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Università degli Studi di Padova

Department of Cardiac, Thoracic and Vascular Sciences

THE ANATOMICAL FEATURES OF RIGHT ATRIAL CAVO-TRICUSPID ISTHMUS CAN IMPACT RADIOFREQUENCY CATHETER ABLATION IN TERM OF SUCCESS RATE AND COMPLICATIONS

Coordinatore: Ch.mo Prof. Annalisa Angelini
Supervisore: Ch.mo Prof. Cristina Basso

Dottorando: Dott.ssa Maria Stella Baccillieri

ANNO ACCADEMICO: 2016-2017

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SCUOLA DI DOTTORATO DI RICERCA IN: Scienze Mediche, Cliniche e Sperimentali

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CICLO XXIX

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A Vincenzo e

Antonina

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RIASSUNTO

Introduzione: Il trattamento ottimale del flutter atriale (AFL) che si propaga lungo un circuito che comprende anche l'istmo cavo-tricuspidale (CTI) è l'ablazione transcatetere con radiofrequenza (RF) che si è dimostrata essere altamente efficace. Nonostante questa alta percentuale di successo l'ablazione può essere estremamente difficoltosa, a causa dell'anatomia altamente variabile del CTI. Abbiamo condotto uno studio per valutare come questa grande variabilità inter-individuale possa impattare sulla RF. L'obiettivo primario di questo studio era il successo della RF, definito come l'ottenimento del blocco bidirezionale del CTI in acuto. L'obiettivo secondario erano qualsiasi complicanza correlabile alla procedura e il tempo di procedura.

Metodi: Sono stati arruolati 337 pazienti consecutivi in un periodo di 54 mesi. Un catetere decapolare 5F era utilizzato per incannulare il seno coronarico (CS) e un secondo catetere multipolare 7F era posizionato anteriormente alla cresta terminale, nella parete libera dell'atrio destro, vicino all'anulus tricuspidale. L'anatomia del CTI era classificata in: CTI (A) semplice (superficie piatta), CTI (B) complessa (recesso tipo borsa di tabacco o superficie concava). Parametri vitali, come la misurazione della pressione arteriosa e della saturazione di ossigeno, venivano monitorizzati per tutta la procedura. I pazienti venivano sedati usando boli di midazolam e fentanyl. L'ablazione veniva terminata quando era evidente il blocco bidirezionale, usando un catetere 8 mm-tip con il limite di potenza di 70 W e un target di temperatura di 60°C. La lunghezza del CTI era misurata come la distanza lineare più corta tra il punto più basso dell'anulus tricuspidale e la vena cava inferiore, nella proiezione fluoroscopica antero-posteriore. Le visite ambulatoriali durante il follow-up erano programmate a 3, 6 e 12 mesi ed includevano un elettrocardiogramma 12- derivazioni ed un ECG di Holter.

Contemporaneamente abbiamo studiato presso l'Unità di Patologia Cardiovascolare dell'Università di Padova, 104 cuori fissati in formalina di pazienti sottoposti ad autopsia di routine. Ogni cuore è stato esaminato da due esperti patologi cardiovascolari. Sono stati valutati: 1. la lunghezza

dell'istmo; 2. la presenza di recessi; 3. il numero di recessi; 4. la posizione dei recessi. E' stata

quindi eseguita l'analisi istologica.

Risultati:

Ablazione: L'età media della nostra popolazione era 62.8 ± 10.6 years (max 84; min 28), i maschi

erano 236 (70%). Recessi sono stati trovati in 37 pazienti (10.9%) e il dato non era correlabile all'età,

al sesso, alle dimensioni dell'atrio sx, alla frazione di eiezione *(p = NS)*. La lunghezza media totale

del CTI era 23.3 ± 3.9 mm (max 35; min 10). Il CTI era più corto nei soggetti con anatomia tipo A

quando paragonati a quelli con anatomia tipo B *(22.9 ± 3.2 vs 25.6±6; p = 0.01)*. L'end-point primario

di efficacia, dimostrato dal blocco bidirezionale, è stato raggiunto nel 99.4% (335/337). L'insuccesso

in acuto dell'ablazione (n = 2 pazienti) era associato ad una anatomia CTI di tipo B.

Riguardo gli obiettivi secondari, è avvenuta una complicanza in 1 paziente (0.29%) con un'anatomia

del CTI di tipo B: un "pop" immediatamente seguito da tamponamento cardiaco ha richiesto una

pericardiocentesi urgente. Il tempo medio totale della procedura di RF è stato 51.6 ± 14.4 minuti,

nessuna differenza trovata tra i 2 gruppi *(p= NS),* ma il blocco bidirezionale del CTI ha richiesto un

tempo di applicazione di RF significativamente più lungo nell'anatomia del CTI di tipo B quando

paragonata al tipo A (8.3 min vs 10.7 min, *p = 0.025*), a dimostrazione che in caso di anatomia

complessa, l'ablazione risulta essere più difficoltosa. Durante il periodo di follow-up medio di 36.7

± 17.2 mesi, il 99.7% (334/335) dei pazienti era libero da recidive di AFL. Nel paziente sintomatico

con recidiva di AFL documentata all'ECG di Holter 24 ore e all'ECG 12- derivazioni, è stata

dimostrata una ripresa di conduzione lungo la linea di ablazione. E' stata ripetuta l'ablazione e il

paziente non ha più avuto altre recidive.

Anatomia: L'età media degli individui era 67 ± 17 anni, con una prevalenza maschile (65%). Il peso

medio del cuore era 457 ± 102 g. La lunghezza dell'istmo centrale era di 24 ± 4.1 mm (range 15 - 38

mm) senza differenze tra i gruppi (24.1 vs 23.6, *p = NS*), rispettivamente. L'istmo centrale nei

pazienti affetti da flutter atriale era significativamente più lungo rispetto agli altri campioni (*p*

<0.01). In 10 dei nostri casi (9.6%), era presente un recesso. Come nella serie clinica di pazienti sottoposti ad ablazione, la presenza di recessi non era correlata all'invecchiamento e al sesso. Il recesso era singolo nella maggior parte dei casi (60%) e la sede più frequente era l'istmo centrale (60%). Nei 4 cuori con diagnosi pregressa di flutter atriale, nessun recesso è stato trovato. Il numero più alto di recessi trovati in un campione era 3. Le regioni con la parete muscolare più sottile sono risultati essere l'anteriore, la parasettale mediale e la medio-centrale.

Conclusioni: La nostra ricerca con studio elettrofisiologico ed anatomico ha fornito informazioni rilevanti per la pratica clinica. L'ablazione transcatetere dell'AFL tipico che coinvolge il CTI è stata confermata essere una procedura di ablazione sicura, efficace e consolidata. L'anatomia del CTI impatta sui parametri di ablazione, come l'applicazione di energia di RF. Inoltre, la procedura difficile è stata associata anche alla lunghezza maggiore dell'istmo. I recessi possono complicare l'ablazione, e sapere dove potrebbero essere presenti è utile per evitarle. Pertanto, nella nostra opinione, il tasso di successo e le complicazioni di ablazione possono essere ottimizzate da una profonda conoscenza dell'anatomia e dell'esperienza del centro.

SUMMARY

Background: Radiofrequency (RF) catheter ablation targeting the isthmus between the tricuspid annulus and the inferior vena cava (IVC) is the established treatment for typical atrial flutter (AFL) due to its high efficacy. Despite this high success rate, ablation of the cavo-tricuspid isthmus (CTI) can be extremely difficult, due to its highly variable anatomy. The aim of this study is to analyze how and why the great inter-individual variability can influence ablation procedure. Primary endpoint was to evaluate the impact of the underlying CTI anatomy on acute and long-term success rate. Secondary endpoint was to determine any ablation related complication and procedure time.

Methods: Over a period of 54 months, 337 consecutive patients underwent CTI ablation. One 5F decapolar catheter was placed within the coronary sinus (CS) and another 7F multipolar catheter was placed anterior to the crista terminalis at the right free wall close to the tricuspid annulus. CTI anatomy was classified into: (A) simple (flat) CTI, (B) complex (pouch-like recess or concave shape) CTI. Vital parameters, such as arterial blood pressure and oxygen saturation were monitored throughout the entire procedure. All procedures were performed under conscious sedation using boluses of midazolam and fentanyl. Termination ablation was decided when bidirectional block was demonstrated. Ablation was performed using 8 mm-tip catheter with a power limit of 70 W and a target temperature of 60°C. The CTI length was measured as the shortest linear distance between the lower hinge point of the tricuspid annulus and the IVC in the frontal fluoroscopic projection. Outpatient follow-up included 12-lead ECG, and Holter ECG monitoring, scheduled at months 3, 6, and 12.

We also examined 104 formalin-fixed hearts from patients who underwent routine clinical autopsy performed at the Cardiovascular Pathology Unit, University of Padua. Every heart was examined by two independent expert cardiovascular pathologists. The following features were assessed: 1. the length of the central isthmus; 2. the presence of pouch-like recesses; 3. the number of the recesses; 4. the position of the recesses. The histological analysis was performed.

Results:

Ablation: Mean age of all patients was 62.8 ± 10.6 years (range $28 - 84$), male was 236 (70%). Deep recesses were found in 37 patients (10.9%) and were not related to aging, gender, left atrial size, and left ventricle ejection fraction ($p = NS$). Total mean CTI length was 23.3 ± 3.9 mm (range $10 - 35$ mm). CTI length was shorter in type A anatomy as compared to type B $(22.9 \pm 3.2$ vs $25.6 \pm 6; p = 0.01)$. The primary endpoint of efficacy, proved by the bidirectional block, was achieved in 99.4% (335/337). Acute ablation failure (n = 2 patients) was associated with a CTI type B anatomy.

Regard to the secondary endpoints, complication occurred in 1 patient (0.29%) with the CTI type B anatomy: a "pop" immediately followed by cardiac tamponade required urgent pericardiocentesis. Total mean procedure time of was 51.6 ± 14.4 minutes, no difference between two groups ($p= NS$), but CTI bidirectional block was obtained with a significantly longer RF application time in CTI type B anatomy as compared to the type A (8.3 min vs 10.7 min, $p = 0.025$); that demonstrates ablation is more difficult in case of complex anatomy. During a mean follow-up period of 36.7 ± 17.2 months, 99.7% (334/335) of the patients were free of AFL recurrences. AFL recurred in 1 symptomatic patient with CTI type B anatomy. The patient underwent second ablation procedure. Conduction across the ablation line was demonstrated. Successful ablation was performed. No new recurrences have occurred until this time.

Anatomy: The mean age of the individuals was 67 ± 17 years, with a male prevalence (65%). The mean heart weight was 457 ± 102 g. The length of the central isthmus was 24 ± 4.1 mm (range 15 - 38 mm) without differences between groups (24.1 vs 23.6, $p = NS$), respectively. The central isthmus in the patients affected by atrial flutter was significantly longer compared to the other cardiac specimens ($p < 0.01$). In 10 of our cases (9.6%), a sub-Eustachian recess was present. As in the clinical series of patients undergoing ablation, the presence of recesses was not related to aging and gender. The recess was single in the majority of cases (60%) and the most frequent location was the central isthmus (60%). In the 4 cases diagnoses with atrial flutter, no recess was found in the CTI.

The highest number of recesses found in one specimen was 3. The regions with the thinnest muscular wall resulted to be the anterior and middle paraseptal and middle central.

Conclusions: Our investigation with both electrophysiological and anatomical study provides relevant information to clinical practice. Catheter ablation of typical AFL involving the CTI has been confirmed to be a safe, effective, and well-established ablation procedure. Nevertheless, the CTI anatomy impacts ablation parameters, such as RF energy application. Moreover, difficult procedure is also associated with longer length of isthmus. Recesses can complicate ablation, and knowing where they might be present is useful to avoid them. Therefore, success rate and ablation complications can be optimized by a deep knowledge of anatomy and centre experience.

ABBREVIATIONS

AFL, atrial flutter

AF, atrial fibrillation

CTI, cavo-tricuspid isthmus

ICV, inferior vena cava

TV, tricuspid valve

RF, radiofrequency ablation

CS, coronary sinus

AV, atrioventricular

AADs, antiarrhythmic drugs

RAO, right anterior oblique

LAO, left anterior oblique

NAO, new oral anticoagulant

PPI, post pacing interval

Part I.

<p style="text-align: center;">**INTRODUCTION**</p>

ATRIAL FLUTTER

Definition and History.

Atrial flutter (AFL) is a frequent arrhythmia second only to atrial fibrillation (AF) in clinical practice. AFL has many clinical aspects that are similar AF but they are different in terms of mechanism and management. Some patients have both AFL and AF and both arrhythmias are associated with a risk of thrombus formation and thromboembolism.

In 1906, Einthoven made an electrocardiographic recording of AFL [1]. Since 1913, Sir Thomas Lewis called attention to the typical saw-tooth pattern and the negative deflections of the atrial waves in leads II and III [2]. In 1921, Sir Lewis and his colleagues have also demonstrated that AFL was due to an intra-atrial circus movement around the vena cava [3]. During the next 50 years, there was much discussion about whether AFL was caused by a rapidly firing atrial focus or is the result of a large circus movement involving the atria. After mapping atrial activation with endocardial and esophageal recordings in 1970, Puech et al. identified two types of AFL, i.e. common and rare AFL. They concluded that the flutter cycle in the human heart involved activation of the whole right atrium and considered that the common type of AFL proceeded cranially along the inter-atrial septum and then caudally on the free wall of the right atrium [4]. Stimulation studies revealed that in postoperative AFL the arrhythmia was based on a reentry mechanism involving a large atrial area. They demonstrated the presence of an excitable gap that allowed the speeding up of the flutter rate during atrial pacing and termination of the arrhythmia by pacing [5-9]. In 1990, Olshansky et al., using a mapping and entrainment pacing technique, demonstrated that a critical area of slow conduction was present inferiorly and posteriorly in the right atrium [10]. Nowadays, it is so-called cavo-tricuspid isthmus (CTI).

Pathologic Studies.

The CTI is a part of the right atrium located between the inferior vena cava (ICV) ostium and the hinge of the leaflets of the tricuspid valve (TV). The CTI reentrant circuit is a relatively new concept that was first introduced by Cosio et al. (1993) [11]. CTI is considered crucial in producing a conduction delay and, hence, favoring the perpetuation of a stable macro-reentrant circuit that has its basis in the anatomical structure of the right atrium. Therefore, the ideal target for radiofrequency ablation (RF) ablation is the critical zone of slowed conduction at the level of the isthmus of right atrium wall between the IVC and the TV [11- 14]. In particular, the route of the re- entrant circuit is bordered anteriorly by the tricuspid annulus and posteriorly by the IVC ostium, the crista terminalis and the Eustachian ridge [13].

Actually, a non uniform terminology exists between electrophysiologists and pathologists. The area between the Eustachian valve or ridge posteriorly, and the hinge of TV anteriorly, is described by an electrophysiologist as the *posterior isthmus*. According to the pathologists, with heart in the anatomic position, this component is *inferior*, and forms the base of a quadrilateral area [15]. The quadrilateral area is formed by Eustachian valve, Thebesian valve, TV, and a line connecting the IVC and TV [16] (Fig. 1A and 1B). Frequently, the area immediately anterior to the IVC ostium is composed mainly of fibrous and fatty tissue, with minimal muscular fibers coursing through it. The clinical implication is that this part of the isthmus needs the least RF energy. The middle part of the quadrilateral is made up of muscular trabeculations separated by delicate membranes. The trabeculations originates either from the wall of the coronary sinus (CS) or else are the continuations of the muscular bundles of the crista terminalis (pectinate muscles). The third anterior sector of the quadrilateral, adjacent to the hinge of the TV, is smooth, showing no evidence of trabeculations. Histological sections have confirmed that in this region the myocardium formes the full thickness of the atrial wall. The muscular trabeculae radiate from the terminal crest in almost parallel fashion without an appreciable cross-over or show abundant cross-over and interlacing trabeculae, particularly in the zone immediately inferior

to the CS ostium [17]. In this area, trabeculae to the right- and left-hand sides of the ostium are interconnected along the inferior rim. On this basis, one can easily speculate that non uniform anisotropic conduction occurs, and thus, a critical area of slow conduction has been identified in this region of the heart and plays an essential role in the AFL circuit [18,19].

Imaging Studies.

By using 64-section multi-detector row computed tomography (Fig. 1C), Saremi et al. showed that the paraseptal isthmus was significantly shorter than the central isthmus and the central isthmus was shorter than the inferolateral isthmus ([20]. At mid-diastole, the central isthmus was straight in a small percentage of patients, concave and pouch like (>5mm) in an almost equal percentage. A sub-thebesian recess greater than 5-mm deep was identified in 45% of patients. A thick Eustachian ridge greater than 4 mm was seen as well. A pre-ablation magnetic resonance imaging study showed that the mean CTI length was 38.6 ± 7.8 mm. Lim et al. found recesses in 41% of patients. They also noted that CTI demonstrating an eccentric, septal recess required more RF energy to achieve isthmus block. The majority of patients (76%) had a concave CTI [21]. By using intracardiac three-dimensional echocardiography, Scaglione et al. demonstrated two different groups of CTI anatomy [22]. Group A patients showed a smooth isthmus with slight irregularities parallel to the tricuspid annulus, probably due to the pectinate muscles coming from the end of the crista terminalis in the low lateral right atrium. In this type of the isthmus, the Eustachian ridge was small. Group B patients presented a different isthmus anatomy due to a prominent Eustachian. The isthmus in these patients was a peak and valleys-shaped structure. A prominent Eustachian ridge correlated with cases of resistant AFL ablation. A conduction gap crossing the isthmus was always present in that site. Chang et al., performed contact NavX mapping of the CTI, and found that the pouch-type CTI had a longer length than the flat-type CTI and a deeper depth than the concave type CTI. The pouch type CTI needed a longer ablation time and more RF pulses for ablation of the CTI [23].

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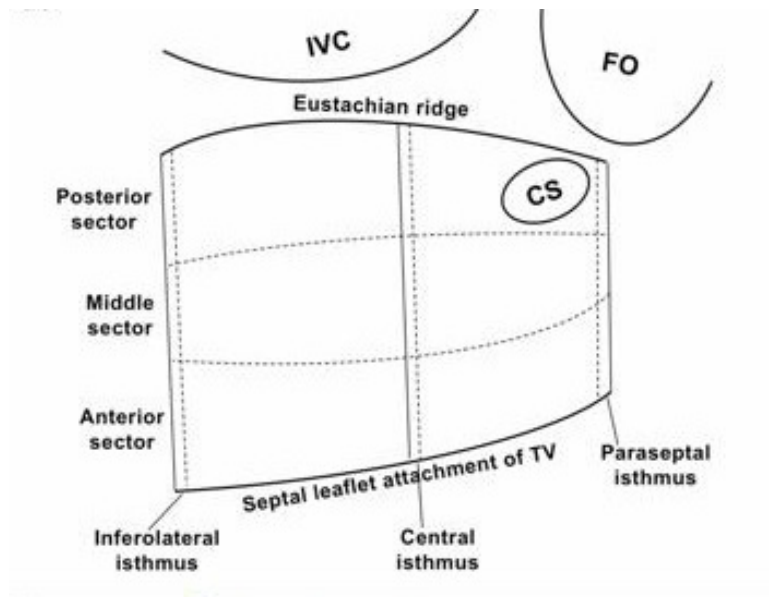
Figure 1A. Schematic view of the CTI regions.
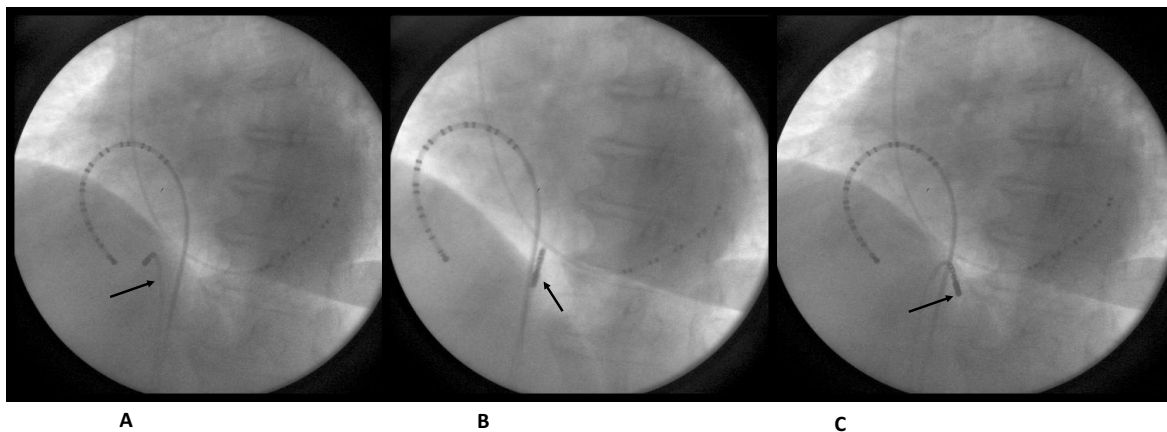
Figure 1B. Position of catheters during ablation procedure. In the left anterior oblique projection (LAO), a multipolar mapping catheter (20 electrodes) is recognizable on the tricuspid ring, to record the electrical activity of the right atrium and the interatrial septal side wall, and a decapolar catheter in the coronary sinus. The other one is the ablation catheter (arrow) showing the three cavo-tricuspid isthmus regions: A: inferolateral isthmus. B: central isthmus. C: paraseptal isthmus.
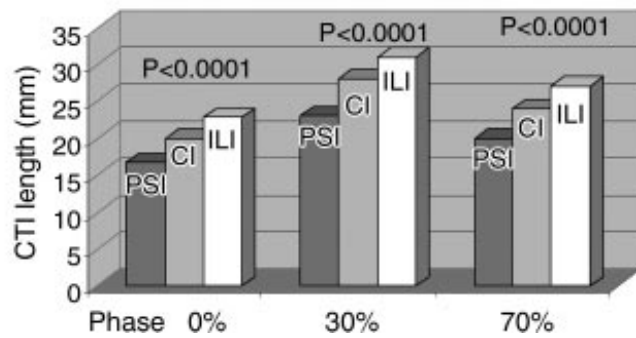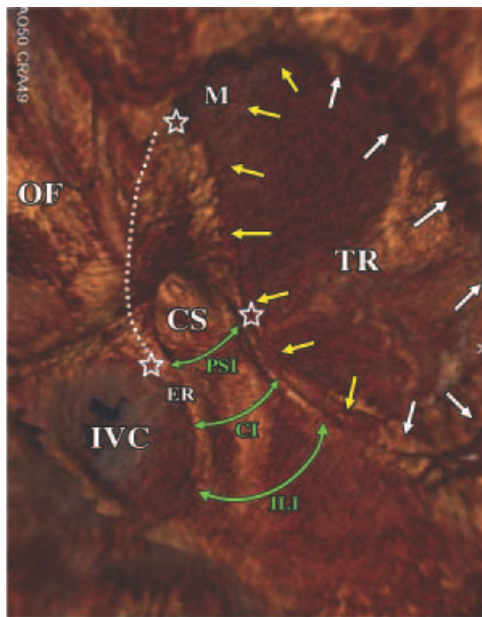
Figure 1C. Left panel: Three levels (green arrows) of the CTI are shown: the inferolateral isthmus (ILI), the central isthmus (CI), and the paraseptal isthmus (PSI). The CI and the PSI are common targets for ablation of atrial flutter. **Right panel:** Graph shows results of comparison of length of three levels of the CTI at three cardiac phases (atrial contraction [0%], mid-ventricular systole [30%], and midiastole [70%]. The paraseptal isthmus was significantly shorter than the central isthmus and the central isthmus was significantly shorter than the inferolateral isthmus at all three cardiac phases.

From: Saremi F, Pourzand L, Krishnan S, et al. Right atrial cavotricuspid isthmus: Anatomic characterization with multi-detector row CT. Radiology 2008;247:658–668.

Clinical Classifications, Epidemiology and Clinical Features.

