pacemaker follow up, can reliably allow a routine long term lead surveillance.

1.5 - Atrial lead implantation technique

As for all the intravenous permanent pacing techniques, the heart chambers are reached percutaneously by the insertion of leads into an intravenous peel-away sheath, inserted into the left or right subclavian or cephalic vein (alternative surgical techniques). After the deployment of the leads, the sheath can be peeled away and removed.

The passive fixation atrial leads are all pre J-shaped and dedicated to the RAA pacing, while active fixation leads come in either form (straight and J- shaped) depending on manufacturer. As discussed above, traditionally the right atrium lead is placed in the RAA when just bradycardia correction is targeted. In some patients, where the RAA position is not suitable (usually because of poor pacing characteristics) the screw-in leads may be placed anywhere else within the right atrium, but most commonly on the lateral wall. There are standard techniques that are used to position the RAA lead. The first

involves placing the distal tip of the lead in the middle of the RA. If a pre-shaped lead is being used, the straight stylet is gradually withdrawn to allow the tip to rise into the RAA. If a straight lead is being used, a J shaped stylet is introduced at this point to let the tip rise into the RAA. The lead is then gently withdrawn to try to intubate the RAA os. If too low, the lead may prolapse on itself and simply withdraw into the superior vena cava. If this happens the pre-shaped lead is straightened again with the straight stylet (or the J shaped stylet is withdrawn from the straight lead) and the procedure repeated, but starting a little higher in the right atrium itself. It is important to be aware that the RAA position varies and can appear different in the standard postero-anterior projection. Therefore, it may be necessary to check the lead position in different fluoroscopic projections (for example, in left anterior oblique view the lead tip should generally point anteriorly).

Furthermore, the classical ‘‘windscreen wiper" movement of the lead tip suggests a good position in the RAA but be aware that this motion is absent in atrial fibrillation. When it is decided to place the lead in a position other than the RAA, it is generally advisable to use an active fixation lead. Positioning is often on the lateral wall, but also in the interatrial septum (for Bachmann bundle or Koch triangle pacing, see below). Again the lead is placed in the mid right atrium and then rotated clockwise to spin the lead laterally (for lateral wall placement) or with a "L" shaped stylet can be rotated counter-clockwise to reach the septum. Sometimes to keep the lead tip free in the right atrium, the whole lead will need to be advanced or retracted as the lead is rotated. Ideally the tip of the lead should be as close to perpendicular to the wall as possible to maximize the chance of getting good fixation, but care is needed as there is a small risk of perforation.

1.6 - Atrial leads pacing sites

Although the traditional atrial region to deploy the lead has been the RAA since the early years of atrial pacing until now, in the last decade new atrial pacing sites have been investigated in the field of the prevention of atrial fibrillation, while fewer alternative pacing sites have been studied in patients just with bradycardia indication. The search for alternative atrial pacing sites has been driven by the observation that atrial activation patterns can influence the incidence of atrial fibrillation. Thus, beside the RAA traditional pacing, the main alternative atrial pacing sites are located in septal positions and the comprehensive literature available about these techniques, mainly describe two kind of septal sites: the high septal (so called the Bachmann bundle pacing) and the low septal position (the so called the Koch triangle pacing).

One of the goal of this alternative atrial pacing is thus to prevent the non-physiologic delay between right and left atrial activation. Pacing from atrial sites that can decrease the dispersion of atrial refractoriness, could decrease the occurrence of atrial fibrillation (16,17, 21-25).

In the same period, another field of research of alternative pacing sites and atrial fibrillation prevention, has been the multisite atrial pacing, intended as dual site right atrial or bi-atrial pacing.

In summary, the main pacing sites and features, currently used in the clinical pacing can be summarized as follows:

- RAA pacing

This is the traditional location for atrial pacing with only bradycardia indications. The lead is placed coming from the above superior vena cava and, once reached the higher part of the right atrium, should be J-shaped medially into the right appendage as discussed above. In that position both the lead fixation technologies are allowed to find anchorage between the pectinate muscles pouches by the lead screwing in the thin atrial

wall or by anchoring the tines of passive leads in such pouches. Especially for these latter, the chronic endocardial fibrosis will improve lead stability over time. The rate of lead dislocation vary in the literature data available but is little bit generally higher for passive leads; conversely the screw-in system has shown an higher perforation incidence rate. However both complications are very rare.

The aim of the present research, included in the second part of the present work, is compare and report data about lead dislocations and perforations and other eventual lead related complications in a large cohort of pacemaker patients; this topic will be therefore extensively discussed below.

- High interatrial septum pacing (Bachmann bundle pacing)

The Bachmann bundle is a specialized electrical connection, incorporating specialized conduction fibers, that runs between right and left atrium. Its routing is deemed to lay in the right atrial postero-superior wall, therefore reaching the left atrium across the interatrial septum. (see below the Fig 7)

Acute studies evaluating the electrophysiologic effect of pacing site upon atrial activation have shown that pacing at the Bachmann bundle resulted in a shorter P wave duration (on the 12 leads ECG) compared with pacing at other atrial sites. The impact of permanent Bachmann bundle pacing upon the occurrence of atrial fibrillation have been investigated in a randomized controlled trial in the early years of this decade. The trial (Bachmann Bundle Pacing Trial) was designed to compare the Bachmann pacing with the traditional RAA pacing in patient with history of paroxysmal atrial fibrillation and indication to pacemaker implantation. In this trial the atrial leads biophysical performances and the implantation surgical times were similar. In patients with Bachmann pacing there was a reduction of developing chronic atrial fibrillation from 75% to 42%.

The Bachmann bundle, as located in the postero-superior aspect of the right atrial free wall, represents the main electrical connection between the right and left atrium. Unlike

other conduction systems sites, such as His or Purkinje sites, there is no atrial typical electrogram deflection (by endocavitary atrial electrophysiologic mapping) which can reliably help to detect the Bachmann bundle. For this reason the lead positioning and pacing at that site is possible only with active fixation leads and its implantation technique is based primarily on fluoroscopy anatomy. (16, 21-23)

- ***Low interatrial septal pacing (Koch triangle pacing)***

As discussed above, the atrial pacing locations that decrease atrial activation and recovery time may be preferable in patients with a history of atrial arrhythmias. In patients with paroxysmal atrial fibrillation, pacing at the interatrial high septum has been shown to have a positive influence on decreasing the number of episodes. Another alternative septal atrial pacing, which has been investigated in the early years of this decade, is the low septal atrial pacing (the so called Koch triangle pacing). In any case, any interatrial septal pacing requires screw-in bipolar leads, and the feasibility of this approach has been reported in small numbers by various centers. (17, 24, 25)