AFL can be divided into two types:

Type I, or typical, (or common) is well described both anatomically and electrically. It is always being interrupted by rapid atrial pacing, with atrial rates from 240-350 bpm.

Type II, or uncommon, (or reverse common), is now fully characterized. It is associated with atrial rates above 350 bpm.

The typical AFL affects virtually the same spectrum of clinical situations of AF, but is rarer than AF in apparently non-cardiac subjects. It may be paroxysmal or permanent. Many patients with paroxysmal AFL have also paroxysmal AF.

Paroxysmal atrial flutter can occur in patients without structural heart disease, while persistent AFL is constantly observed in cardiac patients. It is usually associated with underlying heart disease, such as rheumatic or ischemic heart disease or cardiomyopathy. It can occur as a result of atrial dilatation from septal defects, pulmonary emboli, mitral or tricuspid valve stenosis or regurgitation, or chronic ventricular failure. Toxic and metabolic conditions that affect the heart, such as thyrotoxicosis, alcoholism, and pericarditis can cause AFL. Occasionally, it can be congenital or follow surgery for congenital heart disease [24], or even occur in utero [25,26].

AFL is much less common than AF. Although the exact incidence is not known, it is estimated that its prevalence is less than 1 per thousand of the general population, but it is a common arrhythmia estimated to be present in approximately 10% of patients presenting with a supraventricular tachycardia [27]. The projected prevalence for 2050 was 0.15 million for AFL and 0.44 million for AF and AFL (Fig. 2). In few words, the current prevalence of AF and AFL is high and is projected to increase considerably by 2050. The prevalence increases with age. AFL is more common in men than in women. It is common during the first week after open heart surgery [28]. Permanent AFL with a rapid ventricular rate may lead to a tachycardia-mediated cardiomyopathy. Tolerance of the rapid

ventricular rate during AFL will be influenced by the presence of additional cardiac or pulmonary abnormalities.
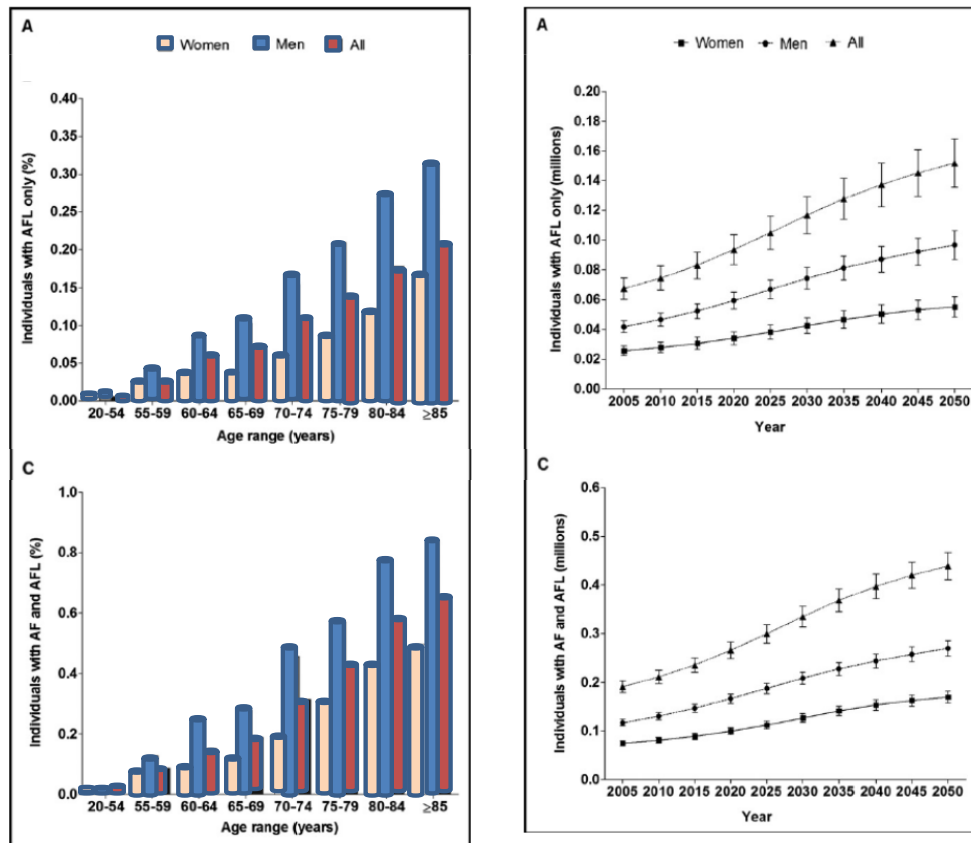
Figure 2. Left panel: Prevalence of (A) AFL only, and (B) AF and AFL stratified by gender and age. **Right panel:** Projected prevalence of (A) AFL only, and (B) AF and AFL from 2005 to 2050.

AFL, atrial flutter; AF, atrial fibrillation

From: Naccarelli GV, Varker H, Lin J, et al. Increasing Prevalence of Atrial Fibrillation and Flutter in the United States. Am J Cardiol 2009; 104:1534–1539.

AFL tends to be unstable, reverting to sinus rhythm or degenerating into atrial fibrillation. Less commonly, the atria can continue to flutter for months or years. In AFL, the atria contract, which

may, in part, account for fewer systemic emboli than in atrial fibrillation. In children, continued episodes of AFL are associated with an increased chance of sudden death. AFL usually responds to carotid sinus massage with a decrease in ventricular rate in stepwise multiples, returning in a reverse manner to the former ventricular rate at the termination of carotid massage (Fig. 3A). Very rarely, sinus rhythm follows carotid sinus massage. Exercise by enhancing sympathetic or lessening parasympathetic tone, can reduce the atrioventricular (AV) conduction delay and produce a doubling of the ventricular rate. Physical examination may reveal rapid flutter waves in the jugular venous pulse. If the relationship of flutter waves to conducted QRS complexes remains constant, the first heart sound will have a constant intensity. Occasionally, sounds caused by atrial contraction can be auscultated.

The atrial rate during typical (type I) AFL is usually 250 to 350 beats/min. Ordinarily, the atrial rated is about 300 beats/min, and in untreated patients the ventricular rate is half the atrial rate, i.e. l50 beats/min (Fig. 3A). A significantly slower ventricular rate (in the absence of drugs) suggests AV conduction.

The hemodynamic tolerance of AFL depends on the baseline clinical situation and the AV conduction ratio. As the atrial rate of the flutter reaches around 300 beats/min, the ventricular rate is quite different if the conduction is 1:1 (very unlikely eventuality in the non-WPW patients), 2:1 (150 beats/min), 3:1 (100 beats/min) or Luciani-Wenckebach. A second aspect to be considered for AFL is the possible abrupt increase in heart rate during adrenergic stimulation linked to the change of the AV conduction ratio. As a result, an AFL can be well tolerated at rest but not the same to the slightest effort. In children, in patients with the pre-excitation syndrome, occasionally in patients with hyperthyroidism, and in those with accelerated AV nodal conduction, AFL ventricular rate may be much faster. Lastly, the possible deleterious effect of some drugs (such as those of the class IC) currently being used for the potentially efficacy in the therapy and prevention of such arrhythmias should be considered. Such drugs tend to slow the atrial rate of flutter (to the range of 200 beats/min)

and may paradoxically favor an AV 1:1 conduction ratio. If, for example, in a patient's basic condition the AV node allows a conduction of 1:1 up to 220 beats/min, during AFL (having an atrial rate of about 300 beats/min), the AV conduction will be 2:1 and the ventricular rate of 150 beats/min. After taking a class 1C antiarrhythmic drugs (AADs), if the atrial rate drops to 220 beats/min, a ratio of 1:1 will be possible and the ventricular rate may suddenly rise to 220 beats/min. Since, as we have said, AF and AFL are arrhythmias affecting similar patients, this problem should also be taken into account when we suggest these drugs for therapeutic or prophylactic purposes to patients with paroxysmal AF. Paroxysmal AFL, like other supraventricular paroxysmal tachycardia, does not involve severe hemodynamic consequences or particularly negative prognostic implications in the "healthy heart" patients, especially if the crises are rare and at a very low rate. In the cardiac patients, of course, the problem is different because a sudden increase in ventricular rate can break an unstable balance. Permanent AFL, similar to permanent atrial tachycardia, when it maintains a steadily high ventricular rate, may also result in the development of secondary cardiomyopathy in an otherwise previously normal heart or in the worsening of cardiac function in patients affected by heart diseases. The abolition of the arrhythmia, with transcatheter ablation, generally improves the function of the pump until the "cardiomyopathy" regresses. Uncommon AFL is rarer than the common one and often alternates with the first one. In general, what it said about the common flutter, it is also true for uncommon AFL.
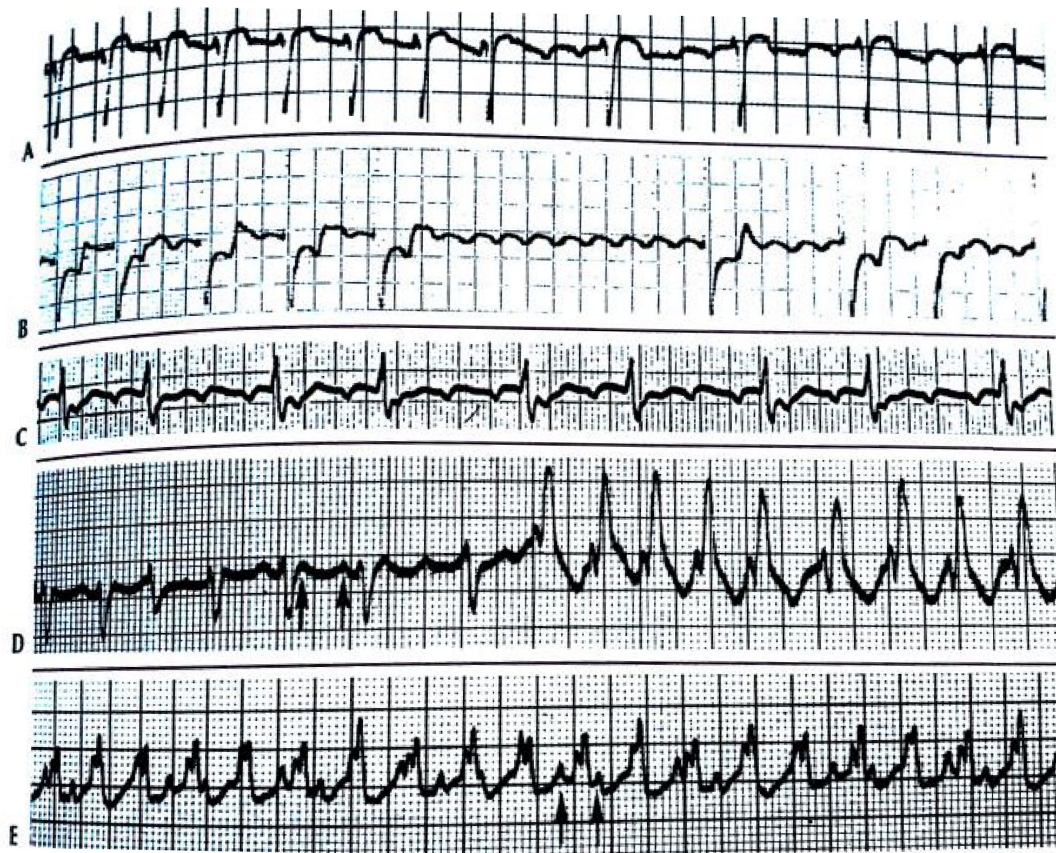
Figure 3. Various manifestations of atrial flutter. A, Atrial flutter at a rate of 300 beats/min conducts to ventricle with 2:1 block. In the mid-portion of the tracing, carotid sinus massage converts the block to 4:1 and the ventricle rale slows to 75 beats/min. B, Carotid sinus. massage produces a transient period of AV block clearly revealing the flutter waves. C, Quinidine has slowed the atrial flutter rate to approximately 188 beats/min. The block is variable. D, Wide QRS complexes with an RSR' configuration in V_1 begin after a short cycle that follows a long cycle in the mid-portion of the ECG strip. This represents functional right bundle branch block. Arrows indicate flutter waves. E, The QRS, complexes are 0.12 sec in duration and have a regular interval at a rale of 200 beats/min. Atrial activity is also regular at a rate of 300 beats/min and independent from ventricular activity (arrows), Thus atrial flutter is present with a probable ventricular tachycardia, an example of complete AV dissociation.

AV, atrioventricular

From: E. Braunwald. Heart Disease. Textbook of Cardiovascular Medicine. 5th ed. 1997. Philadelphia, London,Toronto, Montreal, Sydney, Tokio. W. B. Saunders Company.

Electrocardiographic Recognition of Atrial Flutter.

In typical AFL, flutter waves are atrial complexes of constant morphology, polarity and cycle length in a rate range from 240 to 340 beats/minute with classical aspect (sawtooth) (Fig. 3B and Fig. 4), often best visualized as negative waves in leads II, III, aVF and positive waves in V1 (Fig. 4 and Fig. 5), and evidence of continuous electrical activity, that is to say lack of an isoelectric interval between flutter waves (Fig. 6 and Fig. 7). As a result of perpendicular spatial exploration of the activation line, the isoelectric line may be present in chest leads (Fig. 8). Transition of morphology across the anterior leads is consistent with a counterclockwise atrial circuit with lateral-to-medial activation of the CTI.
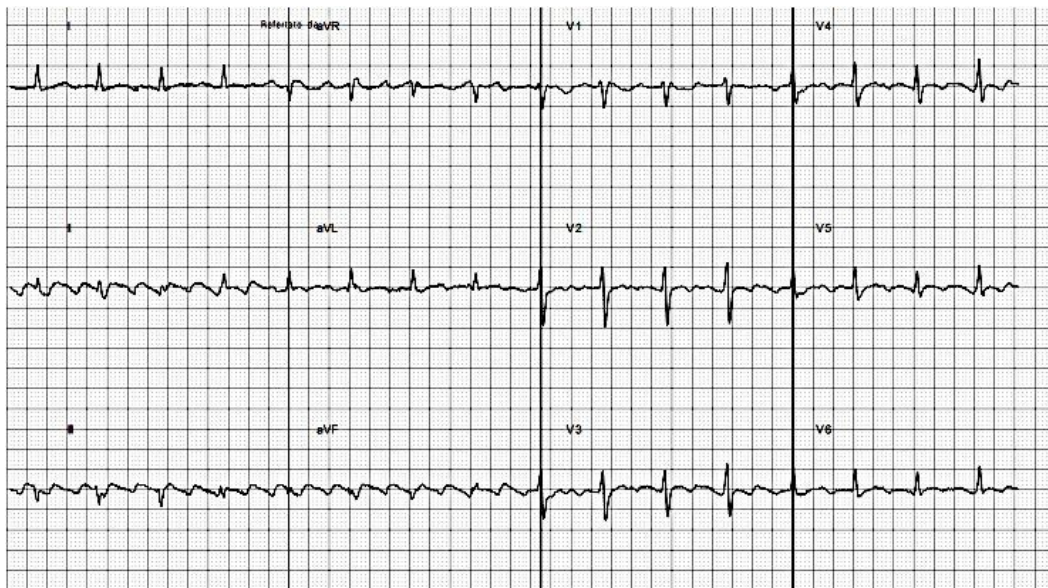
Figure 4. Standard electrocardiogram in common AFL. Note sawtooth waves F.

Figure 5. Simultaneous atrial flutter and sinus rhythm. In this patient with a heart transplant, the recipient atrium exhibits atrial flutter, best seen in leads II, IlI and aVF while the donor atrium exhibits sinus rhythm (best seen in chest leads).
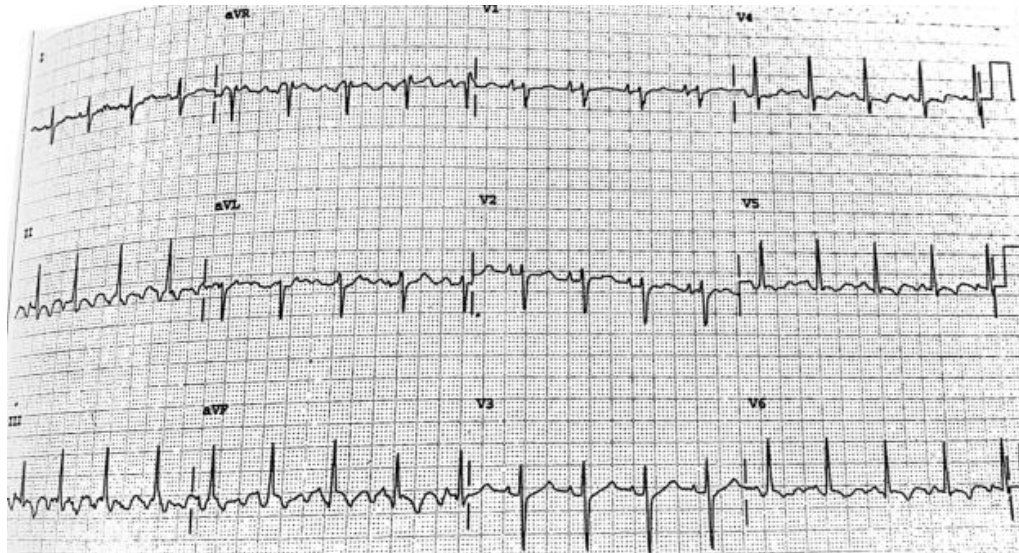
From: E. Braunwald. Heart Disease. Textbook of Cardiovascular Medicine. 5th ed. 1997. Philadelphia, London,Toronto, Montreal, Sydney, Tokio. W. B. Saunders Company.
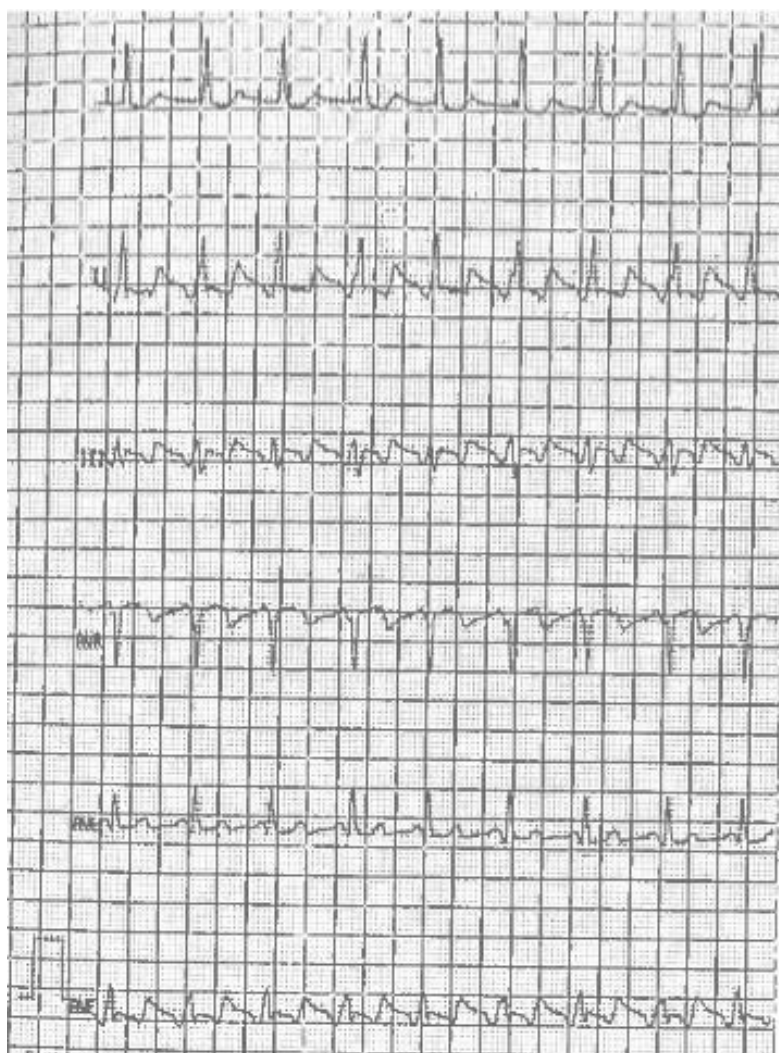
Figure 6. Electrocardiogram peripheral leads in common AFL. Note the classic sawtooth appearance in D2, D3, and aVF. The AV conduction ratio is 2:1.

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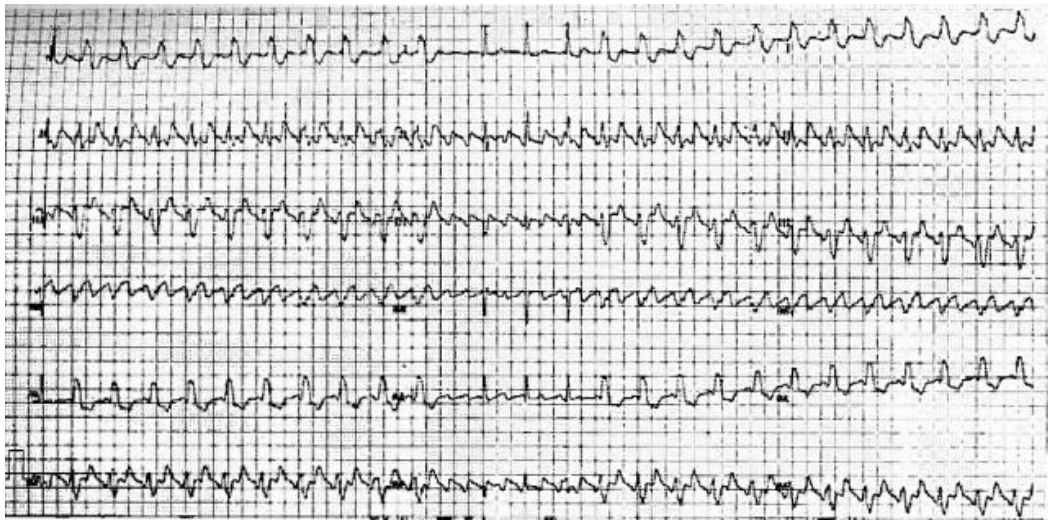
Figure 7. Common AFL. In the peripheral leads, the classic sawtooth waves (without interposed isoelectric) linked to the flutter counterclockwise macro-circuit running through the right atrium. In this case there are periods of QRS aberrancy type left branch block. The branch block appears in the presence of short R-R cycles and disappears during long R-R cycles (linking phenomenon).

From: P. Delise. Le tachiaritmie sopraventricolari. Dall'elettrocardiogramma all'ablazione transcatetere. Ed. 1997. Casa Editrice Scientifica Internazionale.

Figure 8. As a result of perpendicular spatial exploration of the activation line, the isoelectric line may be present in chest leads.

In the ECG uncommon flutter waves generally have a faster rate of the typical flutter and are positive in leads II, III, aVF, broad, inverted flutter waves in V1, which accounts for 5-10% of all CTI-dependent flutter. The AV conduction ratios are as in the typical flutter. The rate in uncommon AFL is 350 to 450 beats/min.
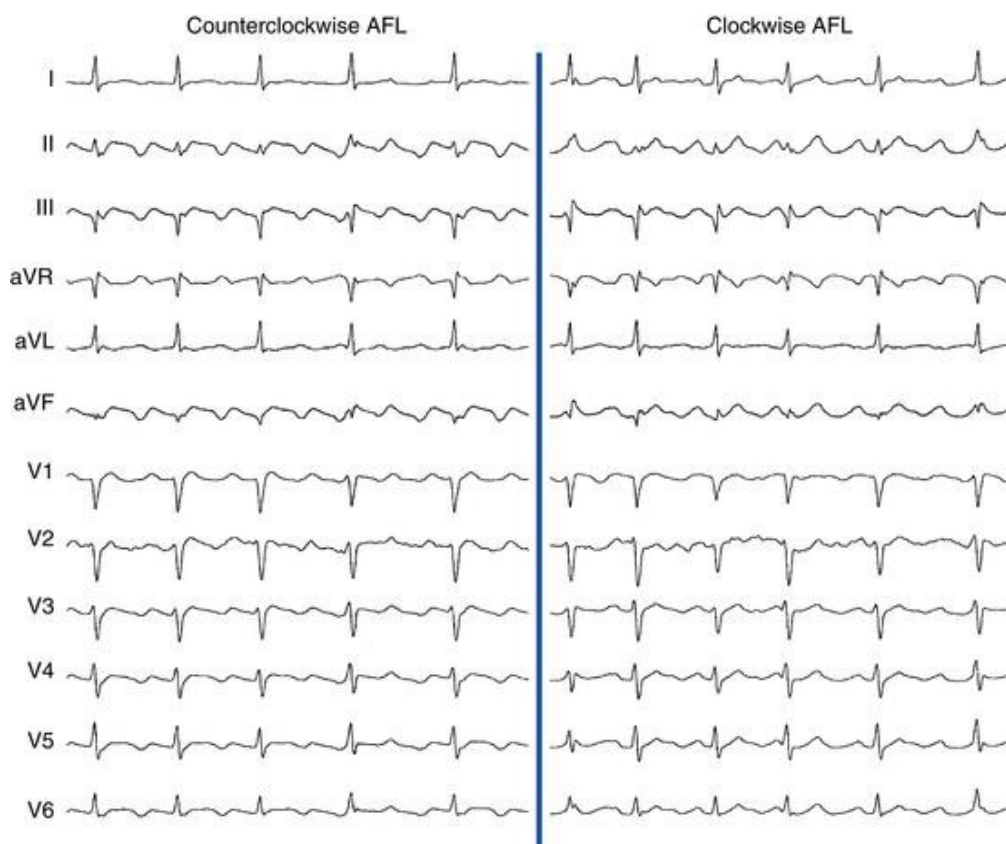
Figure 9. Surface 12-lead ECGs during counterclockwise (left) and clockwise (right) typical atrial flutter. In clockwise atrial flutter, the flutter waves are positive because of a clockwise reentrant pathway.

If the AV conduction ratio remains constant, the ventricular rhythm will be regular; if the ratio of conducted beats varies (usually the result of a Luciani-Wenckebach AV block), the ventricular rhythm will be irregular. Alternation between 2:1 and 4:1 AV conduction often occurs and may be due to two levels of block-2:1 high in the AV node and 3:2 lower down. The irregular ventricular response is frequently due to Luciani-Wenckebach periodicity. Recurrent alternation of short and long ventricular intervals can be due to concealed conduction (Fig. 7). Various degrees of penetration into the AV junction by the flutter impulses also can influence AV conduction. The ratio of flutter waves to conducted ventricular complexes most often is an even number (e.g., 4:1, and so on).

Generally, diagnosis is simple because the conduction ratio to the ventricles (usually 2:1, 3:1, 4:1, Luciani-Wenckebach, etc.) That makes it easily distinguishable. The waves F rate is classically around 300/min (range 230-260). Some difficulties can arise when there is an AV 1:1 conduction to the ventricles (e.g. in the presence of anomalous pathway like Kent, Fig 10). In this case the waves F may be completely or partially masked in the wave T of the previous beat and may be decisive for the diagnosis to be able to modify the AV conduction ratio. This condition is rarely, but not impossible.

Impure flutter (flutter-fibrillation), occurring at a rate faster than pure flutter, shows variability in the contour and spacing of the flutter waves and in certain instances can represent dissimilar atrial rhythms, i.e., fibrillation in one atrium and a slower, more regular rhythm resembling AFL in the opposite atrium. Prolonged atrial conduction time has been found to be a predisposing factor for the development of AFL.

Figure 10. AFL in left posteroseptal accessory pathway. The conduction is 1:1 and the traces simulates a ventricular tachycardia.

Management of Atrial Flutter.

The goals for the management of AFL are similar to those for AF [29,30]. Based on the available evidence [31], the stroke risk in patients with AFL is not much different from that in AF [32]. Furthermore, many patients diagnosed with AFL develop AF [33–35]. Thus, anticoagulation should be used in patients with AFL similar to that in patients with AF.

Rate control in AFL is achieved with the same medications as in AF, but is often more difficult to reach. Perpetuation of AFL requires that the tachycardia circuit be longer than the product of conduction velocity of the circulating impulse and the duration of the refractory period in the circuit (the so-called wave length). To terminate the arrhythmia, therefore, a drug should be given which does not slow conduction velocity but rather prolongs the refractory period within the tachycardia circuit, inhibiting continuation of the circulating wave front [36–38].

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When deciding on pharmacological therapy, side effects and the possible dangers of drug administration should be considered. Class III drugs can produce torsade de pointes arrhythmias [39]. This occurs in 1% to 4% of patients and is related to dose and presence of abnormalities in cardiac and kidney function. As it said, class I drugs may lower the flutter rate, resulting in 1:1 AV conduction and a much faster ventricular rate. Especially in the case of class I-C drugs, this may be accompanied by marked QRS widening and initiation of ventricular tachycardia. QRS widening on ventricular rate increase may vary individually. It is therefore advisable to perform an exercise test after treatment with a class I-C drug has been initiated. If QRS widening on ventricular rate increase occurs, the class I-C drug should be discontinued, and/or a drug prolonging the refractory period of the AV node should be administered. In summary, flecainide, propafenone, dofetilide, and intravenous ibutilide are useful for cardioversion of AFL, but they should be combined with a rate- controlling agent to avoid 1:1 conduction of slowing flutter waves to the ventricles. (Fig. 11). For acute termination of AFL, intravenous ibutilide is more effective for conversion of AFL than AF, whereas vernakalant is less effective in converting typical AFL [40-43].

Verapamil or diltiazem to slow the ventricular response during AFL can be tried. Calcium antagonists can restore sinus rhythm in patients with AFL of recent onset but less commonly terminate permanent AFL. Adenosine produces transient AV block and can be used to reveal flutter waves if the diagnosis of the arrhythmias is in doubt. It generally will not terminate the AFL and can provoke AF [44]. Esmolol, a beta-adrenergic blocker with a 9-min elimination half-life, can be used to slow the ventricular rate [45].

For prevention of recurrence, two aspects have to be considered. The arrhythmia is usually caused by one or more atrial premature beats that can be prevented by class I drugs (flecainide, procainamide, quinidine), class III drugs, and amiodarone. Maintenance of the arrhythmia can be prevented by prolonging the wave length of the circulating impulse by class III drugs [46].
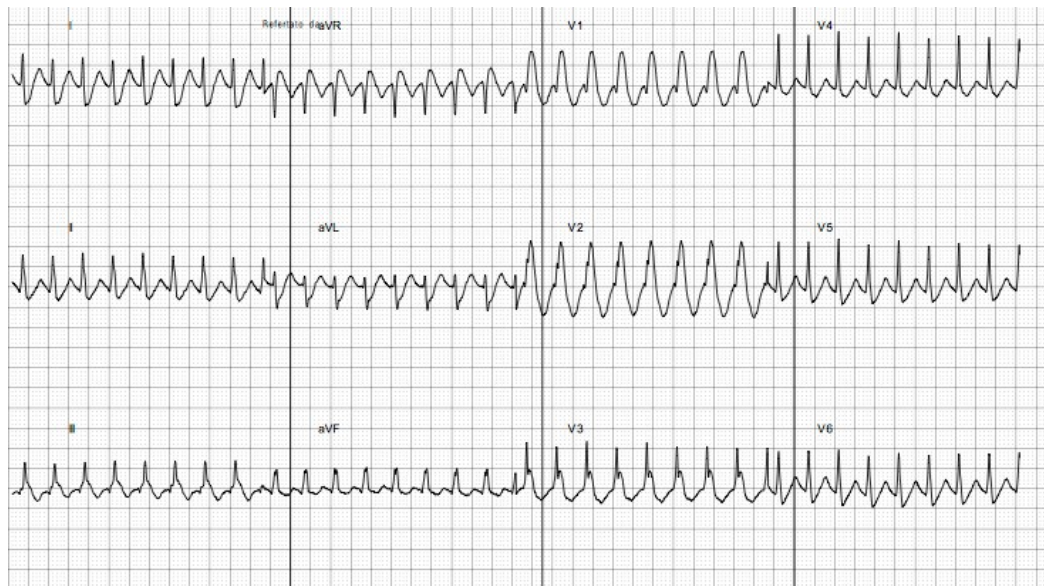
Figure 11. AFL IC (Flecainide). The conduction is 1:1 and the traces simulates a ventricular tachycardia.

External electrical cardioversion has been used to terminate AFL since its introduction by Lown et al [47]. Synchronous direct-current cardioversion of AFL can be performed [48]. It is commonly the initial treatment of choice for AFL, since cardioversion promptly and effectively restores sinus rhythm, often requiring relatively lower energies (<50 joules) than for AF [49,50]. If the electrical shock results in AF, a second shock at a higher energy level is used to restore sinus rhythm or, depending on the clinical circumstances, the AF can be left untreated. The latter can revert to AFL or sinus rhythm. The method is safe and effective, terminating AFL in >90% of episodes.

If the patient cannot be electrically cardioverted or if electrical cardioversion is contraindicated, for example, after large amounts of digitalis are administered, rapid atrial pacing (atrial overdrive pacing) through pacemaker leads or endocardial catheter or catheter in the esophagus [51] or the right atrium can terminate type I (but not type II) AFL effectively in most patients, producing sinus rhythm [52,53] or AF with a slowing of the ventricular rate and concomitant clinical improvement [54-56].

Anticoagulation and transesophageal echocardiogram around cardioversion or overdrive pacing should be used similar to that in AF.

As it said, ventricular rate control during permanent AFL is very difficult. Nevertheless, drugs that prolong the refractory period of the AV node, such as β-blocking agents, calcium antagonists, digitalis, and amiodarone. should be prescribed. Digitalis can be tried alone or with a calcium antagonist or beta blocker. The dose of digitalis necessary to slow the ventricular response varies and at times can result in toxic levels because it is often difficult to slow the ventricular rate during AFL. Frequently, AF develops after digitalis administration and can revert to normal sinus rhythm upon withdrawal of digitalis; occasionally, normal sinus rhythm may occur without intervening AF. Intravenous amiodarone has been shown to slow the ventricular rate as effectively as digoxin [57] and it is the most suggested in the current clinical practice. If the AFL persists, class IA or IC drugs can be tried to restore sinus rhythm and to prevent a recurrence of atrial flutter [58]. Amiodarone, also can help to achieve ventricular rate control. Because of the vagolytic action of quinidine, procainamide, and disopyramide, but primarily because of the ability of class I drugs to slow the flutter rate, AV conduction can be facilitated sufficiently to result in a 1:1 ventricular response to the AFL (Fig. 12). Side effects of these drugs, especially proarrhythimic responses, must be carefully considered. Sometimes treatment of the underlying disorder, such as thyrotoxicosis, is necessary to effect conversion to sinus rhythm. In certain instances, AFL can continue, and if the ventricular rate can be controlled with drugs, conversion to sinus rhythm may not be indicated. Class I and III drugs should be discontinued if flutter remains. It is important to reemphasize that class I or III drugs should not be used unless the ventricular rate during atrial flutter has been slowed with digitalis or a calcium antagonist or beta-blocking drug [59]. In any case, both prevention of recurrent AFL and the ventricular rate control are often difficult to achieve.
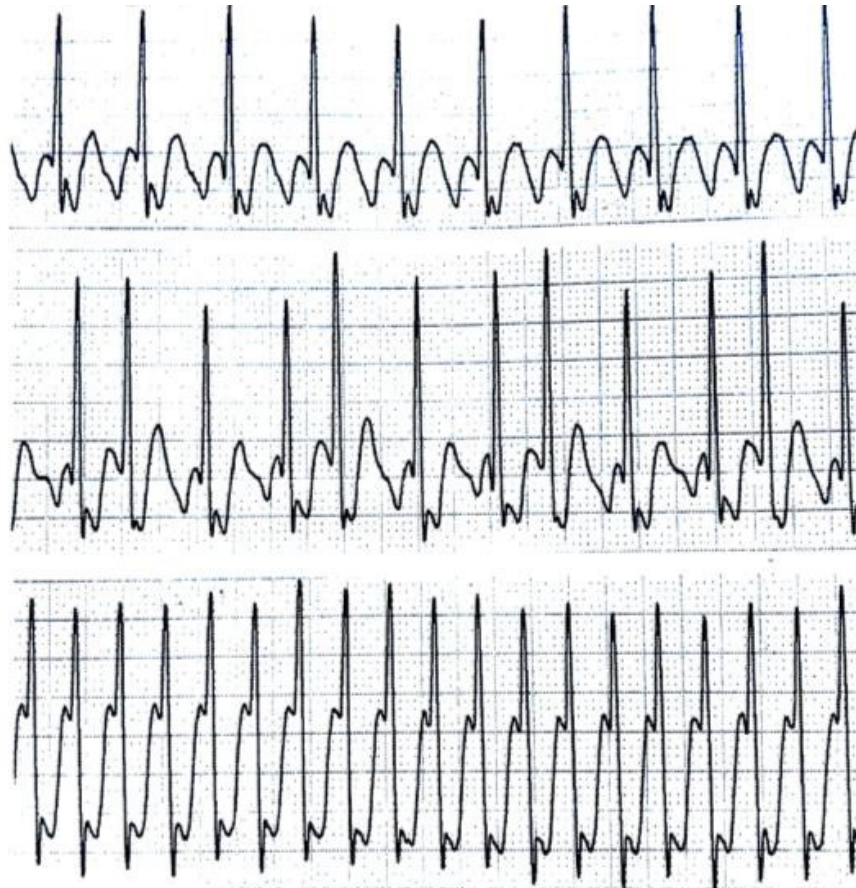
Figure 12. Atrial flutter with 1:1 conduction caused by flecainide. In the top panel, atrial flutter occurs with 2:1 conduction. In the middle panel, 2:1 conduction alternates with 3:2 conduction. In the bottom panel, flecainide has been started and the atrial flutter rate slows, resulting in 1:1 conduction.

From: E. Braunwald. Heart Disease. Textbook of Cardiovascular Medicine. 5th ed. 1997. Philadelphia, London,Toronto, Montreal, Sydney, Tokio. W. B. Saunders Company.

ELECTROPHYSIOLOGY OF ATRIAL FLUTTER

Atrial arrhythmias can be broadly classified as focal, small circuit, or macroreentry. Macroreentry is likely responsible for most form of usual AFL [60]. A definitive contribution to understand the mechanisms of AFL came from clinical electrophysiology. Over the years, it has been first made clear that the common AFL circuit is always located in the right atrium, while the left atrium is passively activated. An entrainment (see below) performed from the right atrium with a post pacing interval–flutter cycle length of 20 msec demonstrates to be within the circuit.

Cavotricuspid isthmus-dependent flutter is the archetypal atrial macro-re-entrant arrhythmia, the anatomical circuit of which has now been well described with both conventional and newer mapping modalities [11,12,61,62]. The most common forms of atrial macro-reentry are variants of classical common and uncommon CTI-dependent flutter (Fig. 13). These include both counterclockwise (type I, common) and clockwise (type II, reverse common) variants, with the circuit originally described as a broad active wavefront rotating around the tricuspid annulus. However, it is now recognized that many variants exist [63,64], such as lower loop reentry and forms in which the active wavefront crosses immediately anterior or posterior to the IVC. Rarely, intra-isthmus reentry can occur.

The macro-reentry of typical AFL in the right atrium, with the left atrium passively activated, therefore, consists of a counterclockwise rotation around the tricuspid ring with a caudocranial direction in the inter-atrial septum and with a craniocaudal direction in the right atrial free wall [60, 65-73]. Particularly, its descending branch occupies the lateral wall of the right atrium, in front of the terminal crest, and the ascendant one occupies the inter-atrial septum. The circuit is stereotyped because it is forced by a series of anatomic barriers: the terminal crest exactly, the IVC ostium, the CS ostium (in the posterior third of Koch's triangle, next to the slow pathway), the Eustachian ridge (combining both IVC and CS ostium) and obviously the tricuspid ring [74]. These anatomic barriers delimit certain restricted areas of myocardial tissue (isthmuses) that represent obligatory crossing

points of the circuit, critical areas to maintaining of reentry. Infact, a zone of slow conduction is typically bounded from the posterolateral to posteromedial inferior right atrium with a central area of block that can include an anatomical (IVC and tricuspid ring) and functional component [10, 75,76].
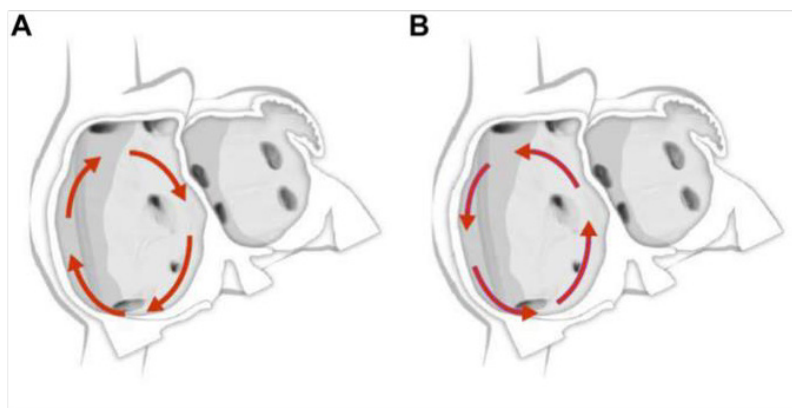
Figure 13. Schematic drawing showing mechanisms of AFL. **A:** Isthmus-dependent reverse type II (clockwise) AFL. **B:** Isthmus-dependent type I (counterclockwise) AFL.

From: Search Engine. ClinicalGate, 2015. https://clinicalgate.com

Tai et al demonstrated that incremental pacing from the low lateral right atrium and CS during sinus rhythm produced the rate-dependent conduction delays in the low right atrial isthmus, especially the middle and septal isthmus contiguous to the posterior triangle of Koch [37]. Furthermore, the gradual conduction delay with unidirectional block in the isthmus was relevant to the development of counterclockwise and clockwise atrial flutter. Patients with clinical AFL had much slower conduction in the low right atrial isthmus and shorter effective refractory periods in the right atrium than those without clinical AFL. This suggests slow conduction in the low right atrial isthmus plays an important role in the development of AFL. Feld et al. also found that conduction velocity was slower in the CTI than in the right atrial free wall and interatrial septum [77]. Furthermore, conduction velocity was slower in the CTI in the patients with type 1 atrial flutter than in those without a history of atrial

flutter. Olgin et al. demonstrated that pacing from the smooth right atrium induced counterclockwise atrial flutter, whereas pacing from the trabeculated right atrium induced clockwise atrial flutter [78]. Hence, the site of uni-directional block during initiation of either form of flutter is in the low right atrial isthmus.

Placing an ablation lesion (surgical or trans-catheter) across the zone of slow conduction abolishes the AFL and prevents recurrence. This can be accomplished near the entrance of the slow zone in the low posterolateral right atrium, at the midpoint of the slow zone in the posterior right atrium, or near the exit at the posteromedial right atrium. The most easily attackable isthmuses for their relatively small extension are two. The first one is interposed between the tricuspid ring and the IVC ostium. The second one is located between the tricuspid ring and the ostium of the CS. In some instances, the second isthmus also includes a portion of atrial tissue beneath the CS ostium and extends for a few millimeters to the Eustachian ridge by involving a myocardial strip interposed between the Eustachian ridge and the same ostium (Fig. 14).

It is possible that several different reentrant circuits exist in patients with atrial flutter. However, this area of slow conduction is rather constant and represents the site of successful ablation of AFL. It is also important in the conversion of AFL to AF [67]. Double potentials can be recorded from this area, with each one reflecting activation on either side of the block [71]. Ventricular activation can modulate the AFL rate, probably through mechanotechnical coupling, and atrial volume changes [73,79]. Ablation results are consistent with a macro-reentry circuit [11,76,80-85].

The diagnosis of AFL is very easy using only the standard electrocardiogram. The endocavitary electrophysiological study provides many interesting data but rarely is indicated for diagnostic purposes.
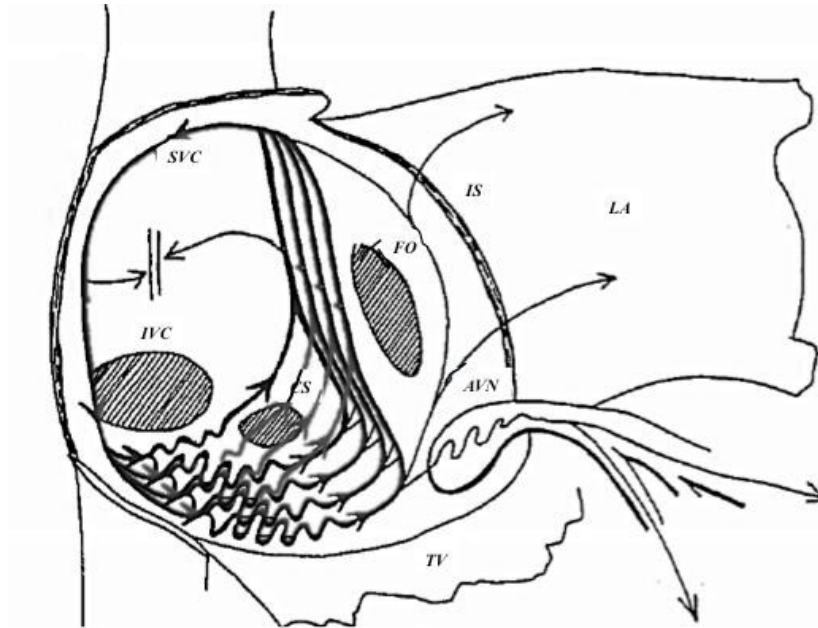
Figure 14. Re-entry circuit in common atrial flutter. Note the two mandatory isthmuses (through which pulses must pass) between ICV and TV and that between CS and TV. The flutter circuit is located entirely in the right atrium with a sense of counterclockwise rotation.

SCV, Superior Vena Cava; ICV, Inferior Vena Cava; CS, Coronary Sinus; FO, Foramen Ovale; IS, Interatrial Septum; AVN, Atrium-Ventricular Node; LA, Left Atrium; TV, Tricuspid Valve.

From: P. Delise. Le tachiaritmie sopraventricolari. Dall'elettrocardiogramma all'ablazione transcatetere. Ed. 1997. Casa Editrice Scientifica Internazionale.

Uncommon Atrial Flutter.

The uncommon AFL is defined as a rapid and organized arrhythmia, such as the typical flutter, but it has a different morphology of atrial waves that are positive in the inferior derivatives. It is believed that in most cases it is linked to an atrial macro-reentry, but the focal origin cannot be excluded in particular cases. Some subjects alternate typical and uncommon AFL episodes. In some of these cases it has been shown that uncommon AFL uses the same circuit of common AFL but in the opposite direction, that is, clockwise rather than counterclockwise.

RADIOFREQUENCY ABLATION OF ATRIAL FLUTTER

Ablation.

Catheter ablation has come a long way since its introduction in the early 1980s [86]. Catheter ablation of arrhythmias is growing at a rapid pace, with a 30-fold increase in the number of procedures from the late 1980s to 1990 [87]; it is now considered first-line therapy in many arrhythmias [88]. AFL has been one of the atrial tachyarrhythmias in which RF ablation has been early and largely used.

Understanding the electrophysiology of the reentrant pathway for common and uncommon AFL, and the anatomy of CTI is essential to developing an ablation ideal approach.

As we known, the common AFL is supported by a macro-reentry located in the right atrium, around the tricuspid ring and with a sense of counterclockwise rotation. The uncommon AFL has a clockwise rotation.

The circuit comprises two tissue isthmuses through which the pulse passes obligatorily: one located between the IVC and the tricuspid ring and the other one located between the tricuspid ring and the CS ostium.

A variable number of catheters inside the atrium can be used for reconstructing the circuit. (Fig. 15 and 16). Classical succession of atrial activation can be documented with these methods.

Two main techniques can lead to the location of the two critical isthmus where radiofrequency can be applied and created the lesion: the anatomical or electrophysiological technique.