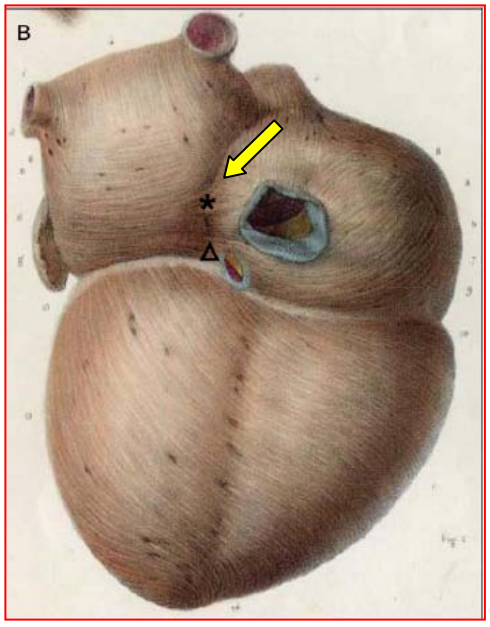
In 2001, Padeletti and coworkers published their data about the low atrial septal pacing. They found that "Koch triangle" low septal pacing was more effective (than RAA pacing) to prevent the occurrence of atrial fibrillation in patients with history of such arrhythmia and sinus bradycardia pacemaker indications. In the same study a particular software algorithm of atrial pacing, designed to inhibit the atrial spontaneous activity and to achieve a constant atrial capture, was tested. The latter mode of "constant" atrial pacing didn't add any further clinical value for the study endpoint. Subsequently the same authors performed a new multicenter randomized trial with mostly the same design and endpoints. To test their hypothesis they have compared the septal atrial pacing (now classified as *higher septal* - i.e. Bachmann pacing - *middle septal* - i.e. fossa ovalis pacing - and *low septal* - i.e. Koch triangle pacing) combined with three dedicated pacing prevention software algorithms mainly designed to avoid the spontaneous atrial activity

by a constant atrial pacing, to prevent the atrial irregular rate by eliminating the long-short atrial cycles and by eliminating the atrial pauses after an effective antitachycardia atrial overdrive rapid pacing. Their results demonstrated that all the atrial septal pacing were feasible and safe, but the adding of a prevention pacing algorithm was not effective for the study endpoint for both RAA or septal pacing sites, while the latter could provide clinical efficacy when added to a septal pacing. (17,24)

The relative efficacy of Bachmann pacing versus Koch triangle pacing remains unknown; the latter is more frequently associated with higher risk of atrial "far-field" (a specific atrial lead sensing dysfunction, resulting in "oversensing" of ventricular activity and loss of lead function). (26- 29)

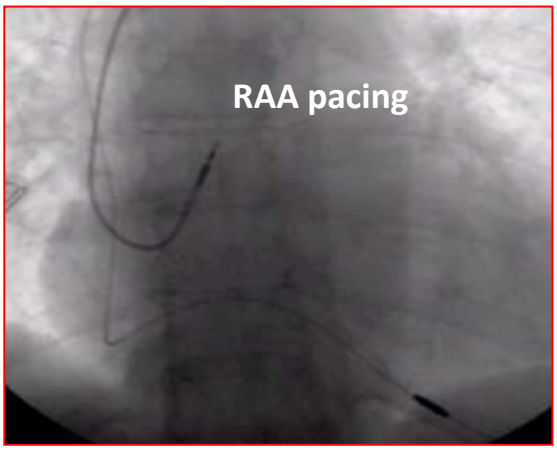
The interatrial conduction represented by the Bachman bundle is displayed in the Fig 7 below.

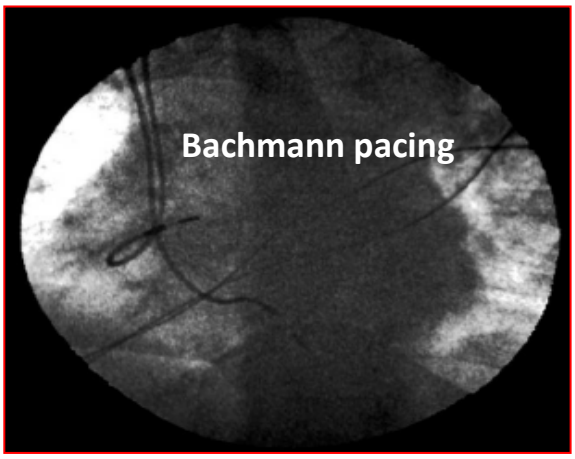
Fig 7: - A postero-superior view of both atria. Aorta and Pulmonary artery have been removed. The yellow arrow indicates the Bachman fascicle routing from right to left atrium (upper interatrial connections). The black triangle below indicates the lower interatrial connections around the coronary sinus os. (from ESC 2013 Copyright)

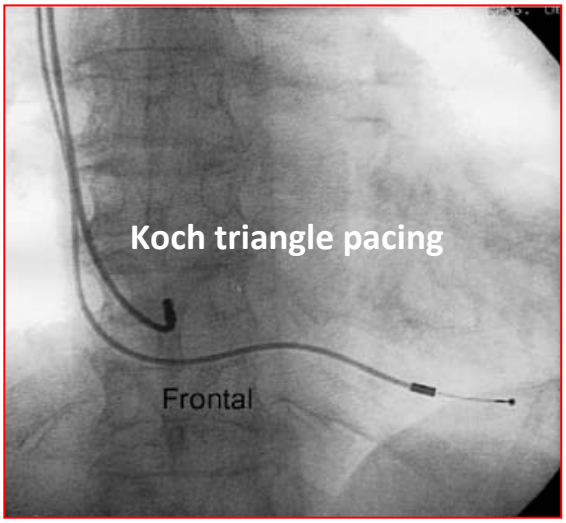


All the three atrial lead positions above described are displayed in the below Fig 8

Fig 8: - ***upper panel*: Fluoroscopy antero-posterior projection of RAA atrial lead positioned J shaped (upper lead)**
- ***middle panel*: Fluoroscopy left anterior oblique projection of Bachmann bundle positioned atrial lead (upper lead)**
- ***lower panel*: Fluoroscopy antero-posterior projection of Koch triangle positioned atrial lead (upper lead)**







- Multi-site atrial pacing

The dual site right atrial (RAA + septal) and biatrial (septal + left atrial via coronary sinus lead) pacing has been also evaluated in the early 2000s. One important trial (DAPPAF study) has been published which has compared the dual site right atrial pacing with RAA pacing alone. The former pacing mode was safe and better tolerated than high RAA pacing alone. (26-28)

As compared with the one-site pacing these multisite techniques require more hardware.

1.7 - Pacemaker software algorithms to *prevent* or *terminate* atrial fibrillation

The observation that the AAI or DDD pacing mode ("physiological pacing", see below) can delay the occurrence of atrial fibrillation in patients with sinus node dysfunction has created the new interest about the "increasing" the "dose" of atrial pacing.

- Although variable in design, the "*preventive*" algorithms in general aim to prevent bradycardia and to avoid large atrial cycle length variations, by: - 1) providing a constant atrial pacing, thus "pace-conditioning" the spontaneous atrial activity, - 2) high pacing rate delivery after atrial ectopies, - 3) increased post-exercise pacing to avoid the abrupt drop in heat rate (all conditions that can promote atrial refractoriness recovery dispersion).

- The algorithms that can "*terminate"* the sudden onset atrial arrhythmias are represented by anti-tachycardia overdrive pacing and atrial defibrillators. Is difficult to interpret studies of the selective effectiveness of anti-tachycardia pacing for atrial fibrillation, in part because this therapy is often delivered and studied in combination with the "preventive" anti-tachycardia therapies. Atrial defibrillators have been proposed in the clinical scenario for a very short period, and are now no longer available.