The anatomical technique consists in positioning the ablation catheter on one or both of the isthmuses by radiological guide. A catheter in the CS should be first introduced to locate the isthmus between the CS and tricuspid valve, so that it can become the radiological reference of its ostium. It is sometime useful to have a catheter in the Hisian area to identify the anterior portion of the tricuspid valve. It is convenient to check the position of the ablation catheter using all of the three standard fluoroscopic projections.

In fact, it is difficult to locate with certainty the position of the tip of a given catheter using a single fluoroscopic projection. The use of two orthogonal projections, like the oblique ones, permits a more accurate location of the exploring electrode within the three dimensions of the heart. The right anterior oblique (RAO) projection defines what is anterior, posterior, superior, and inferior in cardiac planes and permits to open and see "in front" the Koch's triangle, so could be used as reference in order that ablation catheter should be placed in front of the CS ostium. The frontal view could be used to introduce and position catheters in the high-lateral right atrium and follow the catheter during the ablation, in particular when moving from the middle isthmus until to fall in IVC. The left anterior oblique (LAO) projection is generally used to catheterize the CS independently of the venous approach used. This projection defines superior, inferior, anterior, and posterior locations for the right grooves and permits to confirm the correct position of all catheters and to understand if the ablation catheter is pointing against the septum or if it has accidentally moved away from it.

The guided technique by the electrophysiological criteria is based on two principles: 1) the identification of delayed pulse areas localized within one or both isthmuses; 2) locating a point where "concealed entrainment" can be performed. The detection of delayed areas can be performed both in sinus rhythm and during flutter. In both cases, slow pulse progression can be evidenced by recording a fragmented, low voltage electric activity, with increased duration up to 100 msec or more. During AFL, the earliest activation point, compared to the beginning of wave F, is found at the level of the isthmus between the IVC and TV in postero-lateral side (usually the activation is about 100-150 msec before the wave F), then it is in the postero-medial area (proceeding the wave F of -60/70 msec) and finally follows between the CS and the TV.
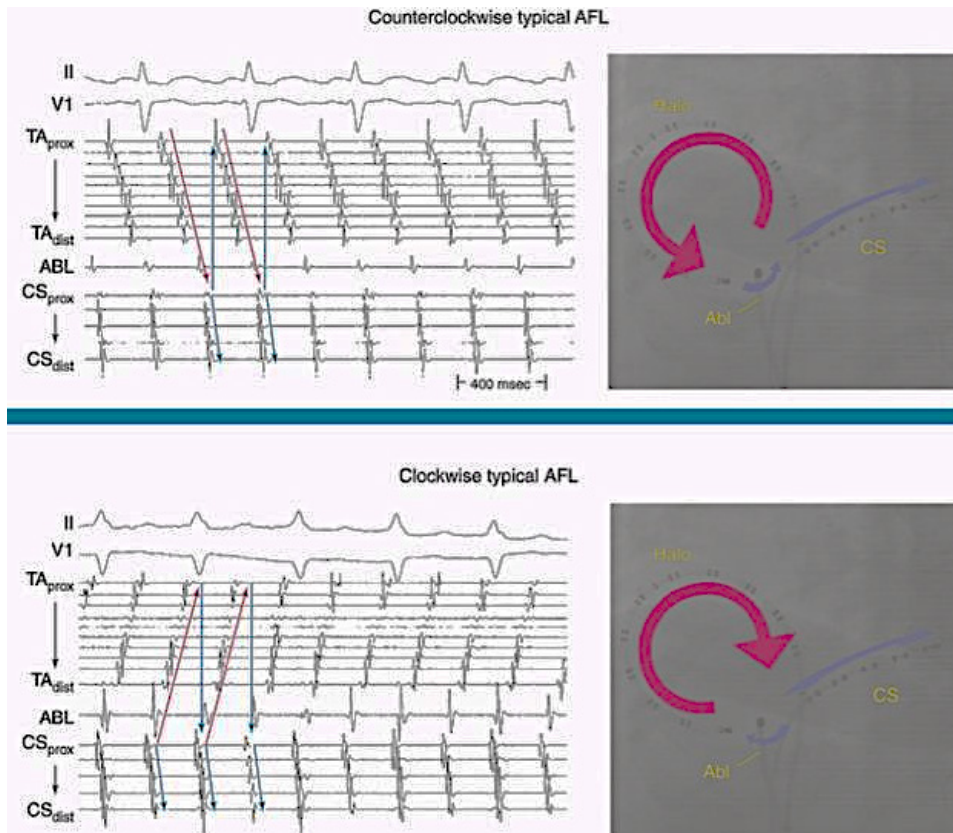
Figure 15. Endocardial activation during counterclockwise (**upper panel**) and clockwise (**lower panel**) typical atrial flutter in the same patient. Catheter position and wavefront activation during the arrhytmia are illustrated in a left anterior oblique fluoroscopic view (right side). The ablation catheter (Abl) is positioned at the cavotricuspid isthmus (CTI), and the Halo catheter is positioned around the tricuspid annulus. The terminal segment of the Halo catheter explores the inferior isthmus, whereas the mid- and proximal electrodes explore the right atrial lateral wall anterior to the terminal crest.

ABL, ablation site; CS, coronary sinus; CSdist, distal coronary sinus pole; CSprox, proximal coronary sinus pole; TAdist, distal tricuspid annulus pole; TAprox, proximal tricuspid annulus.

From: Search Engine. ClinicalGate, 2015. https://clinicalgate.com
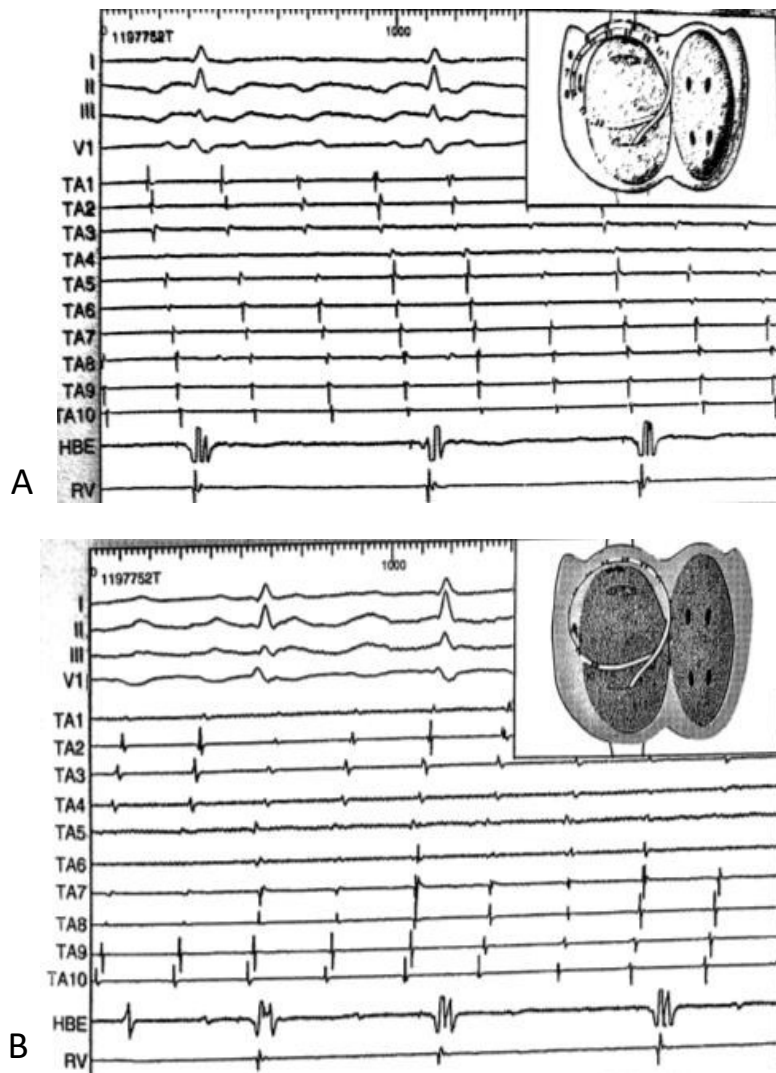
Figure 16. Panel A. Typical atrial flutter, with negative flutter waves in leads II and III. The insert (upper right) is a schematic of the right and left atria. A catheter has been inserted through the inferior vana cava and loops around the right atrium. Electrodes 1 to 10 are marked and correspond to electrogram recordings TA1 to TA10. Note that the atrial activation sequence proceeds in a counterclockwise direction from TA1 to TA10, cephalad up the septum and caudally down the right atrial free wall. HBE = His bundle electrogram; RV = right ventricular electrogram; I, II, III, and V_1= scalar recordings. **Panel B.** Uncommon atrial flutter in the same patient, with flutter waves positive in leads II and III. Recordings as in panel A. Note that the activation sequence travels in a clockwise direction in this example from the same patient.

From: E. Braunwald. Heart Disease. Textbook of Cardiovascular Medicine. 5th ed. 1997. Philadelphia, London,Toronto, Montreal, Sydney, Tokio. W. B. Saunders Company.

The energy has first to be delivered to the tricuspidal side (where the atrial deflection has a lower voltage than the ventricular one) by proceeding then towards the atrial side (where atrial deflection has a higher voltage than the ventricular one).

To find the isthmus between the IVC and TV, the ablation catheter is introduced into the right ventricle. Using LAO (with which the two atrium-ventricular rings in front are seen), the same catheter slowly withdraws into the atrium until its distal pole is placed on the lower edge of the TV. The recording of a good voltage atrial deflection helps to know if you are in the correct position. The energy is delivered here, then along the entire isthmus by retracting the catheter until to the atrium to create a real surgical cut between the IVC and the TV (Fig. 17 and 18).

The "concealed entrainment" described is a phenomenon that occurs when it is stimulated at a critical point of the circuit during spontaneous arrhythmia by capturing the same at a higher frequency. "Concealed entrainment" can be obtained in all three of the above positions. During stimulation, the flutter wave morphology is the same (in the 12 leads) to the spontaneous one, the ST-F interval is as longer as the catheter stimulates at the beginning of a delayed zone and finally when the pacing is stopped, the flutter continues with an interval between the last pacing flutter wave and spontaneous flutter wave equal to the original flutter cycle. In some subjects, with episodes of paroxysmal AFL, the same arrhythmia is not inducible during the electrophysiological study for which there are no alternatives to ablation during sinus rhythm.
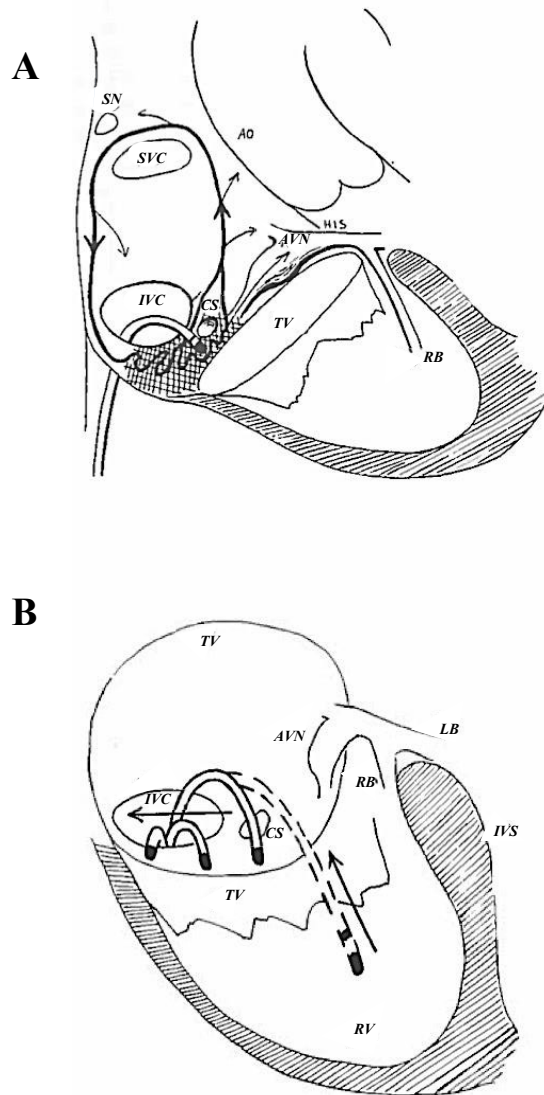
Figure 17. Panel A. Schematic reproduction of common flutter circuit ablation technique putting catheter on the isthmus between CS ostium and TV. In the figure are recognizable superior and inferior vena cava ostium (SVC and IVC, respectively), coronary sinus ostium (CS), tricuspid valve (TV), node-Hisian axis (AVN-His-RB) and aorta (Ao). Furthermore, SN, Sinus Node. Flutter circuit is drawn with the two obliged isthmus between IVC and TV and between CS and TV. **Panel B.** Schematic reproduction of the common atrial flutter circuit ablation technique putting the catheter on the isthmus between IVC and TV. RB, Right Branch; LB, Left Branch; RV, Right Ventricle; IVS, Inter-Ventricular Septum.

From: P. Delise. Le tachiaritmie sopraventricolari. Dall'elettrocardiogramma all'ablazione transcatetere. Ed. 1997. Casa Editrice Scientifica Internazionale.

RAO   LAO
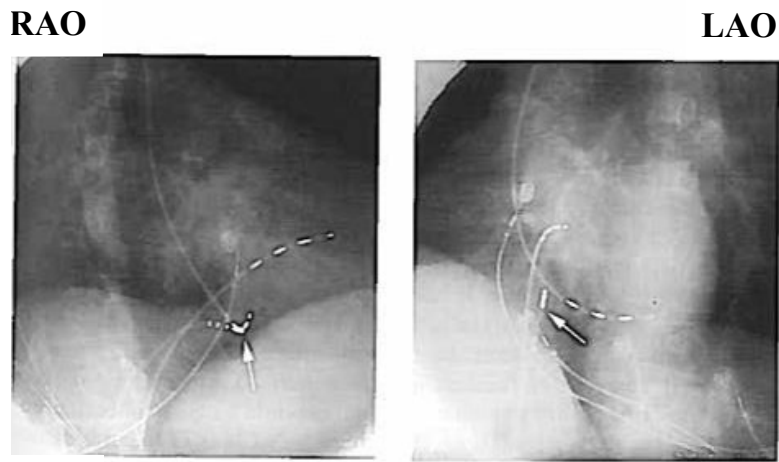
Figure 18. Positioning of catheters during the ablation of the cavo-tricuspid isthmus atrial flutter. In the right anterior oblique projection (RAO), a catheter is recognizable on the bundle of His (to the right looking at the figure), one in the coronary sinus that moves posteriorly, and a third catheter in front of the coronary sinus ostium which directs anteriorly. The latter is the ablation catheter (arrow). In the left anterior oblique projection (LAO), the three catheters are reviewed. The ablation catheter comes forward and rest on the tricuspid ring.

From: P. Delise. Le tachiaritmie sopraventricolari. Dall'elettrocardiogramma all'ablazione transcatetere. Ed. 1997. Casa Editrice Scientifica Internazionale.

Some Authors prefer ablation during sinus rhythm even in subjects with inducible AFL, for greater catheter stability during radiofrequency delivering. The electrophysiological endpoint of ablation during sinus rhythm is to create a bi-directional conduction block between the postero-lateral portion of the atrium that is around the TV and the area in front of the CS ostium (Fig. 19). This block, created by the linear lesion of one of the two isthmuses described above, is the precondition for preventing, countering the macro-reentry of arrhythmia. The demonstration of this block is as follows.

Figure 19. There is a catheter in the Hisian area (His Distal, Inter-medium and Proximal) and one in the postero-lateral tricuspid (LRA) site. Stimulation occurs from the coronary sinus during radiofrequency ablation. Two complexes are showed. Note that in the second complex the Stim-A interval in His-P remains constant. On the contrary in LRA the Stim-A interval changes from 85 to 139 msec. This delay appeared during radiofrequency ablation and is linked to the creation of cava-tricuspid isthmus block.
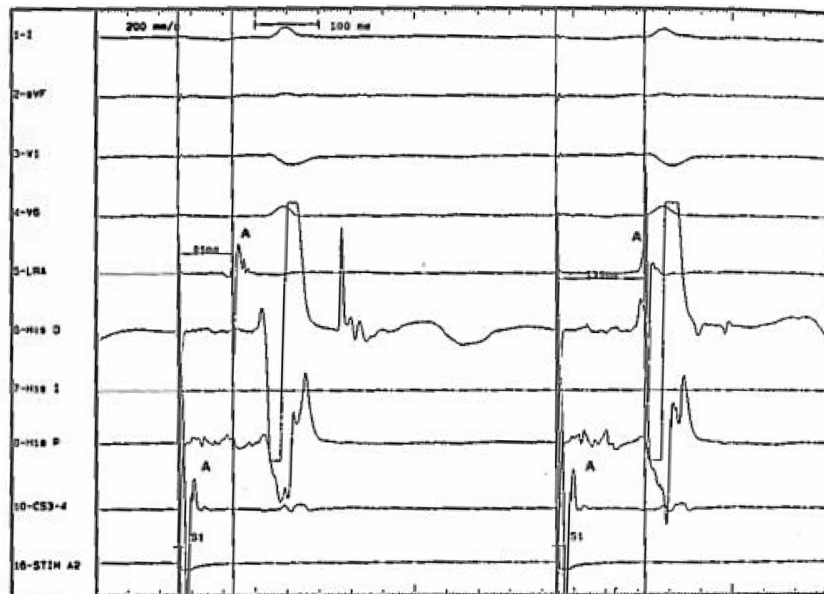
From: P. Delise. Le tachiaritmie sopraventricolari. Dall'elettrocardiogramma all'ablazione transcatetere. Ed. 1997. Casa Editrice Scientifica Internazionale.

Under basal conditions a pacing from the area around the CS ostium is performed and several points of the tricuspid circumference are recorded. The points have to be at least two or three: the Hisian area, the postero-lateral region of the tricuspid valve, and the lateral right atrium. By stimulating the ostium of the CS, the pulse spreads around the tricuspid in a counterclockwise direction along the interatrial septum and in a clockwise direction along the posterior edge of the tricuspid. It follows

that the activation of the Hisian area and the postero-lateral tricuspid wall occurs almost simultaneously while the high right lateral wall is triggered later. After the ablation of one of the two isthmuses, the pulse delivered from the CS is forced to activate the peri-tricuspidal atrial myocardium only in counterclockwise direction. It follows that the Hisian area is activated firstly, then the high right atrial wall and, later, the postero-lateral wall. Similarly under basal condition, if stimulated by the postero-lateral wall, the pulse spreads around the tricuspid both in the clockwise direction (along the side wall) and counterclockwise (along the posterior and medial wall). Therefore, the high right lateral wall and the CS ostium will activate almost simultaneously while the peri-hisian area will be activated later. After the ablation of one of the two atrial isthmuses, the pulse delivered by the postero-lateral wall is forced to activate peri-tricuspid myocardium only in the clockwise direction. It follows that the first activated zone is the high lateral right atrium, then the Hisian area and, only later, the CS ostium (Fig. 20).

In patients in whom this electrophysiological endpoint is reached, of course, the confirmation of the no-reinducibility of the flutter should be searched when it is inducible under basal conditions. The ablation endpoint during induced or persistent AFL is the flutter interruption and restoration of sinus rhythm during ablation. The no-reinducibility of flutter should also be searched and it is useful to document bidirectional block in the isthmus during sinus rhythm (Fig. 21 and 22). In fact, according to some Authors [89], the latter would have the best predictive value for no-recurrence in the follow up.

Both the anatomical and the electrophysiological techniques are characterized by success rates ranging from 70 to 90%.
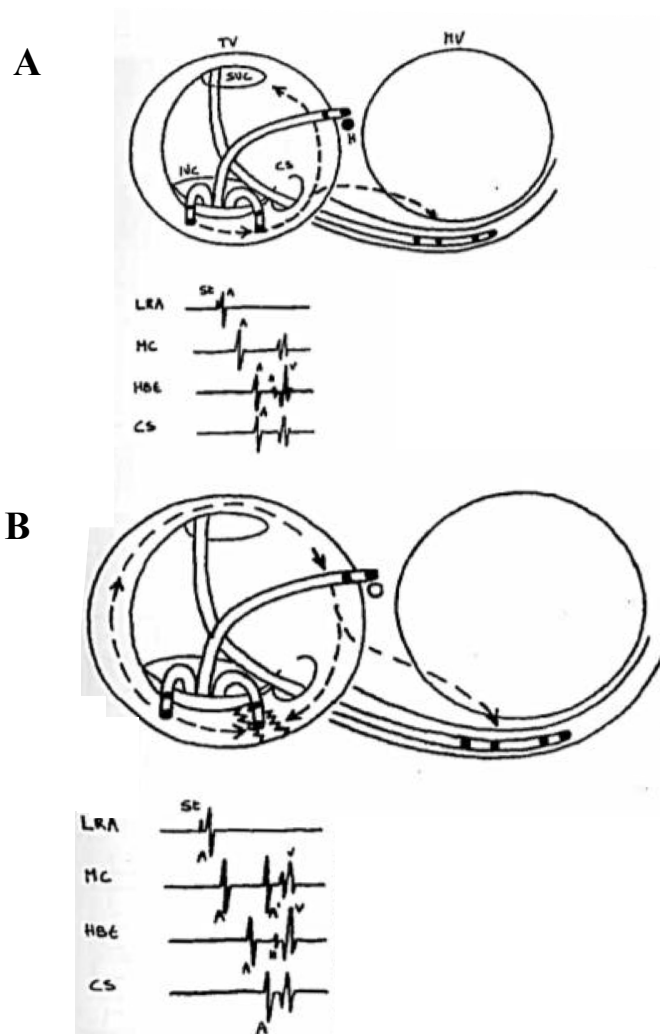
Figure 20. Panel A. The triggering sequence of the tricuspid ring as is normally by stimulating from the postero-lateral region of the tricuspid (LRA). Catheters are placed on His (HBE) bundle, at the posterior side of the tricuspid (MC) and in the coronary sinus (CS). MC activates first, followed by HRE and CS (see also text) that are activated almost simultaneously. **Panel B.** Activation of the tricuspid ring by the stimulation of the postero-lateral region of the tricuspid after a linear lesion of the cava-tricuspid isthmus caused by radiofrequency. After ablation the tricuspid activates in clockwise direction, HBE atriogram is before CS. In MC you see a particular phenomenon. The catheter is positioned on the linear lesion and registers two wavefronts. The first (A) that reaches it in counterclockwise direction and the second (A') which proceeds in clockwise direction. A' follows the HBE atriogram.

From: P. Delise. Le tachiaritmie sopraventricolari. Dall'elettrocardiogramma all'ablazione transcatetere. Ed. 1997. Casa Editrice Scientifica Internazionale.
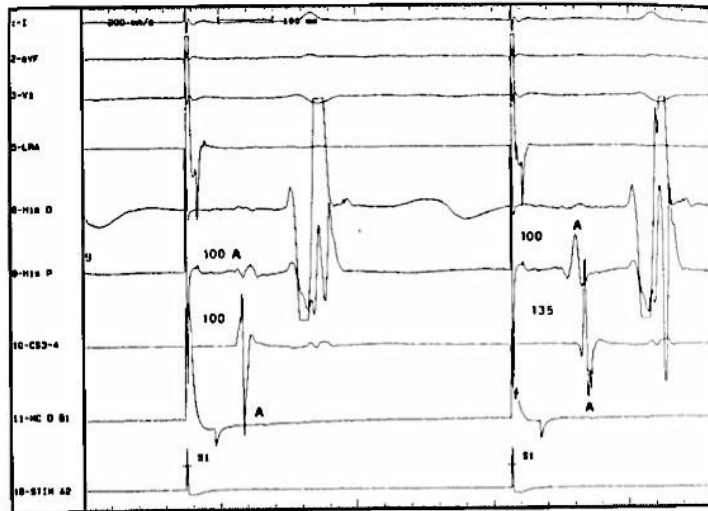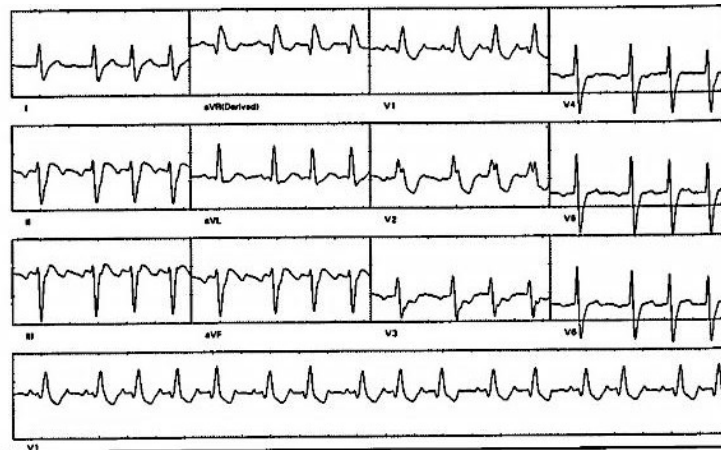
Figure 21. Panel A. There is a catheter in the Hisan area (HBE, His Distal and Proximal), one in the postero-lateral side of the tricuspid (LRA) and one at the coronary sinus ostium (CS 3-4). Pacing is triggered by LRA during radiofrequency ablation. Two complexes are showed. Note that in the second complex the Stim-A interval in His-P remains constant. Conversely, in CS 3-4 the Stim-A interval increases from 100 to 135 msec. Also, while in the first complex the wave A in HBE and CS 3-4 is simultaneous, in the second complex CS 3-4 follows HBE. This delay is linkedto the constitution of a cava-tricuspid isthmus block.