1.8 Atrial permanent pacing procedural complications overview

Apart of the surgical pocket and subclavian access related adverse events, not peculiar of the "atrial pacing", more typical complications related to the atrial permanent pacing have been reported in up to 9% and are all related to the to the atrial lead placements. (29-34)

They are most often related to the chest venous access for leads insertion (haemorrhage, pneumothorax: 2%), to the acute or chronic lead dislodgement (4.2%), to the inadequate lead performance (3.5%) and to the acute pericarditis (up to 5% in patients, in patients receiving active-fixation atrial leads) due to a slight microscopic perforation of the lead screw into the pericardial space, through the thin atrial wall. (30)

Complete lead perforation through the atrial wall, resulting in pericardial effusion or tamponade has been rarely reported. This may require percutaneous drainage or open heart surgery. There have been published only few case reports about this dangerous complication. In all these cases the leads were perforating both pericardium and pleura resulting in right sided pneumothorax and also, all leads had been inserted by left pectoral surgical approach. (29-34)

Another life threatening complication, very rarely reported, is the aortic root perforation by active fixation RAA lead with consequent dramatic clinical presentation with massive cardiac tamponade and needing of emergency open heart surgery. To the best of our knowledge, to date there are just three cases published as case reports, worldwide (35-37)

Trigano et al identified the possible risk factors for cardiac perforation using an active fixation atrial lead: overscrewing the lead, distal push of stylet insertion, abrupt withdrawal of the lead with the exposed screw (while repositioning without previous unscrewing) or inadvertent displacement of the atrial lead while positioning the ventricular one were associated with the RAA perforation. (38)

The atrial lead related complications may occur in any part of the follow up observed period, but in general, the pericardial complications such as the slight atrial wall

perforations and the "reactive" pericardial effusions are typically encountered in the first post-operative month due to typical symptoms occurring (breath movements related chest pain, fever etc.); by contrast the pleural lead migrations, although are very rare, are less predictable and could appear also very late during the follow up.

However, in the 5 cases reported in the literature, the pleural migration timing varied from the immediate post-operative hours to the 7th month after the procedure (29-34).

The lead dislocation are often accidentally discovered during a normal pacemaker follow up (as a deficit of lead pacing or sensing performance) or during the X chest ray scan in the post-implantation routine follow up. The atrial lead dislodgements are often not associated with typical symptoms; very rarely the patients complain palpitations.

The choice of leads with theoretical more reliable stability (screw-in systems) compared with ones less affected by perforation but theoretically prone to more displacement (passive J shaped leads), must be balanced also on the basis of the personal attitude of the implanter physician, since both features are now reliable, safe and allowed by the International Scientific Societies.

2 - ATRIAL PACING: THE PHYSIOLOGICAL HEART PACING

2.1 - *"Physiologic" (atrial based)* pacing for bradycardia indications

The atrial based pacing should be considered as "*physiologic pacing"* since it can provide an atrio-ventricular activation timing resembling the natural orthodromic activation.

When considering any sinus-node disease correction, the question that must be answered is: *"is the patient having also an history of paroxysmal atrial fibrillation ?"*

- In patients with sinus node bradycardia pacing indications and no history of atrial fibrillation, the "physiologic" pacing mode should be adopted either by a single (AAI) or dual (DDD) chambers device. Although this latter technology (incorporating also the ventricular pacing) is a more expensive option, there is a possibility, albeit small (1% per year), of future AV block development, therefore the choice must be individualized accordingly. The RAA pacing is acceptable in all these patients.

- In patient with atrio-ventricular electrical disease the DDD pacemaker is the usual chosen pacing mode, unless is present permanent atrial fibrillation. This latter case require just a ventricular (VVI) pacing.

2.2 - *" Physiologic" (atrial based)* pacing for atrial fibrillation prevention (associated with sinus bradycardia)

In patients with sinus.-node bradycardia associated with history of paroxysmal or persistent atrial fibrillation again a dual chamber pacemaker ("*physiologic*") must be chosen, but in this case a DDD dual chamber device is better than AAI one, since more often anti-arrhythmic therapy is prescribed, which could worsen the atrio-ventricular conduction and also because the combination of a "dual" nodes disease (sinus and atrio-ventricular) is more likely to occur along the follow up.

Several prospective randomized clinical trials have reported that *"physiologic"* pacing, which means the atrial pacing (septal, multisite or RAA pacing), associated with DDD pacemakers with the sparing of ventricular pacing (by means of algorithms to prevent the unnecessary right ventricular pacing), is associated with a lower incidence of permanent atrial fibrillation when compared with single-chamber ventricular pacing (VVI) in sinus rhythm patients with conventional pacemaker indication. Whether the atrial pacing itself is anti-arrhythmic remains still uncertain; on the other hand, the right ventricular VVI pacing is today considered to promote atrial fibrillation, even in preserved AV synchrony during dual-chamber pacing. As discussed above, a number of clinical trials investigated the impact of site specific atrial pacing and advanced atrial pacing algorithms on the secondary prevention of atrial fibrillation. The multisite pacing demonstrated to add only minimal benefit for the prevention of atrial fibrillation; by contrast, in some studies the septal pacing and the specific atrial pacing algorithms were reported to reduce the recurrence of atrial fibrillation in selected patients. However, it remains unclear how to identify these patients. In the clinical practice, the effectiveness of specific atrial pacing algorithms and/or septal pacing has to be tested out in the individual case.

These therapeutic options should be considered in patients with a conventional indication for antibradycardia pacing and, additionally, symptomatic atrial fibrillation. (39-44).

Some authors have also recently assessed the "intra-atrial electrical conduction" by means of electrophysiologic study to identify which patient could benefit from septal pacing. (45)

In conclusion, at the present, atrial permanent pacing to prevent atrial fibrillation is not indicated, unless sinus bradycardia or sick-sinus syndrome are also present.

PART 2

RIGHT ATRIAL ANATOMY INVOLVED IN THE PERMANENT PACING AND COMPARISON AMONG THREE ATRIAL LEADS TECHNOLOGIES

1 - INTRODUCTION

1.1 - Background and Objectives

The atrial permanent pacing, added to the ventricular pacing in the dual chambers pace-makers, is an established technique which allows the cardiac pacing in a physiological way, respecting the atrio-ventricular impulse conduction timing. The right atrial structures involved for the leads positioning are mostly the RAA and less frequently the right atrial septum. The former structure is close to the main right and left ventricles outlets and the supra-valvular tract of the pulmonary artery and aorta. During a pacemaker implantation, the lead positioning in the RAA is achieved thanks to a J shaping of the lead. The J shape can be an intrinsic feature of the lead (J pre-shaped tip) or alternatively it can be obtained by inserting a J shaped stylet into a straight lead (J post-shaping) and actively anchoring the lead in the atrial/appendage wall with a "screw-in" technology. Considering the particular routing made by the atrial lead to reach the appendage, coming from the above superior vena cava (after a left or right subclavian vein cannulation), the lead anchorage and its resulting stability are a striking issues in a electrophysiology procedure. Currently lead shape (J-shape) and lead fixation (active screw-in or passive with silicon tines) are the most used features which characterize the atrial leads manufactory. The lower risk of perforation (passive pre J-shaped systems)

compared with a more reliable stability (screw-in systems) has been addressed in few previous studies.

The gross anatomy of the RAA, its relationships with CT and TS and the consequent procedural implications for electrophysiology procedures and permanent atrial pacing have been poorly previously described (46, 53). The right atrium proper and the RAA are separated from the sinus venosus by a smooth muscular boundary termed CT corresponding externally to the sulcus terminalis. The pectinate muscles are muscular ridges extending anterolaterally from CT to reach the RAA, to form several trabeculations. The largest and most prominent pectinate muscle forming the bridge of the sulcus terminalis internally, upon external inspection, is called TS, literally translated, ‘‘the sagittal worm’’. Although descriptions of the gross structure and fibers orientation of the external right atrium are detailed, the gross anatomy of the pectinate muscles in relation to CT has not been well described. Interestingly enough, CT and pectinate muscles have recently received increasing attention. This stems largely from the discovery that the morphology of CT has a functional role in electrophysiology and cardiac conduction; thus, this structure has inherent implications in arrhythmias (47-53).

Moreover, the atrial wall between the pectinate muscles is quite thin allowing trans-illumination; this could be also a matter of concern for the right atrium catheters instrumentation. See the following Fig 9.