Panel B. Persistent common atrial flutter at the start of procedure of ablation of a cavo-tricuspid isthmus.

From: P. Delise. Le tachiaritmie sopraventricolari. Dall'elettrocardiogramma all'ablazione transcatetere. Ed. 1997. Casa Editrice Scientifica Internazionale.
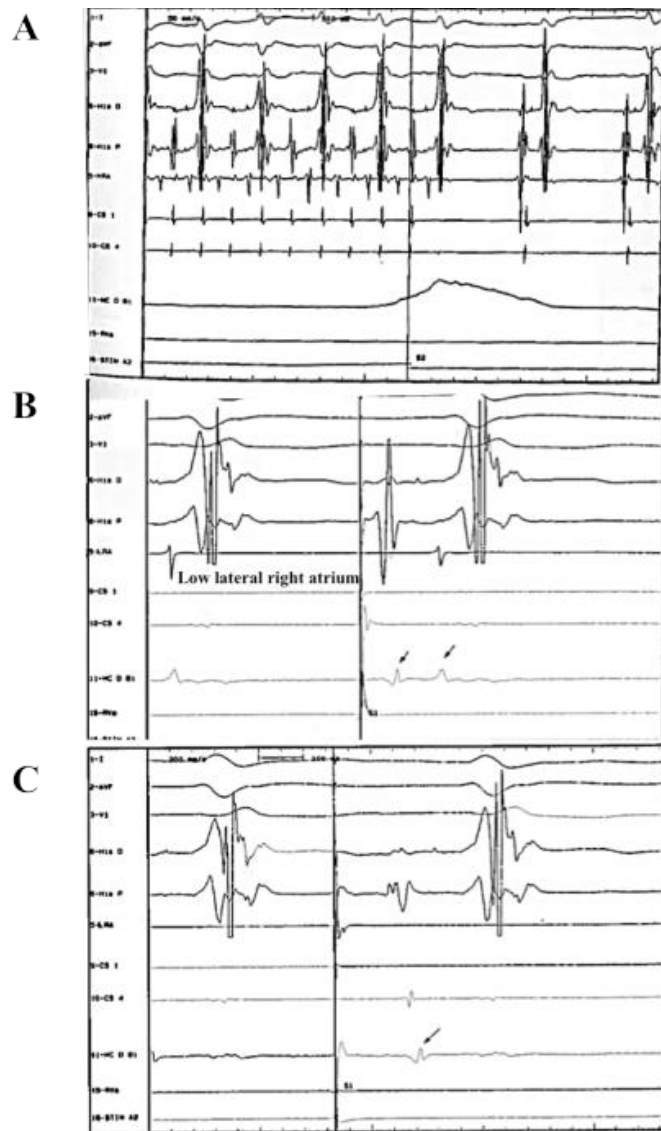
Figure 22. Panel A. By delivering radio frequency from the ablation catheter, the flutter interruption isobtained. **Panel B.** After flutter interruption the atrium is stimulated by the catheter placed in the coronary sinus. Note that the Hisian region is activated firstly and later, with significant delay, the posterior-lateral region of the tricuspid (low lateral right atrium, LRA). The ablation catheter (MC) records two deflections of which the second one is inscribed after LRA. For the interpretation of this phenomenon refer to Figure 20. **Panel C.** After the flutter interruption, the atrium is stimulated by the catheter placed in the right posterior-lateral side. Note that the Hisian region is activated firstly and, later, the proximal coronary sinus (CS 4). The ablation catheter (MC) is activated after CS4.

Indications.

Typical CTI dependent AFL is a common arrhythmia that can cause significant symptoms and sequelae. The electrophysiological substrate underlying AFL is a combination of slow conduction in the isthmus of atrial tissue between the tricuspid annulus and the IVC and conduction block along the crista terminalis and Eustachian ridge. Because of the well-defined anatomic substrate, the disappointing results of AADs in treating AFL [90-93], and that data from clinical trials demonstrated that it may help to prevent hospitalizations [94,95], RF catheter ablation of AFL is a common procedure. Moreover, for patients undergoing AF ablation, creation of a CTI line can be performed safely, easily, and rapidly procedure time [96]. Guidelines for the treatment of AFL have been formalized as for AF, only in the last years [48,97,98]. According to the current recommendations [30,99,100], candidates for RF catheter ablation include (Class I) patients with AFL that is drug resistant, those who are drug intolerant, or those who do not desire long-term drug therapy. Antithrombotic therapy is recommended (Class I) using the same protocol for AF. Moreover, AFL ablation should be considered (Class IIa) in case of documented AFL in patients waiting AF ablation procedure (Fig. 23).

Recommendations	Class[a]	Level[b]	Ref[c]
For patients with atrial flutter, antithrombotic therapy is recommended according to the same risk profile used for AF.	I	B	32
Overdrive atrial pacing of atrial flutter should be considered as an alternative to electrical cardioversion, depending on local availability and experience.	IIa	B	
Management of typical atrial flutter with ablation of the cavotricuspid isthmus is recommended for patients failing antiarrhythmic drug therapy or as first-line treatment considering patient preference.	I	B	99
If atrial flutter has been documented before AF ablation, ablation of the cavotricuspid isthmus should be considered as part of the AF ablation procedure.	IIa	C	

AF = atrial fibrillation.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Figure 23. Recommendations for management of atrial flutter.

From: ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS.The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC). Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Endorsed by the European Stroke Organization (ESO). European Heart Journal 2016;37:2893–2962.

Outcome of Isthmus Block after Radiofrequency Ablation.

Isthmus-dependent common AFL is the most frequent type of macro-re-entrant atrial tachycardia and the treatment of choice is RF catheter ablation with bidirectional conduction block across the CTI [11,13,14,85,101-105]. All the electrophysiologists presume that isthmus block is the end point of the radiofrequency ablation of the CTI. Poty et al. first described the criteria of isthmus block after ablation [103]. If isthmus block occurred, pacing at the proximal CS would show a complete descending activation of the low right atrium and pacing at the low right atrium would show a

complete descending activation of the septum. Tada et al. proposed double potentials along the ablation line as the criteria of isthmus block [106]. The time interval separating the two components of double potentials during a complete block was 135 ± 30 ms. The interval ≥110 ms was always associated with a local block. Isthmus block shifts direction of activation on the side of ablation line opposite from the pacing site, which changes an electrogram configuration.

There are several modes of ablation of the CTI, including radiofrequency using conventional 4-mm tip, radiofrequency using large 8-mm tip, radiofrequency using cooled tip, and cryoablation. There were studies showing that the 8-mm-tip catheter was more effective than the standard 4-mm-tip catheter for ablation of the CTI. Feld et al. performed catheter ablation of type 1 AFL using large- tip electrode catheters and demonstrated an acute success rate of 93% and 97% patients had no recurrence of atrial flutter [107]. Furthermore, a meta- analysis study confirmed that cooled-tip and 8-mm large- tip catheters was equally efficient for CTI ablation with both similar primary success rates and procedure parameters [108]. Cryoablation of the CTI, as compared with RF ablation, produced significantly less pain during application of the energy. Feld et al. performed cryoablation of the CTI and demonstrated an acute success rate of 87.5% and 90.2% of patients had no recurrence of AFL [109].

Ablation AFL outcomes are not always clear. Acute and chronic success rates have varied among studies, and the studies themselves differ in patient numbers, ablation technologies, and procedural end points. In addition, the occurrence of AF after AFL ablation may be a significant shortcoming of this procedure, but the reported incidence of AF after ablation varies widely [110-112]. Finally, important post-ablation outcomes such as mortality, AADs use, and anticoagulation use have not been well described. Thus, many long-term outcomes after AFL ablation are ill-defined. Generally, when AFL termination alone is used as an end point, the substrate for AFL recurrence is often left intact. Documenting bidirectional isthmus block reduces AFL recurrences by ensuring that all patients leave the laboratory with absence of the substrate for AFL. Termination of AFL without creating

bidirectional block was a common phenomenon during ablation procedures in the past. A meta-analysis [113] demonstrated a strong trend toward a higher procedural success with the more stringent end point of isthmus block. Moreover, the acute success rate was 92.7% when using large- tip or irrigated RF catheters, and the recurrence rate of AFL after ablation using large-tip or irrigated RF catheters and the end point of bidirectional isthmus block was 6.7%. In the same meta- analysis, the use of anticoagulation and AADs was common after AFL ablation. In fact, it was found ablation AFL increased AF recurrences. This should suggest that atrial electric disease may be less advanced in patients with AFL alone but is still progressive despite the prevention of flutter [111,112]. This finding was not confirmed by other studies limited, indeed, by a shorter follow up [94,114].

Contrary to catheter ablation of left atrial macro-reentrant tachycardia that it is more complex, with lower success rates and higher recurrence rates [115,116], the isthmus ablation is currently considered a simple procedure and far exceeds the efficacy of both pharmacologic therapy and DC cardioversion coupled with pharmacologic agents [117,118], with a success rate of about 75 to 90 per cent [80-83,97,119-124], 90–97% in centers with extensive experience [125-127].

Nevertheless, ablation cannot be easily achieved in all patients, depending of the complex CTI anatomy. In these patients multiple energy applications and prolonged procedure times are required and the long- term recurrence rate varies from 5% to 12.9% [107-109,128-132].

Complications.

AFL ablation has increased over the last decade, along with its associated major complications. Particularly, cardiac complications, such as pericardial effusion, cardiac tamponade, myocardial infarction due to right coronary artery injury, complete AV block requiring pacemaker implant, are

most common during AFL ablation. The distribution and frequency of complications are reported in Fig. 24.
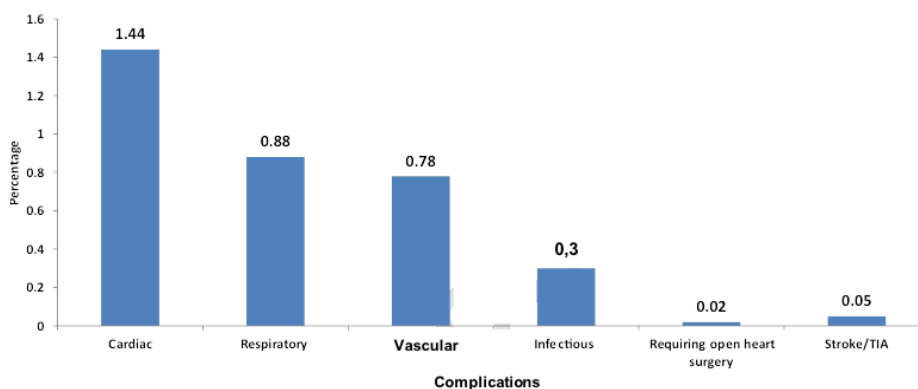
Figure 24. Distribution and frequency of complications after atrial flutter catheter ablations.

From: Patel NJ, Deshmukh A, Pau D, et al. Contemporary utilization and safety outcomes of catheter ablation of atrial flutter in the United States: Analysis of 89,638 procedures. Heart Rhythm 2016; 13(6):1317–1325.

Patel et al [125] found that AFL ablations performed in patients >80 years of age was associated with a significantly higher number of complications (Fig. 25), perhaps because of comorbidities. Santangeli et al [133] reported no difference in total periprocedural complication rates between patients >80 years of age and <80 years of age undergoing AF ablation. This cohort is underrepresented in clinical studies to assess the efficacy and safety of AFL ablations, but it faces the maximum burden of AF and AFL, and outcomes in this cohort could possibly influence care in the future.

Multiple studies have reported variable complication rates ranging from 0.8% to 6% and a mortality of rate of 0.1%. [134]. A meta-analysis by Spector et al. showed a complication rate of 4% and a risk of AFL ablation–related mortality rate of 0% [117]. In both of these studies, procedures were performed in high-volume academic centers. This probably contributed to the low mortality rates

seen. A single-center study from 2004 reported a major complication rate of 2.7% [130]. Another

meta-analysis by Perez et al [113] showed an acute complication rate of 2.6%. Patel et al showed a

complication rate of 3.17% and an in-hospital mortality of 0.17% obtained from hospitals across the

United States [125]. A single-center study from France [135] found same results in complication

rates. This trend of increase in complication rates may be attributable to an overall increase in the

number of hospitals performing this procedure, resulting in a simultaneous decrease in hospital

volume. In fact, both of two U.S. nationwide studies demonstrated an annual hospital volume of $\geqslant$

100 procedures/year was associated with a significantly fewer number of complications in

comparison to an annual hospital volume of <50 procedures/year when adjusted for other

confounding factors (Fig. 26) [125,136].
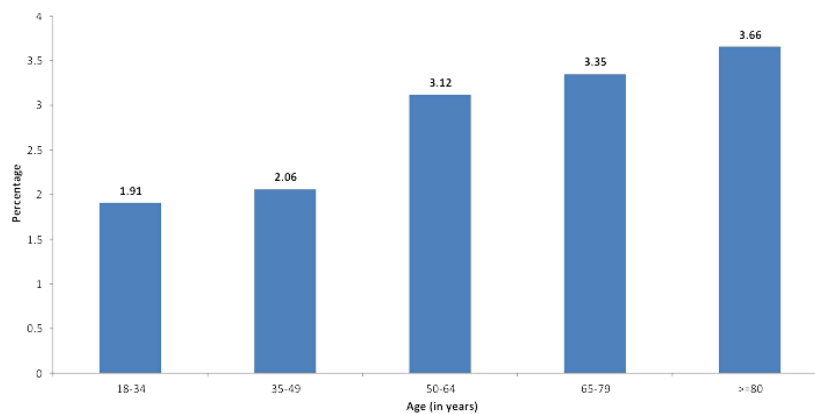
Figure 25. Overall complication rates of atrial flutter catheter ablation stratified by age group.

From: Patel NJ, Deshmukh A, Pau D, et al. Contemporary utilization and safety outcomes of catheter ablation of atrial flutter in the United States: Analysis of 89,638 procedures. Heart Rhythm 2016; 13(6):1317–1325.

The lowest-volume hospitals were also more likely to have a length of hospital stay longer than 2 days.

These results underscore the importance of having experienced high-volume centers, therefore, in addition to age and comorbidities, hospital volumes have strongly emerged as a factor predicting adverse outcomes. Since most ablations are performed in low-volume centers, appropriate measures are needed to determine a volume threshold considered optimum to control the utilization of this procedure at lower-volume centers, thus enhancing its safety.

A multidisciplinary approach involving electrophysiologists, nurses, and technicians, in an environment with appropriate training of the supporting staff for early detection and adequate management of complications associated with ablation, also appears to be important.
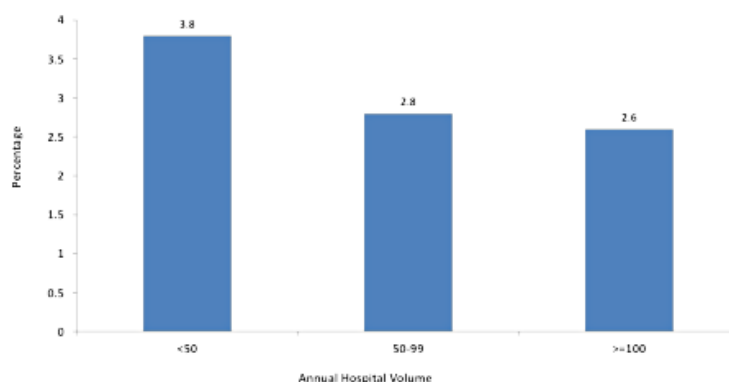
Figure 26. Spline curve illustrating the interaction among hospital volume and probability of the composite endpoint of mortality and complications after catheter ablation of atrial flutter.

From: Patel NJ, Deshmukh A, Pau D, et al. Contemporary utilization and safety outcomes of catheter ablation of atrial flutter in the United States: Analysis of 89,638 procedures. Heart Rhythm 2016; 13(6):1317–1325.

Moreover, the establishment of RF catheter ablation techniques of CVI as the mainstay in the treatment of AFL has renewed new interest in cardiac anatomy. The interventional arrhythmologist

has drawn attention not only to the gross anatomic details of the heart but also to architectural and histological characteristics of various cardiac regions that are relevant to the development or recurrence of tachyarrhythmias and procedural related complications of catheter ablation.

IMPACT OF THE CAVOTRICUSPID ISTHMUS ANATOMICAL FEATURES ON OUTCOMES AND COMPLICATIONS

Despite very high success rates and almost no complications [137], ablation of the CTI can be extremely difficult in some patients with atypical anatomical conditions; the CTI anatomy is complex and associated with a significant inter-individual variability [16,17,20]. Knowledge of the detailed anatomy of this region can significantly improve the safety and success rate of ablation procedures. The morphology and muscular architecture of the CTI in the human heart, regardless of its relevance to clinical practice, is not yet fully understood. There have been only a few anatomical studies on this topic, and only three of them comprehensively investigated the majority of CTI dimensions [16-18,138,139].

Autopsies, angiographic, and echocardiographic studies confirmed that the anatomy of AFL CTI is highly variable [16,140,141]: patients with a short and straight CTI require fewer radiofrequency ablation applications and shorter X-ray exposure. In study of cadaveric hearts the CTI was divided into three parallel levels [16, 18]. With the heart in attitudinal orientation, three levels of the isthmus were identified: paraseptal, inferior, and inferolateral. The paraseptal isthmus forms the base of Koch's triangle and is commonly referred to as septal isthmus. The septal isthmus is the shortest of the three isthmuses but has the thickest wall on heart specimens and it is closest to the AV node, particularly the inferior nodal extensions. The inferior isthmus, also known as the "central isthmus" owing to its location between the other two isthmuses (6 o'clock on LAO), represents the optimal target for ablation since this is the thinnest site between the ICV ostium and the tricuspid valve annulus. It is also shown that most lengths of isthmus are larger in patients with permanent AFL

compared to paroxysmal AFL or control groups [142]. The inferolateral and central isthmuses, despite they are longer, are considered to be better places than paraseptal isthmus for ablation, in order to avoid complications [143]. In fact, ablation at the paraseptal isthmus is associated with a significant risk of AV node injury and conduction block. Additionally, the paraseptal region has the thickest muscular content among the CTI. Therefore, it is not a preferable target for ablation. In cadaver hearts, all three isthmuses have in common a smooth anterior zone being the right atrium vestibule. By contrast, the posterior zone is composed of mainly fatty tissue as it joins the Eustachian valve. Between the anterior and posterior zones, the morphology and thickness of the isthmus are highly variable.

The crista terminalis is also important in AFL. The final ramifications and its non-uniform pattern seems to play a role in the propagation of impulses and has an impact on the success rate of CTI ablation [144]. Ablation of significantly thicker crista terminalis in lineal CTI ablation may necessitate increased radio-frequency energy and be the cause of procedural failure.

Obstacles such as a large Eustachian ridge/valve or a deep sub-Eustachian sinus may also lead to longer and more difficult ablation sessions [145]. These parameters may hinder catheter access to the regions located anterior to the ridge and valve. Also, the Eustachian ridge, due to the presence of muscle fibers, is able to conduct electrical impulses and represents the site of conduction gaps that are difficult to ablate. In these cases, only the complete abolition of the Eustachian ridge using more powerful ablation catheters results in complete bidirectional isthmus block [22]. Moreover, for the electrophysiologist entering the right atrium via the inferior route, the first structure encountered is the Eustachian valve guarding the ostium of the ICV. Normally, it is a thin, insignificant. Occasionally, it is large and may impede access to the most posterior part of the isthmus. The free border of the Eustachian valve continues as the tendon of Todaro that runs in the musculature of the Eustachian ridge. It has been demonstrated that, in patients with a large Eustachian ridge/valve, the paraseptal isthmus block can be obtained only after the complete ablation of the enlarged Eustachian

ridge [23]. In approximately 2% of the population, the Eustachian valve has a strange appearance of varying size. It is known as a Chiari network and when electrophysiologists encounter it, they should be aware of the potential risk of the catheter being caught by the network [146].

Indeed, ablation difficulties are typically caused by tissue thickness, pouches or muscular bridges or trabeculae [147]. In the study of Cabrera et al. [16], in the vast majority of cases (83%) the central isthmus traversed through a recess that is termed the "subeustachian sinus." It is a relatively large pouch-like recess measured with a depth of 3–5 mm.

n the majority of specimens, the pouch was membranous (63%, 19 hearts), with scarce muscular fibers. The presence of sub-Eustachian recesses significantly prolongs ablation time and is associated with a higher risk of complications and a lower rate of success [148]. These recesses are always found slightly to the right of the CS ostium and are never found in the lateral third of the CTI. As a result, the ablation line may be performed more laterally to avoid recesses [137]. Other authors found intertrabecular recesses and trabecular bridges laterally to the sub-Eustachian recesses located in the middle CTI sector [149]. Their transverse arrangement in relation to the long CTI axis (perpendicular to the septal leaflet attachment point) may contribute to enter the catheter between the tissue bridge and the thin atrial wall. The gaps between the bridges and the proper atrial wall may negatively influence the ablation, and more energy may be required to reach the isthmus block.

In anatomical studies with CT scan is seen, a "hook-shaped" morphology, showing a concave or pouch-like segment posteriorly (at the ICV side) and a vestibular part anteriorly in around 28% of the population [20].

The sub-Eustachian recess is an extension of a pouch-like isthmus under the CS ostium. The presence of a large sub-Eustachian recess or deep pouches is associated with significantly more RF applications and complications as compared with straight isthmus. Local radiofrequency delivery may be impaired by this structure because an area of limited blood flow results in delayed catheter tip cooling. In one angiographic study of the CTI, this pouch was observed in 47% of patients [140]. CT scans in normal

population have identified a deep recess combined with a pouch-like (greater than 5 mm in 45% of patients) central isthmus in 45% of mid-diastolic phase images [20]. This finding would be useful in preprocedural planning, where the presence of a large pouch would dictate a central approach to the ablation.

The majority of anatomical obstacles are unfortunately detected only at the time of CTI ablation, which significantly prolongs the procedure time, reduces the success rate, and increases complications.

Part II.

THE ANATOMICAL FEATURES OF RIGHT ATRIAL CAVOTRICUSPID ISTHMUS CAN IMPACT RADIOFREQUENCY CATHETER ABLATION IN TERM OF SUCCESS RATE AND COMPLICATIONS

BACKGROUND AND OBJECTIVES

Radiofrequency (RF) catheter ablation targeting the isthmus between the tricuspid annulus and the inferior vena cava (IVC) is the established treatment for typical atrial flutter (AFL) for its high efficacy. Despite this high success rate, more than 90% [11,12,103,126,150-152], ablation can be extremely difficult, due to great inter-individual variability of the cavotricuspid (CTI) anatomy. In fact, in the clinical setting, these anatomical features are associated with prolonged procedure times, increased total amount of radiofrequency energy, and reduced success rates [140,148,153,154], beyond catheter technology used. Pounce-like recesses and CTI length might be the reasons of majority of these problems.