Another observation that arose during our specimens observation is how close are the relationships of the RAA to the ascending aorta; this has also importance for the atrial lead permanent placement (especially the screw-in systems). See the Discussion paragraph and the following Fig. 10.

Fig 9: - The thin atrial wall, allowing trans-illumination (A) and microscopy section imaging of the same atrial wall portions, between the pectinate muscles (B)

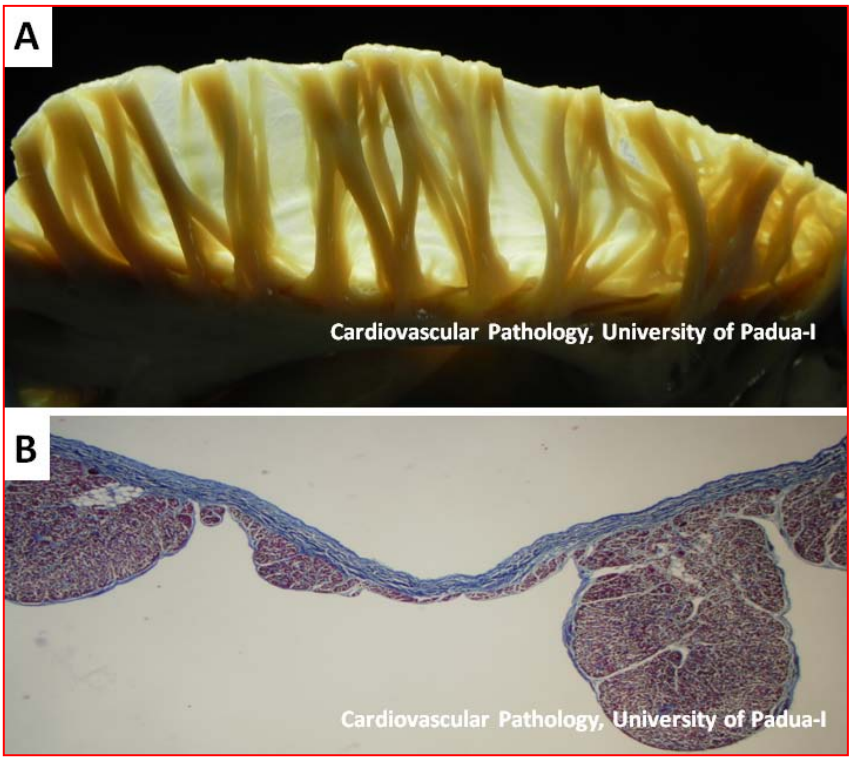
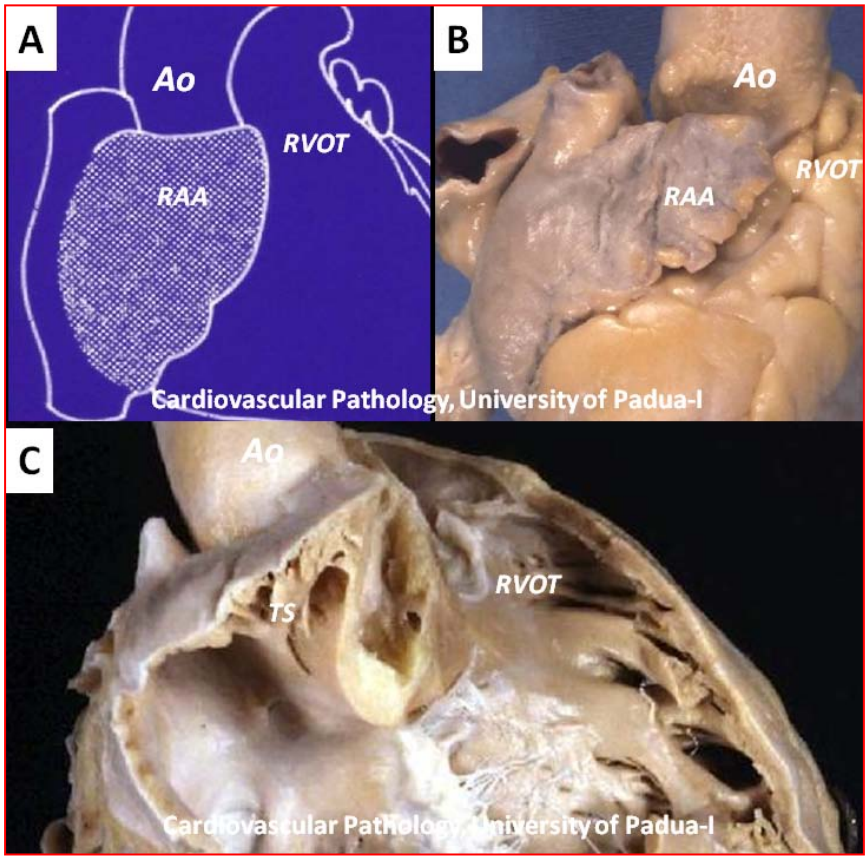


Fig 10: - The close relationships of RAA with the ascending aorta (see text)



In his recent paper, Loukas and co-workers have classified the TS in three main anatomic types (main trunk, double trunk or TS absence). (46)

Their anatomical distribution is shown in the following table.

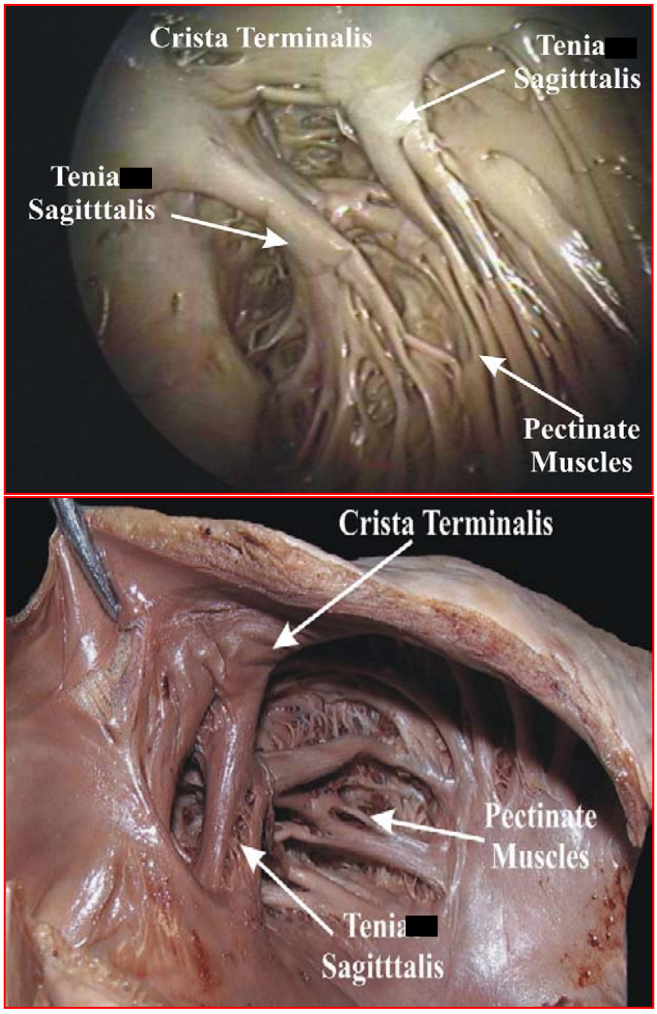
T***able 3: Main TS morphologies (from Loukas and co-workers)***

Type	Occurrence (%)	Morphology
Type A	15	Absent TS
Type B	65	Single TS
Type C	20	Double TS

The further Fig 11 the two figures display the TS when is clearly present in one or in double trunks.