The aim of this study was to assess how and why complex CTI anatomy influences ablation procedure. Primary endpoint was to evaluate the impact of the underlying CTI anatomy on acute and long-term success rate which is defined by achieving a consistent bidirectional block as protection for recurrence of AFL. Secondary endpoint was to determine any ablation related complication and procedure time.

At the same time, we analyzed the anatomy of the CTI region in autopsy hearts in order to find out the presence of any recesses, their number and position and their histology.

METHODS

Study population.

A total of 337 consecutive symptomatic patients underwent RF catheter ablation for recurrent typical counterclockwise AFL and were included in this prospective analysis between April 2013 and October 2017.

Exclusion criteria were as follows: (1) absence of informed patient consent; (2) age <18 years; (3) AFL recurrence after a previous ablation session, both AFL or atrial fibrillation (AF); and (4) pregnancy.

Typical AFL was identified by predominantly negative flutter waves in leads II, III, and aVF and positive in lead V1, with a regular atrial rate between 240 and 340 bpm, as the documentation during standard ECG or Holter ECG monitoring. AADs treatment was discontinued at least fifteen days before hospital admission in case of amiodarone, four half-lives before if class IC drug. For patients already receiving oral anticoagulation, this was withdrawn two days prior to the procedure to obtain an international normalized ratio of < 2.0 during the procedure, or 24-36 hours before in case of new oral anticoagulant (NAO). Venous thromboses were systematically prevented by subcutaneous low-molecular-weight heparin administrated after CTI ablation.

Transthoracic two-dimensional imaging combined pulsed Doppler echocardiography were performed before ablation in all patients. Left ventricular ejection fraction was determined by calculating the end diastolic and end systolic volumes. Left atrial size was measured at end systole in the parasternal long axis view.

Electrophysiological Study and Mapping.

All procedures were performed in the fasting state, under conscious sedation using boluses of midazolam and fentanyl and local anaesthetic were used to make it comfortable and virtually painless.

Vital parameters such as arterial blood pressure and oxygen saturation were monitored throughout the entire procedure. All standard ECG leads were recorded continuously throughout the procedure to facilitate rapid review, however only leads I, II, and V1 were displayed in real time. Leads I, II, and V1 were filtered through a 1 – 500 Hz bandpass filter, whereas bipolar intracardiac electrograms from all catheters used were acquired with a filter bandwidth of 30 - 500 Hz and amplified at high gain (0.1 mV/cm). The recording displayed at a sweep speed of 150 msec and the stimulation with a 2-ms output pulse width set at 4 times the threshold amplitude were performed using a cardiology monitoring system (Manta Electrophysiology).

Firstly, one 5F decapolar catheter (5F Supra CS catheter, Biosense Webster) was placed through left brachial vein, within the coronary sinus (CS) with the proximal electrode pair positioned at the ostium. Hence, two catheters were introduced through the right femoral vein into the right atrium. This allowed the insertion and movement of the catheters up into the heart under X-ray guidance, in particular one 7F 20 electrodes catheter (Livewire Duo-Decapolar, St. Jude Medical) that was placed anterior to the crista terminalis at the right free wall close to the tricuspid annulus and an 8F/8-mm-tip electrode deflectable catheter (Blazer II XP, Boston EP Technologies) used as mapping/ablation catheter in all patients.

Fluoroscopic examination during catheter-electrode mapping and ablation procedures was usually performed using frontal and oblique projections. We used the frontal view to introduce and position catheters in the right ventricular apex and in lateral free wall of the right atrium. Left anterior oblique (LAO) projection, a 45-degree tilt, was generally used to catheterize the CS.

Coronary sinus activation sequence.

If the patient was in AFL at the time of the procedure, AFL was diagnosed when the intracardiac electrogram, displayed the following activation sequence: high right atrium then low right atrium, a counterclockwise IVC–tricuspid isthmus activation sequence followed by left atrial activation

established with the decapolar catheter. Therefore, the CS activation sequence was always from proximal to distal (Fig. 27). Together with the typical ECG findings, a proximal-to-distal CS activation sequence was not considered diagnostic for, but rather was believed highly suggestive of CTI-dependent flutter as the underlying tachycardia mechanism.
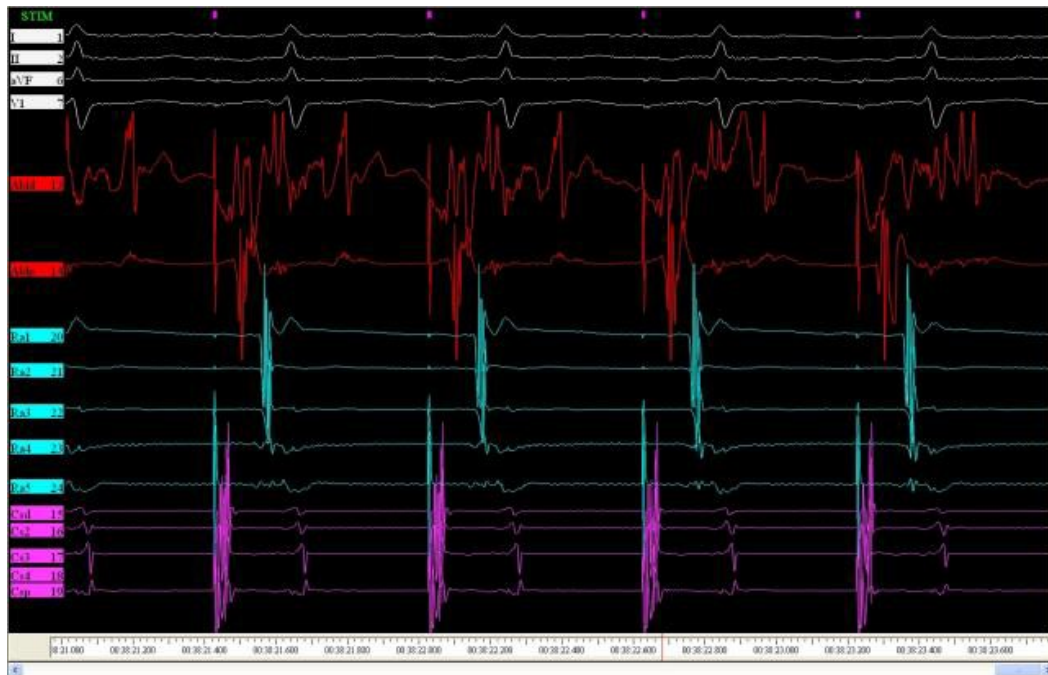
Figure 27. Coronary sinus (CS) activation sequence is always from proximal to distal in typical atrial flutter. It is possible to see a continuous potential recorded by ablation catheter.

Endocardial mapping.

Once the diagnosis of CTI-dependent flutter was suspected from the surface ECG and the CS activation sequence, more detailed intra-atrial mapping was performed. Using the CS as a stable reference, putting mapping/catheter ablator approximately within the right atrium and around the tricuspid annulus, the direction of impulse propagation during tachycardia was evaluated. For the majority of patients with CTI-dependent counterclockwise flutter, the atrial electrogram recorded on

the mid-isthmus lies within the plateau phase of the flutter wave.

Concealed Entrainment and Post Pacing Interval.

As we know, entrainment can be employed in the right atrium and CS, to confirm and exclude the right and left atria as the chamber of arrhythmia origin respectively [5,56,105]. Entrainment involves pacing from multiple, separate sites within the right atrium at cycle lengths of 10-20ms faster than the tachycardia cycle length, observing its effect on flutter wave morphology and estimating proximity of pacing site to tachycardia circuit by analysis of the post pacing interval (PPI). The pacing site is considered to lie within the tachycardia circuit when the PPI is within 30 mses of the tachycardia cycle length. Entrainment from sites which are outside the flutter circuit will demonstrate manifest fusion on the surface ECG and the PPI will exceed the flutter cycle length by more than 30 msec. In our study, if the patient was in AFL, an isthmus participation in the arrhythmic circuit was demonstrated by entrainment maneuvers (concealed entrainment in the isthmus) (Fig. 28).

Many patients with a history of AFL who were been referred for ablation procedure were in sinus rhythm at the time of their procedure. If the 12 leads electrocardiogram recorded during the clinical arrhythmia was consistent with CTI-dependent flutter, and the medical history gave no cause to suspect a left atrial origin, RF ablation of the CTI directly was performed. No attempt AFL induction, but preserved bidirectional isthmus conduction was only verified under stimulation from proximal pole of CS catheter.
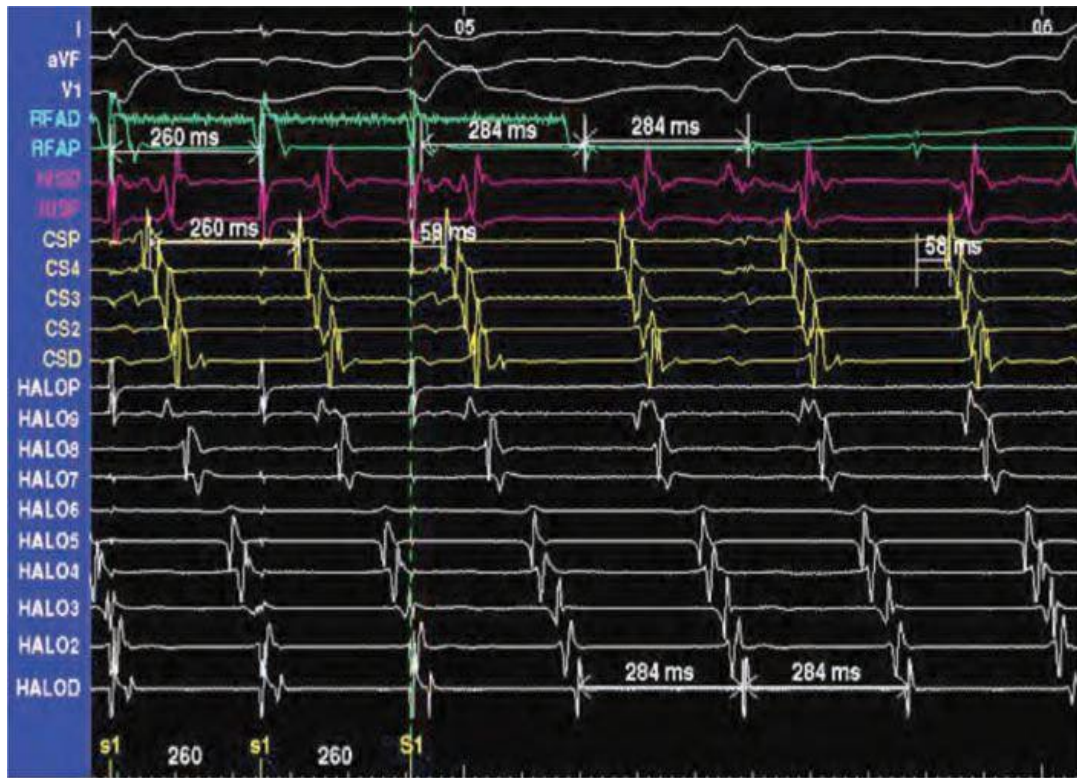
A

B

Figure 28. Endocardial electrograms from the RF, Halo, CS, and His bundle catheters, and surface ECG leads I, aVF, and V1, demonstrating concealed entrainment during pacing at the CTI in typical AFL (A) and reverse typical AFL (B). Halo D-Halo P, bipolar electrograms from the distal to proximal poles of the Halo catheter around the TVA; CSP-D, bipolar electrograms recorded from the proximal to distal CS catheter electrode pairs; HISP&D, bipolar electrograms recorded from the proximal and distal His bundle catheter; RFAP&D, bipolar electrograms recorded from the proximal and distal electrode pairs of the mapping/ablation catheter at the CTI.

From Feld GK, Srivatsa U, Hoppe B. Ablation of isthmus dependent atrial flutters. In: Huang SS, Wood MA, editors. Catheter ablation of cardiac arrhythmias. Philadelphia: Elsevier; 2011.

Radiofrequency Catheter Ablation.

Ablation was performed in the patient's presenting rhythm, be it flutter or sinus rhythm. In the case of the latter, continuous pacing was performed from the proximal pole of the CS (cycle length 600 msec) as this location is more stable than a pacing catheter positioned in the inferolateral right atrium.

RF delivery using 8mm tip ablation catheter was applied point-by-point. Ablation was started at the tricuspid annulus site (the CTI end) when a stable electrogram with a small atrial and large ventricular amplitude was observed (a:V electrogram amplitude ratio was of ~1:2). The ablation catheter was placed at 6 o'clock position and was pulled back using a drag technique from the tricuspid annulus to the inferior vena cava (IVC), applying energy for up to 60 seconds at each successive ablation point. The catheter was carefully moved after each application, under fluoroscopic guidance, to produce as much as possible a linear lesion with contiguous RF points until the IVC was reached. LAO projection was used to pull back the catheter from tricuspid side until the mid-isthmus, hence frontal projection was preferred to reach the IVC. RF energy was delivered through the EPT-1000 Cardiac Ablation System Controller (EP Technologies, Inc.) with a power limit of 70W and a target temperature of 60°C.

The procedure end point was defined as a complete bidirectional isthmus block between the tricuspid valve (TV) and the IVC (posterior isthmus) described elsewhere [14,103,104,152].

The presence or absence of bidirectional isthmus conduction block was assessed during pacing from the CS ostium (Fig. 29) and low lateral right atrium at a cycle length 600 msec while performing RF delivery over the line. As it is known, a craniocaudal activation of the septum (proximal CS pole activated after His bundle region) during pacing of the low lateral right atrium indicates a counterclockwise block in the isthmus, whereas a craniocaudal activation (low after high right atrium) of the lateral right atrium during pacing of the proximal CS indicates a clockwise block. We searched for a reversal of the right atrial depolarization sequence established by a complete cavotricuspid map using a multipolar mapping catheter straddling the line of block [155]. We also looked for widely separated local double potentials (an isoelectric interval >100msec) along the ablation line [106,156,157], during atrial pacing [151,152] (Fig. 30 e 31).

When signs of conduction block were observed during RF application with proximal CS pacing, one extra RF application lasting 1 minute was performed at that site, again. In patients with AFL,

ablation was continued also after AFL interruption was obtained during RF application. Ablation was continued until isthmus block was achieved (Fig. 32).

The persistent status of the bidirectional block was assessed continuously over the 30-minute period after bidirectional block occurrence. On occasion, conduction resumed after ablation. A complete RF ablation sequence was reinitiated until the bidirectional block was observed again, resetting the 30-minute waiting period.

A cumulative time of RF delivery defined as the time [min] to achieve bidirectional CTI block, measured from the first RF application was recorded, and procedure time defined as skin-to-skin total time spent for procedure, including time to search for venous approach, catheter positioning and RF ablation, proof of bidirectional block, maneuvers to delineate the patient's CTI anatomy were calculated.
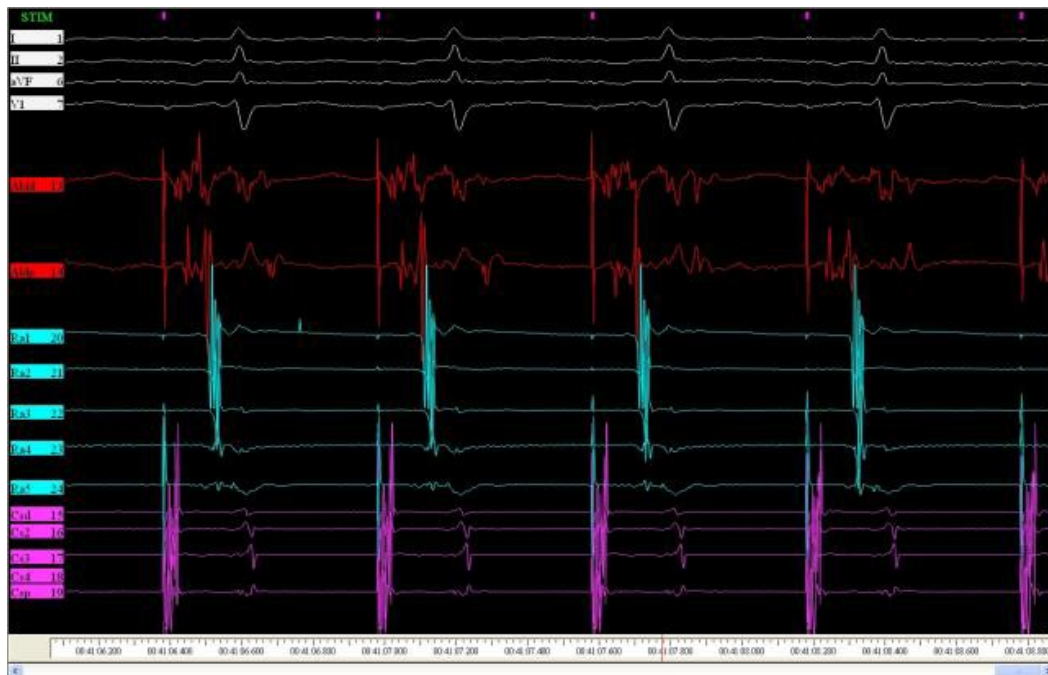
Figure 29. The presence or absence of bidirectional isthmus conduction block was assessed during pacing from the coronary sinus ostium (purple). It is possible to see a continuous potential recorded by ablation catheter (red), again.

Figure 30. During pacing from the coronary sinus ostium (purple). It is possible to see a continuous potential recorded by distal electrode ablation catheter (gap), and a narrow double potential recorded by proximal electrode ablation catheter (red).
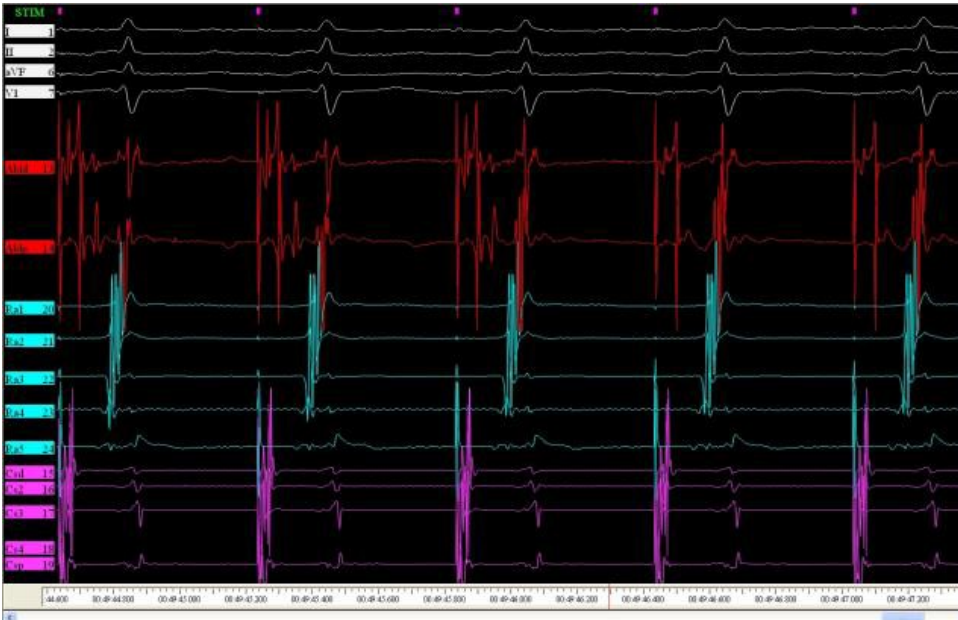
Figure 31. Bidirectional isthmus conduction block assessed during pacing from the coronary sinus ostium (purple). Note reversal activation of the right atrial depolarization sequence recorded by multipolar mapping (blue). It is possible to see widely separated double potentials recorded by ablation catheter (red).

Figure 32. Surface ECG leads I, aVF, and V1 and endocardial electrograms from the coronary sinus catheter (CSP-D), the ablation catheter (CARTO P&D), and power, impedance, and temperature readouts, show termination of AFL and restoration of sinus rhythm immediately after initiating ablation near the tricuspid valve annulus.

From: Huang SS, Wood MA, editors. Catheter ablation of cardiac arrhythmias. Philadelphia: Elsevier; 2011.)

Cavotricuspid Isthmus Anatomy Classification.

Previous anatomic and angiographic reports studying human hearts have pointed to the anatomic variability of the isthmus, reporting a variable width and different morphologies of CTI [18,19,140]. Some authors revealed variable isthmus anatomy makes the catheter ablation a difficult task and they advised to adjust strategy for improving its efficacy and safety [148]. In particular, the presence of Eustachian valve or concave isthmus was associated with statistically more RF applications, and the same trend was seen for patients with deep pouches [140].

In our study, CTI was classified into groups: (A) simple (flat) CTI, (B) complex (pouch-like recess

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or concave shape) CTI, according to anatomy features found during ablation procedure. During procedure, additional pull back maneuvers were performed septally and laterally to the initial line of ablation to further delineate the patient's CTI anatomy. The CTI length was measured as the shortest linear distance between the lower hinge point of the tricuspid annulus and the IVC using frontal fluoroscopic projection. We carefully looked for deep recesses in order to assess their position along CTI. Procedures were classified as "difficult" if we found deep recesses. All remaining procedures were considered as "easy".

Follow-Up.

After the hospital discharge, usually next day, Class I or III AADs were prescribed to all patients with previous concomitant AF. Aspirin 160 mg was administered for four weeks unless systemic anticoagulation with warfarin or NAO was indicated. In this case warfarin continued to be administered for at least four weeks.

Outpatient follow up included 12-lead ECG, and Holter ECG monitoring, scheduled at months 3, 6, and 12. Patients were encouraged to contact one of the physicians if they experienced recurrent palpitations.

ANATOMY STUDY

We examined 104 formalin-fixed hearts from patients who underwent routine clinical autopsy performed at the Cardiovascular Pathology Unit, University of Padua. The exclusion criteria corresponded to severe alteration of the heart specimen due to preexisting pathologies or inadequate preservation/dissection technique. The cause of death was primary cardiac in almost half of the

population (47% of patients), but only the cases in which the pathology did not involve the right ventricle were selected. 4 patients (3,8%) had a history of atrial flutter and were analyzed separately.

Macroscopic analysis.