Fig 11: - <u>upper panel</u>: TS double trunk (Type C of Loukas et al) (46)

- <u>lower panel</u>: TS main single trunk (Type B of Loukas at al) (46)



In the first section of the present part, the current literature and our original data, regarding the RAA anatomy (and the related atrial structures involved in the permanent atrial pacing) are reviewed and compared.

The second section is a retrospective analysis which has been performed by comparing three main atrial pacing lead technologies and the related procedural safety. In the present study a single center population of patients has been recruited, who underwent to a dual chamber pace-maker implantation.

1.2 - Atrial leads procedural safety: the study hypothesis

Atrial leads are used in over 60% of pacemaker implants in the USA. Complications have been reported in up to 9% of these lead placements. (54,55)

The problem of atrial lead stability, which was a matter of concern in the early days of dual-chamber pacing, has been partially solved in recent years by the use of the screw-in mechanism, both in J-shaped and straight leads. Encouraging data are available on the safety and performances of screw-in atrial systems, both with an exposed mannitol-coated helix and an extendable/retractable helix. (53,55,56) Pre-J-shaped leads have been seen to offer an advantage over straight leads in terms of their lower rate of acute dislocations. (58)

Recently, a randomized comparative study was carried out on J-shaped leads with and without active-fixation mechanisms. Both types showed similar performances, though more pericardial complications occurred in the active-fixation study group (up to 6% of cases). (48) Similar data and concerns regarding pericardial complications have emerged from other studies and case reports. (32-38,59-62).

It has also been reported that the pre-J-shaped, screw-in system can cause right-sided pneumothorax due to right atrial free wall perforation and pleural migration. (63)

We hypothesized that straight atrial leads, by reducing pressure on the tip, could lower the rate of atrial perforation associated with screw-in systems in comparison with pre-J-shaped leads. Moreover, when screw-in leads are positioned in the RAA, straight leads may be more prone to acute intra-procedural dislodgment than J-shaped leads. This may actually be advantageous, in that the lead can be promptly repositioned avoiding delayed repositioning (reintervention). In short, this feature of straight leads could enable a "primary stability" to be checked more effectively during the procedure.

We therefore conducted a retrospective study to analyze the peri-procedural performance and complication rate of active and passive-fixation pre-J-shaped leads, in comparison with straight active-fixation leads inserted into the RAA and “post-shaped” in a J-fashion.

2 - METHODS

2.1 - Anatomical RAA review

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, have been examined, to analyze the macroscopic anatomy of CT and TS. Attention was paid to the anatomic variability of TS in its "entrance" into the RAA.

All hearts were preserved in a formalin solution. For the aim of the present analysis, specimens with right atrial surgery were excluded. In order to correct inter-individual variability among examiners, each specimen was examined by three co-investigators, independently. After the right atrial wall dissection, starting at the entrance of the superior vena cava to the inferior vena cava, the RAA was opened obliquely to expose the TS. Observations of CT as well as gross structural characteristics (including orientation of pectinate muscles, variation in TS and relationship to CT) were also digitally analyzed and stored by means of pre-specified specimen related codes, never including the cadaver anagraphic data.

2.2 - Data collection and study groups definitions

2.2.1 - Study population and informatics systems

The present study was conducted as a retrospective analysis of data collected in a single, high-procedural volume, tertiary center. From January 2004 to January 2010, we analyzed data from 1464 consecutive patients who underwent new device implantation for brady-arrhythmia indications, CRT and primary or secondary sudden death ICD prevention. Among these patients, 915 received a passive J pre-shaped active or passive fixation lead or a straight screw-in atrial lead, and constituted the study population. The

remaining 549 patients received only a ventricular lead and were excluded from the present analysis.

All demographic data, clinical and ECG diagnoses, device and lead specifications (models, manufacturing codes and serial numbers), procedural biophysical data, surgical techniques adopted, patients' comorbidities and precise descriptions of any complications were recorded in a dedicated database (DIGISTAT® United Medical Softwares, Florence Italy; CE certification as Medical Device and quality management system, under ISO 9001:2000 and ISO 13485:2004) that was updated daily and had export data capabilities to Excel and SPSS formats for Windows. In order to precisely classify procedural complications, the specific nosologic codes for procedures and diseases regarding all hospital admissions and discharges for pacemaker and ICD lead malfunctions (Italian National Health System DRG procedure and disease codes, based on ICD9 Classification) were obtained by means of specific queries submitted to the Hospital Informatics Service database. These data were "cross-assessed" to overcome any possible inappropriate reporting and coding of adverse events during data compilation at the end of the procedures and on discharge.

Written informed consent for device implantation was obtained from all the study patients.

2.2.2 - Study groups and description of atrial leads

Patients were divided into 3 groups according to the type of atrial lead implanted:

1) Group S-FIX = straight screw-in lead (165 patients, 18%)

2) Group J-PASS = passively fixed J pre-shaped lead (690 patients, 75.4%)

3) Group J-FIX= actively screwed-in fixed J pre-shaped lead (60 patients, 6.6%)

All group S-FIX patients received a 52/53 cm length extendable/retractable non-pre-shaped actively-fixed lead (Medtronic 5076/4076 straight Capsure Fix models; Minneapolis MN, USA), which was screwed into the RAA and "post-shaped" in a J

fashion by means of a pre-shaped stylet. The 1.8 mm length helix was exposed and screwed in by applying a specified number (on average 15) of clockwise turns for the initial placement, as recommended by the user manual, followed by a higher number of rotations to extend or retract the helix, for new placement attempts, in case of prompt displacement. The ventricular lead was positioned before the atrial lead; this was done in order to avoid the risk of inadvertently displacing the atrial lead while positioning the ventricular lead. Attention was paid to avoid over-screwing and to check for the typical right appendage lead swinging (windscreen wiper). The measured sensing and pacing thresholds were recorded at the end of each procedure, at least 30 minutes after lead placement, when both parameters are often improved and the injury (and oedema) caused by the helix has presumably begun to heal.

The group J-PASS patients were implanted with the following J-shaped atrial lead models: Cristalline ICM08JB 53 cm model (Vitatron, Arnhem, The Netherlands) in 479 cases (69.4%); Fineline 4480 model (Boston Scientific, S. Paul, Minnesota, USA) in 22 cases (3.2%); Capsure 4574, 5554, 5594 models (Medtronic) in 174 cases (25.2%); Isoflex S 1944, or Optisense 1999 models (St Jude Medical, St Paul, Minnesota, USA) in 11 cases (1.6%); Stelid 2 BJF25D model (Sorin Group, Saluggia, VC, Italy) in 6 cases (0.9%). Cumulatively, 94.6 % of all the passive-fixation atrial leads implanted were Vitatron or Medtronic models.

Patients belonging to group J-FIX were implanted with the following extendable/rectractable screw-in J shaped lead models: a 52 cm length lead Medtronic 5568 Capsure Fix, in 58 cases (96%) and with a 52 cm length “MRI compatible” lead 5086 Medtronic Capsure Fix-MRI in 2 patients (4%) (Medtronic Minneapolis MN, USA). The same care described for the S-FIX group procedure, was taken for the placement and screwing of these last leads.

All the procedures were performed by 3 experienced operators with the same skill and learning curve. All the leads used were bipolar, silicone- or polyurethane-insulated, with steroid-eluting tips.

At the end of the procedure, the following measurements were obtained: P wave amplitude (mV); pacing impedance (ohm); pacing threshold (V, at 0.5 msec of stimulus duration), by means of the same pacing system analyzer for all cases (Medtronic PSA, Minnesota USA).

Lead-related complication rates were analyzed up to 3 months post-implantation and were defined as all adverse events related to lead implantation which prolonged hospital stay and/or required pharmacological or surgical intervention.