The gross examination of the cardiac specimen in every clinical autopsy at our Center is performed according to the minimum standard required in the routine autopsy practice for the adequate assessment of cardiac death in the general population [158]. Focusing on the right side of the heart, the superior vena cava is transected 2 cm above the point where the crest of right atrial appendage meets the superior vena cava (to preserve sinus node), while the inferior vena cava is transected close to the diaphragm. The right atrium is opened from the inferior vena cava to the apex of the right atrial appendage. Once emptied of blood, the total heart weight is assessed. At the end of the diagnostic procedure, the hearts are fixed in 10% neutral buffered formalin solution. In order to display the area of interest, the right atrium was opened by cutting the anteroposterior commissure of the tricuspid valve along the acute margin. The CTI is a quadrilateral area of the right atrial wall bounded posteriorly by the Eustachian valve and ridge, medially by a line traced between the superior extent of the ridge of the Eustachian valve and the tricuspid orifice at the base of the triangle of Koch superomedially (the so called paraseptal isthmus), anteriorly by the septal tricuspid leaflet attachment and laterally by a line from the terminal crest to the right end of the septal leaflet (the so called inferolateral isthmus). The vertical line dividing this quadrilateral area in two almost symmetrical parts is the central isthmus [18,149] (Fig. 33). Every heart was examined by two independent expert cardiovascular pathologists. The following features were assessed:

1. The length of the central isthmus

2. The presence of pouch-like recesses

3. The number of the pouch-like recesses

4. The position of the pouch-like recesses
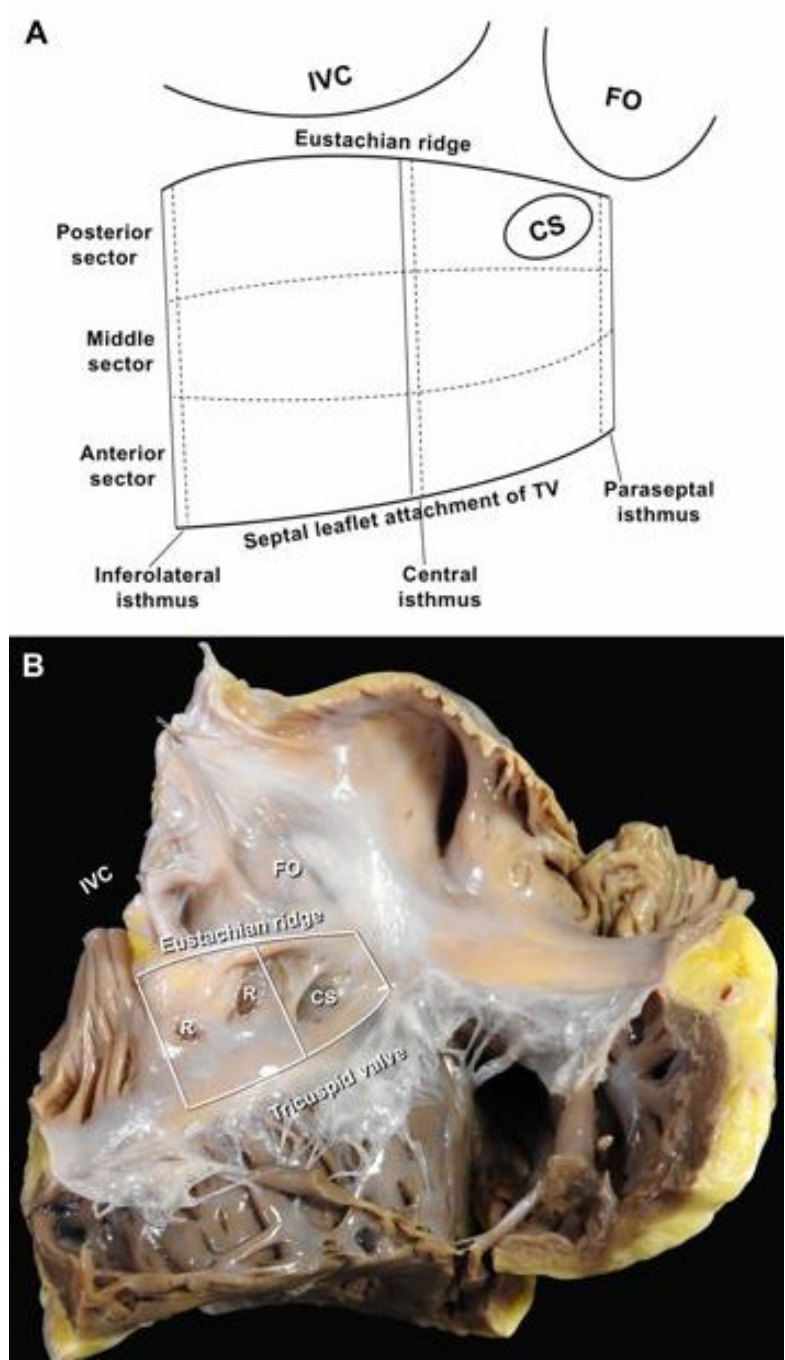
Figure 33. (A) Schematic view of the CTI region. (B) Photograph of a heart specimen in which the area of interest is highlighted. IVC, inferior vena cava; FO, foramen ovale; CS, coronary sinus; TV, tricuspid valve; R, recess.

Histological analysis.

The CTI was subdivided into three segments (from the Eustachian ridge to the tricuspid valve attachment): the posterior, the middle and the anterior sector (Fig. 34). Full thickness samples of the right atrial wall were taken in a sagittal plane, including the three sectors, at three different levels (the two lateral borders of the CTI and the central isthmus), as previously described [16]. The blocks were then processed for histological examination. The paraffin-included sections (5 μm thick) underwent serial cutting, deparaffinization and staining by hematoxylin-eosin and Heidenhain trichrome. Histological sections stained by Heidenhain trichrome were observed at light microscope (Olympus; BX51 lenses) at different magnifications and after digitally acquired in .jpeg format. At every level (inferolateral, central and paraseptal isthmus), the distance from epicardium to endocardium was measured in every sector (posterior, middle and anterior). The distance from the endocardium to the right coronary artery was also measured. The morphometric analysis was performed with an image analyzer system and a commercially available software (Image-Pro Plus Version 4.0, Media Cybernetics, MD, USA). Two observers, blind to clinical data, performed the morphometric analyses.
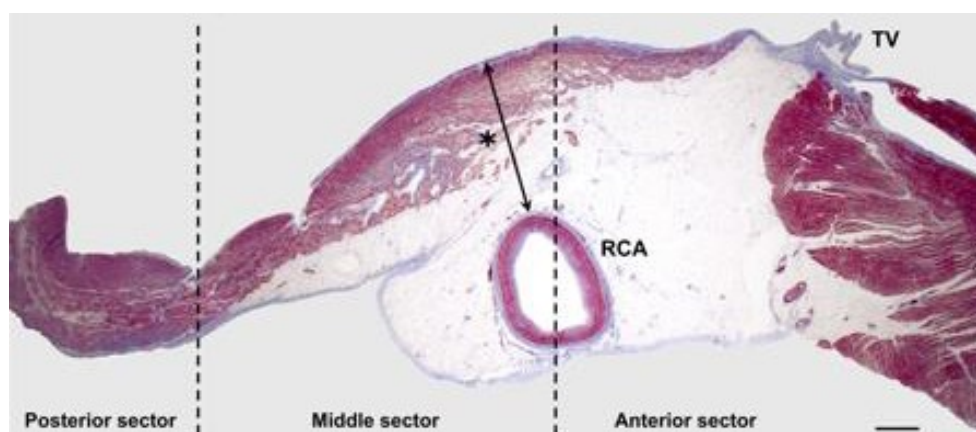
Figure 34. Histological section of the inferolateral isthmus of an illustrative case. The three sectors of the CTI (posterior, middle and anterior) are indicated. The myocardial thickness is measured at these three levels. The minimal distance between the adventitia of the right coronary artery and the endocardium is also assessed (*). TV, tricuspid valve; RCA, right coronary artery. Heidenhaim trichrome stain. Scale bar = 1 mm.

Statistical Analysis.

Continuous variables were expressed as mean ± standard deviation. Discrete variables are presented as absolute and percentages.

Categorical variables were compared by Chi-Square Test. The comparison between patients underwent ablation who had a simple CTI anatomy and those had a complex anatomy groups were analyzed by Student's unpaired (two-sample) *t* test for continuous variables. A probability value <0.05 was considered as statistically significant.

The same statistical analysis was used for both ablation and anatomy data.

All analyses were performed by the Stata software version 11.0.

RESULTS

ABLATION

Patients' characteristics.

Over a period of 54 months, a total of 337 patients underwent first time AFL ablation. Mean age of all patients was 62.8 ± 10.6 years (range 28 - 84), male was 236 (70%). Structural heart disease was present in 186 of 337 patients (55.2%). Hypertensive cardiomyopathy in 134 (39.8%) and ischemic heart disease in 29 (8.6%) were the most frequent diseases. Two hundred and thirty two of the 337 patients (68.8%) had a history of AFL and AF. Before ablation, 64 (19%) patients were on amiodarone therapy, 163 (48.4%) were on class IC drugs (propafenone and flecainide) therapy. In 93 patients (27.6 %) of the latter group, drug converted AF into AFL. One hundred and sixteen (34.4%) used warfarin and 93 (27.6%) used NAO. External electrical cardioversion had been performed in 64 patients (19%)

because they had previously decided not to accept ablation at first. Tab. I summarizes clinical baseline patients characteristics.

	CTI A (Simple, Flat) n=300	CTI B (Complex, with Recesses) n=37	P value
Age (years) (mean ± SD) range	63.5±9.7 42-84	59.6±14.2 28-76	NS
Left Atrial Size (mm) (mean ± SD) range	39.1±7.6 30-52	37±12 32-50	NS
EF (%) (mean ± SD) range	62.1±7.4 56-69	64.1±4.5 59-70	NS

Table I. Clinical baseline patients characteristics. EF, Left Ventricle Ejection Fraction.

Radiofrequency catheter ablation.

Total mean CTI length was 23.3 ± 3.9 mm (range $10 - 35$ mm). Deep recesses were found in 37 patients (10.9%), males were 24 (64.9%). Recesses finding was not related to aging, gender, left atrial size, and left ventricle ejection fraction ($p=NS$). On the contrary, CTI length was shorter in type A anatomy as compared to type B $(22.9 \pm 3.2$ vs $25.6 \pm 6; p = 0.01)$.

The primary endpoint of efficacy defined as bidirectional CTI block, was reached in 99.4% (335/337) of cases with no difference between groups. Acute ablation failure (n = 2 patients) was associated with type B CTI anatomy. There was no difference in procedure success among the different three operators ($p = NS$). Total mean radiofrequency application time for all procedures was 8.7 ± 3.7

minutes (range 3 – 25 minutes). The amount of radiofrequency application time, to achieve bidirectional isthmus block, during the procedure was significant shorter in type A CTI anatomy as compared to type B (8.3 ± 3 min vs 10.7 ± 6 min; *p = 0.025*) respectively; that demonstrates ablation is more difficult in case of complex anatomy.

Regard to the secondary endpoints, complication occurred in 1 patient (0.29%) with the CTI type B anatomy: a steam pop immediately followed by cardiac tamponade required urgent pericardiocentesis that solved complication.

Total mean procedure time was 51.6 ± 14.4 minutes, no statistically difference between two groups (*p* = NS). Tab. II shows procedure and ablation parameters for each group.

	CTI A (Simple, Flat) n=300	CTI B (Complex, with Recesses) n=37	P value
CTI Length (mm) (mean ± SD) **range**	**22.9±3.2** **10-29**	**25.6±6** **10-35**	**0.01**
RF Application Time (min) (mean ± SD) **range**	**8.3±3** **3-17.8**	**10.7±6** **4.6-25**	**0.025**
Procedure Time (min) (mean ± SD) **range**	**50.4±14.2** **20-110**	**57.3±14.5** **30-90**	**NS**

Table II. Procedure and ablation parameters.

Follow-Up.

After a mean follow-up time of 36.7 ± 17.2 months (range 4–54 months), 99.7% (334/335) of patients were free of AFL recurrences. Typical AFL recurred in 1 symptomatic patient with CTI type B anatomy. AFL was documented at 24 hours Holter ECG monitoring and 12 lead ECG. The patient underwent second ablation procedure. Conduction across the ablation line was demonstrated. Successful ablation was performed. No new recurrences have occurred until this time.

At the end of follow up 184 of 335 patients (54.9%) were treated with AADs; 39 (11.6%) patients with amiodarone, 145 (43.3%) with flecainide.

ANATOMY

The mean age of the individuals was 67 ± 17 years, with a male prevalence (65%). The mean heart weight was 457 ± 102 g. The length of the central isthmus was 24 ± 4.1 mm (range 15 - 38 mm) without differences between groups (24.1 vs 23.6, $p = NS$), respectively. The central isthmus in the patients affected by atrial flutter was significantly longer compared to the other cardiac specimens ($p < 0.01$). In 10 of our cases (9.6%), a sub-Eustachian recess was present. As in the clinical series of patients undergoing ablation, the presence of recesses was not related to aging and gender. The recess was single in the majority of cases (60%) and the most frequent location was the central isthmus (60%). In the 4 cases diagnoses with atrial flutter, no recess was found in the CTI. The highest number of recesses found in one specimen was 3 (Fig. 35).

Figure 35. Photograph of hearts in which one and more recesses were found. * , coronary sinus; Black arows, recesses

The examination of the myocardial thickness at the different levels is displayed in Tab. III. The regions with the thinnest muscular wall resulted to be the anterior and middle paraseptal and middle central.

	Sector		
Level	Posterior	Middle	Anterior
Inferolateral (mean ± SD)	3.0 ± 2.4	1.7 ± 1.3	2.5 ± 0.4
range	1.2 – 6.5	0.2 – 2.8	2.3 – 3.1
Central (mean ± SD)	1.9 ± 1.7	1.0 ± 0.9	2.1 ± 0.8
range	0.7 – 4.3	0.1 – 2.2	1.5 – 3.3
Paraseptal (mean ± SD)	2.6 ± 1.8	1.0 ± 1.2	0.9 ± 0.8
range	0.9 – 5.1	0.2 – 2.7	0.2 – 1.9

Table III. Mean myocardial thickness (mm) across the three different levels and three sectors of the CTI.

The assessment of the distance between the endocardium and the right coronary artery is described in Tab IV and the sizes, diameter and area, of recesses in Tab V.

Level	Distance
Inferolateral (mean ± SD)	6.2±2.5
range	3.7-8.4
Central (mean ± SD)	6.1±3.6
range	0.9-8.7
Paraseptal (mean ± SD)	4.0±2.6
range	0.7-4.5

Table IV. Mean minimal distance (mm) between endocardium and right coronary artery.

	Number of recesses	Diameter (mm)	Area (mm^2)
Case 1	3	2.1 3.1 3.7	1.6 3.2 4.9
Case 2	1	8.4	47.5
Case 3	2	5.4 14.6	11.0 115.7
Case 4	1	3.7	9.6
Case 5	1	2.5	3.3
Case 6	1	11.5	73.1
Case 7	1	16.5	41.4
Case 8	1	15.3	103.2
Case 9	2	3.4 2.9	4.6 3.6
Case 10	1	3.7	6.7

Table V. Sizes of recesses.

DISCUSSION

This study investigated the relationship between CTI anatomy and AFL ablation and confirms that catheter ablation of typical AFL involving the CTI is a safe, effective, and well-established ablation procedure. Nevertheless, as other papers reported, it appears that the CTI anatomy impacts ablation parameters and that is why ablation can become difficult in some patients, depending of their complex CTI anatomy that influences inevitably ablation outcomes. In particular, the reported complex anatomy typically addresses tissue thickness, pouches or muscular bridges or trabeculae [23, 147], but especially pouch-like recess and/or long CTI. All these features are associated with reduction of success rate and with prolonged procedure time, increasing ablation complications. More RF energy applications and a prolong fluoroscopy time are needed in patients with complex CTI morphologies [153-154].

In our study, both CTI length and characteristics, such as the presence of pouch-like recesses, were factors associated statistically with more RF applications. In other words, with a more difficult ablation. Nevertheless, the procedure time was not different between groups. Moreover, it is important to mention that the acute success rate, defined as bidirectional block achieved during the ablation procedure, was high in both group, the duration of the procedure was about equal and the arrhythmia recurrence rates were very low, as well. In our series, although small numbers, we cannot ignore all (2) ablation failures and all recurrences (1) were associated with a complex CTI anatomy.

This finding leads basically to some considerations:

1) electrophysiologists should have appropriate anatomic knowledge and relevant experience. Knowledge of the detailed anatomy of CTI region can significantly improve the safety and success rate of ablation procedures.

2) Sub-Eustachian recesses are common findings with a prevalence reaching 47-80% [16,20,140,149]. In our series, the recesses prevalence was 10.9% in ablation population and 9.6 % in anatomy study. The apparent disparity with the previous series published in the literature

found an explanation in the different definition of recesses. In fact, we focused the attention on those "pouch-like" since they are likely to represent an obstacle to catheter ablation. Noteworthy, our anatomical data are confirmed by our electrophysiological data in different population. We found recesses at mid-isthmus and at the IVC side. We never found them at the TV side. Other authors found intertrabecular recesses and trabecular bridges laterally to the sub-Eustachian recesses located in the middle CTI sector [149]. Since the presence of sub- Eustachian recesses was associated with significant prolonged ablation time, and a higher risk of complications, with a lower rate of success [137, 148], evaluating their presence along CTI would be useful in planning ablation strategy. In our opinion, hence, search for recesses should become a common approach before starting of RF applications to adjust ablation goal in order to perform lesion line far from recesses.

3) Frequently, the area immediately anterior to the IVC ostium is composed mainly of fibrous and fatty tissue, with minimal muscular fibers coursing through it. The clinical implication is that this part of the CTI could need less RF energy to form lesion. 4) Actually, a non uniform terminology exists between electrophysiologists and pathologists. Nowadays, a unique nomenclature should be better find out, in order to favor dialogue among the specialists. A consensus in the terminology should increase the comprehension and the collaboration finalized to improve work of each other.

Clinical implications.

The majority of anatomical obstacles in patients candidates to CTI ablation are unfortunately detected only at the time of procedure. The purpose of our study was to review the anatomy and electrophysiology of the CTI in order to improve acute and long-term outcome of RF ablation for the patients with AFL, despite the complexity of the anatomy.

We found that in patients with pouch-like recesses, the CVI is longer and more RF energy application is needed to achieve CTI block when compared with CVI simple. However, we cannot exclude that the thickness of the myocardium can influence the RF energy level.

Look for the recesses within CTI may facilitate the choice of ablation technique. CTI anatomy and thickness should be better defined before starting ablation. That should lead to improve success rate and reduce the ablation complications.

STUDY LIMITATIONS

Ablation

The primary limitation of our study is that a single center is involved. Another limit was that AADs were advised at the discharge to 54.9% patients having pre-ablation history of AF. Therefore, our results on post-ablation AFL recurrence do not reflect the pure effect of trans-isthmic ablation but rather the combination of pharmacological and ablative treatments in almost more half population. Furthermore, the effect of anatomy of the isthmus on fluoroscopy time was not among the considered variables.

Anatomy

The limitations of this study reside on the fact that all of the measurements were made on autopsied, structurally normal heart specimens that had been fixed in formaldehyde. This fixing might have resulted in some slight changes in the size and shape of the hearts. However, the use of 10% paraformaldehyde did not cause significant changes in the dimensions of the atrial tissue; the dimensions of fixed hearts are similar to those that are unfixed. In our study we revealed, in a real world scenario, that length of CTI was shorter in patients with simple CTI (group A) than in patients with complex CTI (group B). These data have not been confirmed by analysis on the autopsy hearts, perhaps for reasons described above or for a low number of hearts examined.

CONCLUSIONS

Our electrophysiological and anatomical study has provided relevant information to clinical practice. Catheter ablation of typical AFL involving the CTI has been confirmed to be a safe, effective, and well-established ablation procedure. Nevertheless, the CTI anatomy impacts ablation parameters, such as RF energy application. Moreover, difficult procedures are associated with longer CTI. Recesses can complicate ablation, and knowing where they might be present is useful to avoid them. Therefore, success rate and ablation complications can be optimized by a deep knowledge of anatomy and centre experience.

REFERENCES

1. Einthoven W. The telecardiogramme. Arch Internat Physiol 1906;4:132–141.

2. Lewis T. Observations upon a curious and not uncommon form of extreme acceleration of the auricle: atrial flutter. Heart 1913;4:171–178.

3. Lewis T, Drury AN, Iliesc TT. A demonstration of circus movement in clinical flutter of the auricles. Heart 1921;8:341.

4. Puech P, Latour H, Grolleau R. Le flutter et seslimites. Arch Mal Coeur 1970;61:116–124.

5. Waldo AL, MacLean WAH, Karp RB, et al. Entrainment and interruption of atrial flutter with atrial pacing: studies in man following open heart surgery. Circulation 1977;56:737–744.

6. Allessie MA. Lammers W, Bonke FIM, et al. Intra-atrial reentry as a mechanism for atrial flutter by acetylcholine and rapid pacing in the dog. Circulation 1984;70:123-131.

7. Boineau JP. Atrial flutter: a synthesis of concepts. Circulation 1985;72:249-257.

8. Disertori M, Inama G, Vergara C, et al. Evidence of a reentry circuit in the common type of atrial flutter in man. Circulation 1983;67:434-440.

9. Frame LH, Page RL, Hoffman BF. Atrial reentry around an anatomic barrier with a partially refractory excitable gap. A canine model of atrial flutter, Circ Res 1986; 58:495-511.

10. Olshansky B, Okumura K, Hess PG, et al. Demonstration of an area of slow conduction in human atrial flutter. J Am Coll Cardiol 1990;16:1639-1648.

11. Cosio FG, López-Gil M, Goicolea A, et al. Radiofrequency ablation of the inferior vena cava-tricuspid valve isthmus in common atrial flutter. Am J Cardiol 1993;71(8):705–709.

12. Fischer B, Haissaguerre M, Garrigues S, et al. Radiofrequency catheter ablation of common atrial flutter in 80 patients. Journal of the American College of Cardiology. 1995;25:1365–1372.

13. Saoudi N, Cosio F, Waldo A, et al. Classification of atrial flutter and regular atrial tachycardia according to electrophysiologic mechanism and anatomic bases: a statement from a joint expert group from the Working Group of Arrhythmias of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. J Cardiovasc Electrophysiol 2001;12:852–66.

14. Cauchemez B, Haissaguerre M, Fischer B, et al. Electrophysiological effects of catheter ablation of inferior vena cava-tricuspid annulus isthmus in common atrial flutter. Circulation 1996; 93:284–294.

15. Tai CT and Chen SA. Cavotricuspid Isthmus: Anatomy, Electrophysiology, and Long-Term Outcome of Radiofrequency Ablation. PACE 2009; 32:1591–1595.

16. Cabrera JA, Sanchez-Quintana D, Farre J, et al. The inferior right atrial isthmus: Further architectural insights for current and coming ablation technologies. J Cardiovasc Electrophysiol 2005;16:402–408.

17. Waki K, Saito T, Becker AE. Right atrial flutter isthmus revisited: Normal anatomy favors nonuniform anisotropic conduction. J Cardiovasc Electrophysiol 2000;11:90–94.

18. Cabrera JA, Sanchez-Quintana D, Ho SY, et al. The Architecture of the Atrial Musculature Between the Orifice of the Inferior Caval Vein and the Tricuspid Valve: The Anatomy ofthe Isthmus. J Cardiovasc Electrophysiol 1998; 9:1186-1195.

19. Cabrera JA, Sanchez-Quintana D, Ho SY, et al. Angiographic anatomy of the inferior right atrial isthmus in pts with and without history of common atrial flutter. Circulation 1999;99(23): 3017–3023.

20. Saremi F, Pourzand L, Krishnan S, et al. Right atrial cavotricuspid isthmus: Anatomic characterization with multi-detector row CT. Radiology 2008;247:658–668.

21. Lim KT, Murray C, Liu H, et al. Preablation magnetic resonance imaging of the cavotricuspid isthmus. Europace 2007;9:149–153.

22. Scaglione M, Caponi D, Di Donna P, et al. Typical atrial flutter ablation outcome: Correlation with isthmus anatomy using intracardiac echo 3D re-construction. Europace 2004;6:407–417.

23. Chang SL, Tai CT, Lin YJ, et al. The electroanatomic characteristics of the cavotricuspid isthmus: Implications for the catheter ablation of atrial flutter. J Cardiovasc Electrophysiol 2007; 18:18–22.

24. Balaji S, Johnson TB, Sade RM, et al. Management of atrial flutter after the Fontan procedure. J Am Coll Cardiol 1994;23:1209-1215.

25. Flack NJ, Zosmer N, Bennett PR, et al. Amiodarone given by three routes to terminate fetal atrial flutter associated with severe hydrops. Obstet. Gynecol. 1993;82 (4 Pt. 2, Suppl.):714-716.

26. Chang, JS, Chen VC, Tsai CH, et al. Successful conversion of fetal atrial flutter with digoxin: Report of one case. Acta Paediatr Sin 1994;35:229-234.

27. Wellens HJ. Contemporary management of atrial flutter. Circulation 2002;106 (6):649-652.

28. Naccarelli GV, Varker H, Lin J, et al. Increasing Prevalence of Atrial Fibrillation and Flutter in the United States. Am J Cardiol 2009; 104:1534–1539.

29. Wellens HJ. Contemporary management of atrial flutter. Circulation 2002;106:649–652.

30. ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS.The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC). Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Endorsed by the European Stroke Organization (ESO). European Heart Journal 2016;37:2893–2962.