Dislodgments were defined as all lead movements which required repositioning because of loss of lead performance, occurred after the end of the procedure.

2.3 - Statistics

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 or χ^2 test for categorical variables, and unpaired Student's t-test for continuous variables. A p value < 0.05 was considered statistically significant. For continuous variables comparison among more groups, ANOVA was used, with Bonferroni testing adjustment. For the same comparison among discrete variables, χ^2 test (3 x 2 contingency tables) was used.

For all analyses, commercially available computer software (SPSS version 12.0) was used.

3 - RESULTS

3.1 - Anatomic RAA review

TS leaves orthogonally CT, along its routing to the inferior right atrium. In our cases series, TS showed 3 main types of anatomic variability with regard to the presence of a *main trunk* (type 1, found in 76 cases), a *double TS* (type 2, found in 13 cases) and a fine arborization without a clear-cut TS (type 3, found in 10 cases). Additionally, in one case we have found three clear TSs.

These data are displayed in the following Table 4 and are comparable with the available related literature data.

Table 4: distribution of the different TS morphologies classified in the present study

Type of TS and morphology	Occurrence N=% (100 specimens)
1- Main Trunk	**76**
2- Double	**13**
3- Absence	**10**
4- Triple	**1**

The RAA region proximally to TS ("**antral RAA region"**) is close to the supra-valvular and root of aorta, without a clear pericardial space in between, while the distal part of the RAA, behind the TS ("**saccular RAA region"**) is near but not in such a close relation with the pulmonary artery having in this part a better freedom of movement. This region could represent a safer region for leads placement, especially for screw-in technology (see discussion).

In the following Fig. 12 are shown the specimens, from our collection, representing RAA atrial lead placement proximally and distally with respect to TS.

The Fig. 13 shows an example of a single main TS (the most frequent type in our observations).

Fig 12: ***- <u>A panel</u>: atrial lead placed in the RAA " proximally" to TS***

- <u>B panel</u>: another atrial lead placed in the RAA "behind" TS

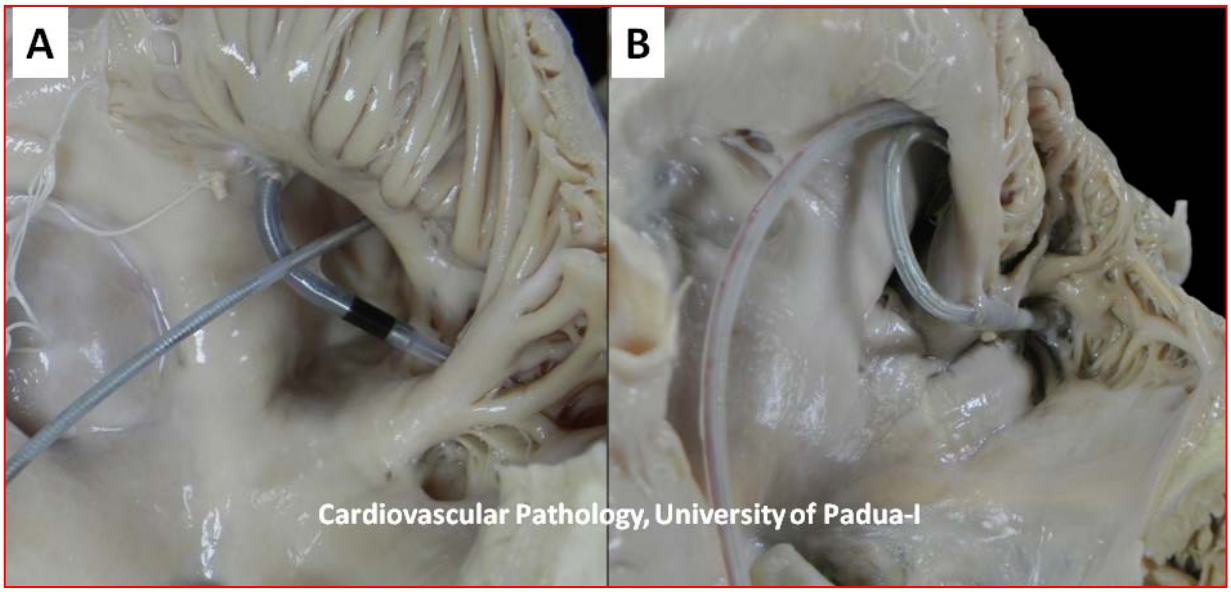
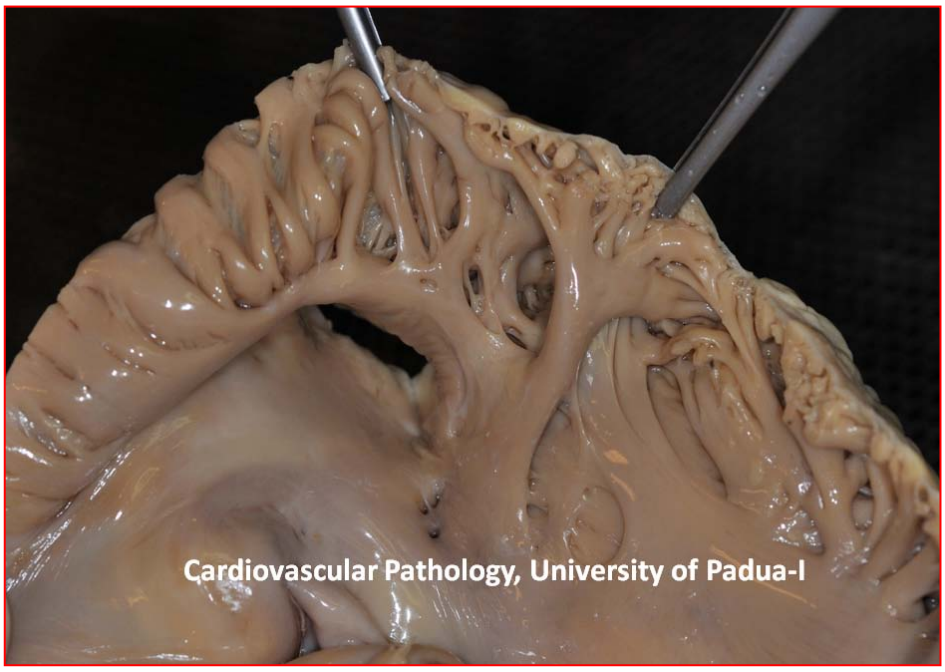


Fig 13: ***An example of a single main TS (the most frequent in our study)***



3.2 - Atrial leads placement procedural data

The mean age of the 915 study patients was 76.7 +/- 10 years and 573 (62.6%) were male. The patients received either a pacemaker (784 patients, 86%) or an ICD (131 patients, 14%). Pacing modes were: AAI pacemakers in 7 cases (0.8%); dual-chamber systems in 785 cases (85.8%); CRT systems in 123 cases (13.4%).

Group S-FIX patients were slightly but significantly younger, compared with J-PASS but not with J-FIX patients (74.8+/-10.8 versus 77.3 +/-9.8 years and vs 74.9+-9.5, p=0.000 and 0.5 respectively).

RAA active fixation was successfully performed in all S-FIX group patients during the index procedure; in 2 patients a new screw attempt was necessary because of immediate displacement. In no patients was necessary an alternative positioning, outside the RAA. In 4 patients of J-PASS group, an alternative lead system was used after unsuccessful lead placement due to immediate dislodgement (J-shaped screw-in atrial leads were chosen in all these cases). In S-FIX group, the pacing threshold was slightly but significantly higher compared with the J-shaped systems.

All the procedural data are shown in the following Table 5.

Table 5: Clinical and procedural data and complication rate assessed up to the third post-implantation month.

Variables	Group S-FIX N=165	Group J-PASS N=690	Group J-FIX N=60	P value S-FIX vs J PASS	P value J-PASS vs JFIX	P value S-FIX vs J- FIX
Sex, male (n/%)	112/67.9 %	416/60.3 %	45/75 %	0.07	0.02	0.02
Age (years)	74.8 +-10.8	77.3+-9.8	74.9+-9.5	0.000	0.9	0.5
AAI mode (n/%)	1/0.6 %	6/0.9%	0	0.7*	0.4	0.4*
DDD mode (n/%)	138/83.6 %	591/85.7 %	56/93.3 %	0.7	0.4	0.4
CRT system (n/%)	26/15.8 %	93/13.5 %	4/6.7 %	0.7	0.4	0.4
AtrialPacing Threshold (V)#	1.2 +-0.7	0.6+-0.5	1.0+-0.4	0.000	0.4	0.000
Atrial Sensing (mV)#	3.1+-1.6	4.2+-1.9	2.7+-1.3	0.000	0.000	0.1
AtrialImpedance (Ohm)#	628.4+-176.4	564.2+-128.2	593.7+-172.5	0.004	0.1	0.09
Complications(n/%)	1/0.6 %	1/0.1 %	1/1.7 %	0.3*	0.1*	0.4*
AtrialLead Dislodgment (n/%)	0	16/2.3 %	1/1.7%	0.04	0.7	0.2*

***** = Fisher exact test ; # = data presented as mean +-standard deviation

3.3 - Procedural complications

The rates of cumulative complications were similar in the 3 groups: 1 complication (0.6%) was observed in S-FIX group patients, 1 complication (0.1%) in the J-PASS group and 1 complication (1.7%) in J-FIX group (p=ns for all). In the S-FIX group, we observed 1 case of pericarditis (considered as pericardial irritation, without effusion and resolved with anti-inflammatory therapy). In the J-PASS group, 2 cases of sustained atrial fibrillation (following lead placement and requiring pharmacological cardioversion) were documented; in one of these cases the patient was affected by a paroxysmal atrial fibrillation, and though mechanically induced, it was not considered a lead related complication. In the J-FIX group patients 1 case of right pneumothorax was recorded, due to right pleural migration of the atrial lead, without pericardial effusion, which was diagnosed promptly the day after the procedure and resolved by means of vacuum thoracic drainage.

The rate of dislodgements was significantly higher in J-PASS group patients compared with S-FIX group patients but not with J-FIX patients (16 cases, 2.3% in J-PASS patients *vs* 0 cases in S-FIX patients, p=0.04 and *vs* 1 case, 1.7%, in J FIX group patients, p=0.7).

Lead dislodgement in the J-PASS group patients was documented in 7 (1%) patients by means of routine chest X ray on the second post-procedural day and, in the remaining 9 (1.3%) cases, by ECG evidence of lead malfunction (loss of pacing and/or sensing dysfunction) over the first 15 post-procedural days. In 13 (1.9%) cases, the leads were repositioned by a surgical re-intervention, while in the remaining 3 (0.4%) cases they were repositioned by using a steerable diagnostic EP catheter via a right femoral access. In these 3 cases, the leads had detached from the atrial appendage and had spontaneously retracted, with the J shape “closed”, into the distal superior vena cava; anchorage was restored by means of a “hooked-down” maneuver. In one case a new dislodgement occurred after repositioning; the lead was then removed in a third procedure and a VVI

40/min pacing mode was adopted. In the J-FIX group the single case of the cited pleuro-pericardial complication due to the lead migration was even considered as dislodgement, according with the study definition of this latter complication.

In the present series an atrial lead extraction was necessary in one of the J-PASS study patients, 5 months after the implant, which was removed just by pulling back the lead, without the use of leads extracting tools; we therefore have no strong data regarding this issue in the present comparison.

In the above table 5 all the procedural and clinical data as well as complications rate are displayed.

4 - DISCUSSION

4.1 - Main findings

In our anatomical cases series, three main types of TS were classified. These data are similar to the current literature. In at least 10 % of cases TS was absent, but when it is present it can virtually separate the RAA into 2 different regions: the proximal (*antral*) or the distal (*saccular*) RAA. The former is in close relationship to the aortic root. For the second section of the present study, in our large cohort of pacemaker patients, the straight screw-in atrial leads implanted in the RAA displayed an excellent stability and an acceptable safety profile and performance in comparison with J-shaped systems.

4.2 - Anatomical considerations

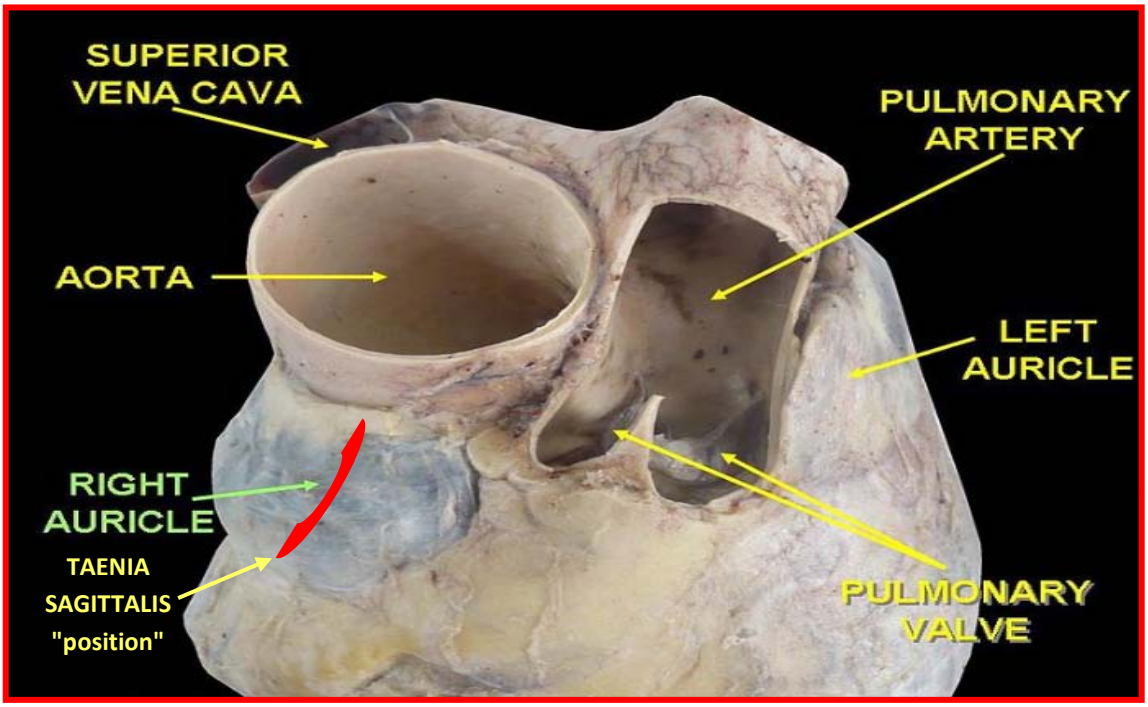
The RAA region proximally to TS ("antral"), is in close relationship with the aortic root, without a clear pericardial space in between, while the distal part of the RAA, behind TS ("saccular"), is near but not in a "so close" relationship with the pulmonary artery, due to its "less linked" nature to the contiguous cardiac vessels or structures, and has consequently a better freedom of movement. This could have critical importance especially during RAA instrumentation by means of electrophysiology temporary catheters for mapping and ablation procedures, which should be moved with much caution in this area, because they could look as "wandering" into the right atrium while they are not. This is also important for permanent pacing leads, which require a stable anchorage in this area. During the atrial lead placement in RAA, the typical lead swinging (windscreen wiper) is the best radiologic marker of distal RAA lead anchorage, thus displaying the relatively freedom of RAA systolic-diastolic movements. The "antral RAA" may represent a dangerous region for atrial leads anchorage, primarily because of the thin cardiac atrial wall between the pectinate muscles and also in patients with aortic root enlargement or aneurysmatic dilatations. In this case, the absence of a clear

pericardial space (due to the down-wrapping of the parietal pericardium, descending from the aortic root and then up-covering the right atrium), may have a role in the clinical presentation of an accidental RAA perforation, which could be not "announced" by cardiac tamponade but abruptly involving the aorta.

Conversely, the distal "saccular region" could represent a safer region for leads placement, especially for screw-in technology, due to its relative freedom from the surrounding structures. These considerations may have a great speculative but a smaller clinical value because of the very low complication rates of RAA atrial leads placement found in our cases and in the current literature. In particular, in our cohort of patients, no aortic perforation occurred.

In the Fig. 10 (page 41) and in the following Fig. 14, is shown the anatomy of RAA and its relationships with aortic root and pulmonary artery.

Fig 14: Relationships between the RAA and the ascending aorta and the pulmonary artery root. As discussed above, the proximal portion of the RAA in its routing "embraces" the aorta root and finally it reaches the pulmonary artery.



4.3 - The atrial lead shape

Recent data have shown that the shape of atrial leads might have a greater impact on their short- and long-term performance than the mechanism of fixation (53,57,63). Three major studies have been conducted by the same group to compare the influence of the mechanism of fixation and the shape of the atrial lead; two studies analyzed the influence of the shape in two screw-in atrial lead systems, and one compared the effect of active versus passive fixation of J-shaped leads. (54,58,63) In these case series, a 5.9% rate of early and late lead dislodgement was recorded (up to 7.8% over a long-term follow-up) for the straight screw-in leads, whereas no dislodgement of J-shaped leads was reported (both actively fixed). The rates of subacute pericardial complications were similar in both groups. (58,63) When the same authors compared the role of the mechanism of fixation of J-shaped leads (passive versus active fixation) in a third study, they found out that both mechanisms performed well; however, in the active-fixation group, a higher (cumulatively 6%) rate of pericardial irritation or effusion was observed. They specified that, in all cases, an attempt was first made to position the lead in the RAA, and that an alternative placement onto the atrial free wall was necessary in 31% of patients in the active-fixation group. (54) In conclusion, they hypothesized that the shape of the lead may influence lead stability more than the mechanism of placement does. (54)

In our study no lead dislodgment was reported in the active-fixation S-FIX study group. Our hypothesis is that, when screw-in leads are positioned in the RAA, straight leads may be more prone to acute intra-procedural dislodgment than J-shaped leads. This may actually be advantageous, in that the lead can be promptly repositioned; by contrast, dislodgment of a J pre-shaped lead, which might keep the position longer, tends to occur later, therefore necessitating a "re-do" procedure. In short, this feature of straight leads enables *primary stability* to be checked more effectively during the procedure. Another advantage of straight leads may be that they can be easily used in alternative positions

after a failed attempt at RAA positioning. In our series, however, this necessity never arose. Our results are in light disagreement with those of Luria and colleagues. (54) The latter, analyzed data between selected groups of patients in a prospective, randomized controlled fashion, comparing two different leads models, which leads to more clear conclusions about each specific features tested in the study, but are applicable to the specific leads models used.

The pericardial complication rates reported in the present study are slightly lower than those reported more recently by the Israeli group, (54) where patients were prospectively assessed for any sign of pericardial complication, including the use of echo imaging in all the patients on the second post-procedural day; the same group reported a lower pericardial complication rate with screw-in leads in a previous study, that did not involve such a meticulous methodology. (54,58)

We observed only 1 pericardial complication in a patient with a screw-in lead; this was promptly resolved with NSAID therapy.

Regarding the single case of lead perforation and migration into the pleuro-pericardial space, occurred in the J-FIX groups patients, fluoroscopy imaging (during re-intervention for lead removal) revealed that the lead was not typically swinging in the RAA, even though the position in the appendage appeared to be correct in all the fluoroscopy projections. It had probably been screwed into the anterior aspect of the right atrial wall, which is contiguous with the pleuro-pulmonary structures. When checking the lead position, looking for the typical swing (windscreen wiper) of the lead in the RAA may help to avoid this rare complication. (32-38)

In a recent case report, 3 cases of active lead perforation causing cardiac tamponade were analyzed; in all 3 cases, the lead had been placed outside the RAA, in the right atrial free wall. (62)

The RAA may probably comply with the cardiac cycle-related movements of a screwed-in lead better than the right atrial free wall does.

The recent literature suggests that lead shape may play a greater role than the fixation mode in the reliability and performance of atrial leads, and that the RAA seems to be a safe placement site for atrial pacing leads. When active-fixation pre-J-shaped leads are used, the rate of pericardial complications seems to be higher. (62, 63) In our case series, “post-shaped” active-fixation leads displayed a better stability in comparison with J pre-shaped passive-fixation leads and acceptable safety performances when compared to both J-shaped systems.

4.4 - Study limitations

The first part of the study has also involved specimen with previous right atrial minor surgery; even though the targeted structures (TS course and presence) were not modified by such surgery, the routing of TS could have been modified, into its RAA "entrance".

Another limitation is related to the second part of the present study which was conducted as a retrospective analysis. The lack of randomized study group assignment was the primary limitation, though the large number of these unselected consecutive patients may offer an adequate snapshot of the safety profile of this technique. Moreover, in all (but one) patients who had previously undergone cardiac surgery, active fixation was the first choice; in all the other cases, the atrial leads were randomly chosen.

Atrial fibrillation has never been demonstrated to be related to the lead shape or fixation system; on the contrary the relation of lead perforation with screw-in systems is well established. Although the present comparison of complications seems to offer an equivalent safety profile, these adverse events should be considered separately.

No reliable data on the procedure time and fluoroscopy time were available; these parameters were therefore omitted from the present comparison. Also, the follow up

observation period and data recruitment (pacing and sensing thresholds and leads impendence) is limited up to the third month post implantation; in our clinical habits, out of this time window the devices follow up is scheduled each 6 (ICD CRT devices) or 12 (pacemakers) months and not always completed by leads thresolds measures. The same observation period was considered critical for leads and device implantation related adverse events, aiming the safety comparison.

In the study group J-PASS, different models of passive leads were considered, though almost 95% of the models were Vitatron or Medtronic lead systems.

Over the study period, the atrial leads were randomly selected by the operators, in order to increase their experience in the use of different systems. Nevertheless, passive-fixation leads were used four times more often than active-fixation ones; this suggests a possible selection bias.

The lack of a routine echo imaging after the procedure, as used in another prospective randomized study above discussed, could explain the lower pericardial complication rate here reported.

5 - CONCLUSIONS

The distal "saccular" RAA could represent a safer region for atrial leads placement, compared with the proximal "antral" RAA, which is close to the ascending aorta. The two RAA regions are separated by the TS, which is absent in at least 10% of cases.

However, in our case series, the procedural complications of all the 3 available leads technologies were very low. In particular, no aortic perforations occurred.

Straight screw-in atrial leads, “J post-shaped” in the RAA, offer a better stability compared with the passive J pre-shaped fixation and displayed a similar acceptable safety profile compared with both the J-shaped systems.

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