31. AHA/ACC/HRS Guideline for the Management of Pts With Atrial Fibrillation: Executive Summary. A Report of the American College of Cardiology/American Heart Association Task

Force on Practice Guidelines and the Heart Rhythm Society. J Am CollCardiol 2014;64 (21):e1- e76.

32. Vadmann H, Nielsen PB, Hjortshoj SP, et al. Atrial flutter and thromboembolic risk: a systematic review. Heart 2015;101:1446–1455.

33. Bertaglia E, Zoppo F, Bonso A, et al. Long term follow up of radiofrequency catheter ablation of atrial flutter: clinical course and predictors of atrial fibrillation occurrence. Heart 2004;90:59–63.

34. Seara JG, Roubin SR, Gude-Sampedro F, et al. Risk of atrial fibrillation, stroke, and death after radiofrequency catheter ablation of typical atrial flutter. Clin Res Cardiol 2014;103:543–552.

35. Brembilla-Perrot B, Girerd N, Sellal JM, et al. Risk of atrial fibrillation after atrial flutter ablation: impact of AF history, gender, and antiarrhythmic drug medication. J CardiovascElectrophysiol 2014;25:813–820.

36. Crijns HJGH, Van Gelder IC, Kingma JH, et al. Atrial flutter can be terminated by a class III antiarrhythmic drug, but not by a class I C drug. Eur Heart J 1994;15:1403–1408.

37. Tai CT, Chen SA, Chiang C-E, et al. Characterization of low right atrial isthmus as the slow conduction zone and pharmacological target in typical atrial flutter. Circulation 1997;96:2601– 2611.

38. Cosio FG, Delpon E. New anti-arrhythmic drugs for atrial flutter and atrial fibrillation: a conceptual breakthrough at last? Circulation 2002;105:276–278.

39. Roden RM. Risks and benefits of antiarrhythmic therapy. N Engl J Med 1994; 331: 785–791.

40. Bronis K, Metaxa S, Koulouris S, et al: Review of a novel atrial selective antiarrhythmic agent and its place in current treatment of atrial fibrillation. Hosp Chronicles 2012;7:171–181.

41. Nair M, George LK, Koshy SK. Safety and efficacy of ibutilide in cardioversion of atrial flutter and fibrillation. J Am Board Fam Med 2011;24:86–92.

42. Volgman AS, Carberry PA, Stambler B, et al. Conversion efficacy and safety of intravenous ibutilide compared with intravenous procainamide in patients with atrial flutter or fibrillation. J Am Coll Cardiol 1998;31:1414–1419.

43. Vos MA, Golitsyn SR, Stangl K, et al. Superiority of ibutilide (a new class III agent) over DL-sotalol in converting atrial flutter and atrial fibrillation. Heart 1998;79:568–575.

44. Botteron GW, and Smith JM. Spatial and temporal inhomogeneity of adenosine's effect on atrial refractoriness in humans: Using atrial fibrillation to probe atrial refractoriness. J CardiovascElectrophysiol 1994;5:477-484.

45. Shettigar UR, Toole JG, Appunn AO. Combined use of esmolol and digoxin in the acute treatment of atrial fibrillation or flutter Am Heart J 1993;126:368-374.

46. Singh S, Zoble RG, Yellen L, et al. Efficacy and safety of oral dofetilide in converting to and maintaining sinus rhythm in patients with chronic atrial fibrillation or atrial flutter: the symptomatic atrial fibrillation investigative research on dofetilide (SAFIRE-D) study. Circulation 2000;101: 2385–2390.

47. Lown B, Amarasingham R, Neuman J. New method for terminating cardiac arrhythmias: use of synchronized capacitor discharge. JAMA 1962;182:548–555.

48. Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC Guidelines for the management of pts with atrial fibrillation: executive summary. J Am CollCardiol 2006;48:854–906.

49. Reisinger J, Gstrein C, Winter T, et al. Optimization of initial energy for cardioversion of atrial tachyarrhythmias with biphasic shocks. Am J Emerg Med 2010;28:159–165.

50. Pinski SL, Sgarbossa EB, Ching E, et al. Acomparison of 50-J versus 100-J shocks for direct-current cardioversion of atrial flutter. Am Heart J 1999;137:439-442.

51. Tucker KJ, and Wilson C. A comparison of transesophageal atrial pacing and direct current cardioversion for the termination of atrial flutter: A prospective randomized clinical trial. Br Heart J 1993;69:530-535.

52. Manolis AS, Dragazis I, Kapelakis I, et al. Transesophageal overdrive pacing: A simple and versatile tool. Hosp Chronicles 2013;8:143–145.

53. Poulidakis E, Manolis AS. Transvenous temporary cardiac pacing. Rhythmos 2014;9:20–27.

54. Yoshitake N, Tanoiri T, Nomoto J, et al. Patterns of interruption of atrial flutter induced by rapid

atrial pacing. JpnCirc J 1990;58:181-189.

55. Baeriswyl G, Zimmerman M, and Adamec R. Efficacy of rapid atrial pacing for conversion of atrial flutter in medically treated pts. ClinCardiol 1994;17:246-250.

56. Cosio FG, Lopez GM, Arribas F, et al. Mechanisms of entrainment of human common flutter studied with multiple endocardial recordings. Circulation 1994;89:2117-2125.

57. Cochrane AD, Siddins M, Rosenfeldt FL, et al. A comparison of amiodarone and digoxin for treatment of supraventricular arrhythmias after cardiac surgery. Eur J CardiothoracSurg 1994;8: 194-198.

58. Crijns, HJ, Van Gelder IC, Lie KI. Benefits and risks of antiarrhythmic drug therapy after DC electrical cardioversion of atrial fibrillation or flutter. Eur Heart J 1994;15 (Suppl. A):17-21.

59. Till JA, Baxendall M, Benetar A. Acceleration of the ventricular response to atrial flutter by amiodarone in an infant with Wolff-Parkinson-White syndrome. Br Heart J 1993:70:84-87.

60. Kalman J, Fitzpatrick A, Epstein L, et al. Intracardiac echo identifies the crista terminalis and Eustachian ridge as barriers during Type I atrial flutter in man. PACE 1995;18:857.

61. Schilling RJ, Peters NS, Goldberger J, et al. Characterization of the anatomy and conduction velocities of the human right atrial flutter circuit determined by noncontact mapping. Journal of the American College of Cardiology 2001;38:385–393.

62. Shah DC, Jais P, Haissaguerre M, et al. Three-dimensional Mapping of the Common Atrial Flutter Circuit in the Right Atrium. Circulation 1997;96:3904–3912.

63. Nakagawa H, Lazzara R, Khastgir T, et al. Role of the tricuspid annulus and the eustachian valve/ridge on atrial flutter. Relevance to catheter ablation of the septal isthmus and a new technique for rapid identification of ablation success. Circulation 1996;94(3):407-424.

64. Waldo AL. Atrial flutter: new directions in management and mechanism. Circulation 1990; 81:1142-1143.

65. Schoels W, Offner B, Brachmann J, et al. Circus movement atrial flutter in the canine sterile pericarditis model: Relation of characteristics of the surface electrocardiogram and conduction properties of the reentrant pathway. J Am Coll Cardiol 1994;23:799-808.

66. Ortiz J, Nozaki A, Shimizu A, et al. Mechanism of interruption of atrial flutter by moricizine: Electrophysiological and multiplexing studies in the canine sterile pericarditis model of atrial flutter. Circulation 1994;89:2860-2869.

67. Lammers WJEP, Ravelli F, Disertori M, et al. Variations in human atrial flutter cycle length induced by ventricular beats: Evidence of a reentrant circuit with a partially excitable gap. J Cardiovasc Electrophysiol 1991;2:375-387.

68. Ravelli F, Disertori M, Cozzi F, et al. Ventricular beats induce variations in cycle length of rapid (type II) atrial flutter in humans: Evidence of leading circle reentry. Circulation 1994;89: 2107-2116.

69. Ortiz J, Niwano S, Abe H, et al.: Mapping the conversion of atrial flutter to atrial fibrillation and atrial fibrillation to atrial flutter. Insights into mechanisms. Circ Res 1994;74:882-894.

70. Pinto JM, Graziano JN, Boyden TA. Endocardial mapping of reentry around an anatomical barrier in the canine right atrium: Observations during the action of the class IC agent, flecainide. J Cardiovasc Electrophysiol 1993;4:672-685.

71. Shimizu A, Nozaki A, Rudy Y, et al. Characterization of double potentials in a functionally determined reentrant circuit: Multiplexing studies during interruption of atrial flutter in the canine pericarditis model. J Am Coll Cardiol 1993;22:2022-2032.

72. Scholes W, Kuebler W, Yang H, et al. A unified functional/anatomic substrate for circus movement atrial flutter: Activation and refractory patterns in the canine right atrial enlargement model. J Am Coll Cardiol 1993;21:738-741.

73. Waxman MB, Yao L, Cameron DA, et al.: Effects of posture, Valsalva maneuver and respiration on atrial flutter rate: An effect mediated through cardiac volume. J Am Coll Cardiol 1991;17:1545-1552.

74. Waldo, AL. Atrial flutter: Mechanisms, clinical features, and management. In Zipes DP, and Jalife J. (eds.): Cardiac Electrophysiology: From Cell to Bedside. 2nd ed. Philadelphia, W. B. Saunders Company,1994,p. 666.

75. Kalbfleisch SJ, el-Atassi R, Calkins H, et al. Association between atrioventricular node reentrant tachycardia and inducible atrial flutter. J Am CollCardiol 1993;22:80-84.

76. Interian A Jr, Cox MM, Jimenez RA, et al. A shared pathway in atrioventricular nodal reentrant tachycardia and atrial flutter: Implications for pathophysiology and therapy. Am J Cardiol 1993;71:297-303.

77. Feld GK, Mollerus M, Birgersdotter-Green U, et al. Conduction velocity in the tricuspid valve-inferior vena cava isthmus is slower in patients with type I atrial flutter compared to those without a history of atrial flutter. J Cardiovasc Electrophysiol 1997;8:1338–1348.

78. Olgin JE, Kalman JM, Saxon LA, et al. Mechanism of initiation of atrial flutter in humans: Site of unidirectional block and direction of rotation. J Am Coll Cardiol 1997;29:376–384.

79. Waxman MB, Kirsh JA, Yao L, et al. Slowing of the atrial flutter rate during 1:1 atrioventricular conduction in humans and dogs: An effect mediated through atrial pressure and volume. J CardiovascElectrophysiol 1992;3:544-557.

80. Lesh, MD, Van Hare GF, Epstein LM, et al. Radiofrequency catheter ablation of atrial arrhythmias: Results and mechanisms. Circulation 1994;89:1074-1089.

81. Epstein LM, Chiesa N, Wong MN, et al. Radiofrequency catheter ablation in the treatment of supraventricular tachycardia in the elderly. J Am CollCardiol 1994;23:1356-1362.

82. Toboul T, Saoudi N, Atallah G, et al. Catheter ablation for atrial flutter: Current concepts and results. J CardiovascElectrophysiol 1992;3:641-652.

83. Calkins H, Leon AR, Deam AG, et al.: Catheter ablation of atrial flutter using radiofrequency energy. Am J Cardiol 1994;73:353-356.

84. Isber N, Restivo M, Gough WB, et al. Circus movement atrial flutter in the canine sterile pericarditis model: Cryothermal termination from the epicardial site of the slow zone of the reentrant circuit. Circulation 1993;87:1649-1660.

85. Feld GK, Fleck RP, Chen PS, et al. Radiofrequency catheter ablation for the treatment of human type I atrial flutter: Identification of a critical zone in the reentrant circuit by endocardial mapping techniques. Circulation 1992;86:1233-1240.

86. Scheinman MM, Morady F, Hess DS, et al. Catheter-induced ablation of the atrioventricular junction to control refractory supraventricular arrhythmias. JAMA 1982;248:851–855.

87. Scheinman MM, Huang S. The 1998 NASPE prospective catheter ablation registry. Pacing and clinical electrophysiology. Pacing ClinElectrophysiol 2000;23:1020–1028.

88. Guidelines for Clinical Intracardiac Electrophysiological and Catheter Ablation Procedures. A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. (Committee on Clinical Intracardiac Electrophysiologic and Catheter Ablation Procedures). Developed in collaboration with the North American Society of Pacing and Electrophysiology. Circulation 1995;92:673–691.

89. Saoudi N, Atalla HG, Kirkorian G, et al. Catheter ablation of the atrial myocardium in human type I atrial flutter. Circulation 1990;81:762-771.

90. Cosedis Nielsen J, Johannessen A, Raatikainen P, et al. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. N Engl J Med 2012;367:1587-1595.

91. Wilber DJ, Pappone C, Neuzil P, et al. ThermoCool AF Trial Investigators. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in pts with paroxysmal atrial fibrillation: a randomized controlled trial. JAMA 2010;303:333–340.

92. Arbelo E, Brugada J, Hindricks G, et al. Atrial Fibrillation Ablation Pilot Study Investigators. The atrial fibrillation ablation pilot study: a European Survey on Methodology and results of catheter ablation for atrial fibrillation conducted by the European Heart Rhythm Association. Eur Heart J 2014;35:1466–1478.

93. Calkins H, Reynolds MR, Spector P, et al. Treatment of atrial fibrillation with antiarrhythmic drugs or radiofrequency ablation: two systematic literature reviews and meta-analyses. CircArrhythmElectrophysiol 2009;2:349–361.

94. Bandini A, Golia P, Caroli E, et al. Atrial fibrillation after typical atrial flutter ablation: a long-term follow-up. J Cardiovasc Med (Hagerstown) 2011;12:110–115.

95. Dewland TA, Glidden DV, Marcus GM. Healthcare utilization and clinical out- comes after catheter ablation of atrial flutter. PLoS One 2014;9:e100509.

96. Wazni O, Marrouche NF, Martin DO, et al. Randomized study comparing combined pulmonary vein-left atrial junction disconnection and cavotricuspid isthmus ablation versus pulmonary vein- left atrial junction disconnection alone in pts presenting with typical atrial flutter and atrial fibrillation. Circulation 2003;108(20):2479–2483.

97. Zipes DP, Di Marco JP, Gillette PC, et al. AHA/ACC guidelines for clinical intracardiac electrophysiologic procedures. Circulation 1995;92:673-691.

98. Calkins H, Brugada J, Packer DL, et al. HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for personnel, policy, procedures and follow-up. Heart Rhythm 2007;4:816–861.

99. Bun SS, Latcu DG, Marchlinski F, et al. Atrial flutter: more than just one of a kind. Eur Heart J 2015;36:2356–2363.

100. Calkins H, Hindricks G, Cappato R, et al. HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. Heart Rhythm October 2017;14(10):e275-e444.

101. Klein GJ, Guiraudon GM, Sharma AD, et al. Demonstration of macroreentry and feasibility of operative therapy in the common type of atrial flutter. Am J Cardiol 1986;57:587–591.

102. Saoudi N, Derumeaux G, Cribier A, et al. The role of catheter ablation techniques in the treatment of classic (type 1) atrial flutter. Pacing Clin Electrophysiol 1991;14(11 Pt 2):2022 -2027.

103. Poty H, Saoudi N, Aziz AA, et al. Radiofrequency catheter ablation of type 1 atrial flutter. Prediction of late success by electrophysiological criteria. Circulation 1995;92:1389-1392.

104. Poty H, Saoudi N, Nair M, et al. Radiofrequency catheter ablation of atrial flutter. Further insights into the various types of isthmus block: application to ablation during sinus rhythm. Circulation 1996;94:3204–3213.

105. Shah DC, Haissaguerre M, Jais P, et al. Atrial flutter: contemporary electrophysiology and catheter ablation. Pacing Clin Electrophysiol 1999;22:344–359.

106. Tada H, Oral H, Sticherling C, et al. Double potentials along the ablation line as a guide to radiofrequency ablation of typical atrial flutter. J Am Coll Cardiol 2001;38:750–755.

107. Feld G, Wharton M, Plumb V, et al. EPT- 1000 XP Cardiac Ablation System Investigators. Radiofrequency catheter ablation of type 1 atrial flutter using large-tip 8 or 10 mm electrode catheter and high-output radiofrequency energy genera- tor: Results of a multicenter safety and efficacy study. J Am Coll Cardiol 2004;43:1466–1472.

108. Costa AD, Cucherat M, Pichon N, et al. Comparison of the efficacy of cooled tip and 8 mm-tip catheters for radiofrequency catheter ablation of the cavotricuspid isthmus: A meta-analysis. Pacing Clin Electrophysiol 2005;28:1081–1087.

109. Feld Gk, Daubert JP, Weiss R, et al. Cryoablation Atrial Flutter Efficacy Trial Investigators. Acute and long-term efficacy and safety of catheter cryoablation of the cavotricuspid isthmus fro treatment of type 1 atrial flutter. Heart Rhythm 2008;5:1009– 1014.

110. Waldo AL, Feld GK. Inter-relationships of atrial fibrillation and atrial flutter: mechanisms and clinical implications. J Am CollCardiol. 2008;51:779 –786.

111. Halligan SC, Gersh BJ, Brown RD, et al. The natural history of lone atrial flutter. Ann Intern Med. 2004;140:265–268.

112. Moreira W, Timmermans C, Wellens HJJ, et al. Can common-type atrial flutter be a sign of an arrhythmogenic substrate in paroxysmal atrial fibrillation? Clinical and ablative consequences in pts with coexistent paroxysmal atrial fibrillation/flutter. Circulation. 2007;116:2786–2792.

113. Perez FJ, Schubert CM, Parvez B, et al. Long-term outcomes after catheter ablation of cavo-tricuspid isthmus dependent atrial flutter: a meta-analysis. Circ Arrhythm Electrophysiol 2009;2(4): 393–401.

114. Schmieder S, Ndrepepa G, Dong J, et al. Acute and long-term results of radiofrequency ablation of common atrial flutter and the influence of the right atrial isthmus ablation on the occurrence of atrial fibrillation. Eur Heart J 2003; 24:956–962.

115. Esato M, Hindricks G, Sommer P, et al. Color-coded three-dimensional entrainment mapping for analysis and treatment of atrial macro-reentrant tachycardia. Heart Rhythm 2009;6:349–358.

116. Huo Y, Schoenbauer R, Richter S, et al. Atrial Arrhythmias Following Surgical AF Ablation: Electrophysiological Findings, Ablation Strategies, and Clinical Outcome. J CardiovascElectrophysiol 2014;25:725–738.

117. Spector P, Reynolds MR, Calkins H, et al. Meta-analysis of ablation of atrial flutter and supraventricular tachycardia. Am J Cardiol 2009;104:671–677.

118. Crijns HJ, Van Gelder IC, Tieleman RG, et al. Long-term outcome of electrical cardioversion in pts with chronic atrial flutter. Heart 1997;77:56–61.

119. American College of Cardiology Cardiovascular Technology Assessment Committee: Catheter ablation for cardiac arrhythmias: Clinical applications, personnel and facilities. J Am CollCardiol 1994;24:828-833.

120. Lesh MD, Van Hare GF. Status of ablation in patient with atrial tachycardia and atrial flutter. PACE 1994;17:1026-1033.

121. Scheinman MM. Patterns of catheter ablation practice in the United States: Results of the 1992 NASPE survey. North American Society of Pacing and Electrophysiology. PACE 1994;17:873-875.

122. Hindricks G. The Multicenter European Radiofrequency Survey (MERFS): Complications of radiofrequency catheter ablation of arrhythmias. The Multicenter European Radiofrequency Survey (MERFS) Investigators of the Working Group on Arrhythmias of the European Society of Cardiology. Eur Heart J 1993;14:1644-1653.

123. Kay, GN, Epstein AE, Dailey SM, et al. Role of radiofrequency ablation in the management of supraventricular arrhythmias: Experience in 760 consecutive pts. J CardiovascElectrophysiol 1993; 4:371-389.

124. Olshansky B, Wilber DJ, Hariman RJ. Atrial flutter: Update on the mechanism and treatment. PACE 1992;15:2308-2335.

125. Patel NJ, Deshmukh A, Pau D, et al. Contemporary utilization and safety outcomes of catheter ablation of atrial flutter in the United States: Analysis of 89,638 procedures. Heart Rhythm 2016; 13(6):1317–1325.

126. Natale A, Newby KH, Pisanó E, et al. Prospective randomized comparison of antiarrhythmic therapy versus first-line radiofrequency ablation in pts with atrial flutter. J Am Coll Cardiol 2000; 35(7):1898–1904.

127. Puech P. Atrial flutter and its limits. In: Bayés A, Cosine J. Diagnosis and treatment of cardiac arrhythmias, Pergamon Press, Oxford, New York, Toronto, Sydney, Paris, Frankfurt, 1980;pp.216-231.

128. Tai CT, Chen SA, Chiang CE, et al. Long-term outcome of radiofrequency catheter ablation for typical atrial flutter: Risk prediction of recurrent arrhythmias. J Cardiovasc Electrophysiol 1998;9:115–121.

129. Paydak H, Kall JG, Burke MC, e al. Atrial fibrillation after radiofrequency ablation of type I atrial flutter: Time to onset, determinants, and clinical course. Circulation 1998;98:315–322.

130. Calkins H, Canby R, Weiss R, et al. Results of catheter ablation of typical atrial flutter. Am J Cardiol 2004;94:437–442.

131. Ellis K, Wazni O, Marrouche N, et al. Incidence of atrial fibrillation post-cavotricuspid isthmus ablation in patients with typical atrial flutter: Left atrial size as an independent predictor of atrial fibrillation recurrence. J Cardiovasc Electrophysiol 2007;18:799–802.

132. Chinitz JS, Gerstenfeld EP, Marchlinski FE, et al. Atrial fibrillation is common after ablation of

isolated atrial flutter during long-term follow-up. Heart Rhythm 2007;4:1029–1033.

133. Santangeli P, Di Biase L, Mohanty P, et al. Catheter ablation of atrial fibrillation in octogenarians: safety and outcomes. J CardiovascElectrophysiol 2012;23:687–693.

134. Bohnen M, Stevenson WG, Tedrow UB, et al. Incidence and predictors of major complications from contemporary catheter ablation to treat cardiac arrhythmias. Heart Rhythm 2011;8:1661–1666.

135. Brembilla-Perrot B, Filali ML, Zinzius PY, et al. Is ablation of atrial flutter always safe? Pacing ClinElectrophysiol 2012;35:1061–1066.

136. Deshmukh A, Patel NJ, Pant S, et al. In-hospital complications associated with catheter ablation of atrial fibrillation in the United States between 2000 and 2010: analysis of 93 801 procedures. Circulation 2013;128: 2104–2112.

137. Gami AS, Edwards WD, Lachman N, et al. Electrophysiological anatomy of typical atrial flutter: the posterior boundary and causes for difficulty with ablation. J Cardiovasc Electrophysiol 2010;21(2):144–149.

138. Kozöwski D, Hreczecha J, Skwarek M, et al. Diameters of the cavo-sinus-tricuspid area in relation to type I atrial flutter. Folia Morphol (Warsz) 2003;62(2):133–142.

139. Wang K, Ho SY, Gibson DG, et al. Architecture of atrial musculature in humans. Br Heart J 1995;73(6):559–65.

140. Heidbüchel H, Willems R, Van Rensburg H, et al. Right atrial angiographic evaluation of the posterior isthmus: relevance for ablation of typical atrial flutter. Circulation 2000;101(18): 2178–2184.

141. Marcos-Alberca P, Sanchez-Quintana D, Cabrera JA, et al. Two-dimensional echocardiographic features of the inferior right atrial isthmus: the role of vestibular thickness in catheter ablation of atrial flutter. European Heart Journal Cardiovascular Imaging 2014;15(1): 32–40.

142. Da Costa A, Mourot S, Romeyer-Bouchard C, et al. Anatomic and electrophysiological differences between chronic and paroxysmal forms of common atrial flutter and comparison with controls: an observational study. Pacing and Clinical Electrophysiology 2004;27(9):1202–1211.

143. Anselme F, Klug D, Scanu P, et al. Randomized comparison of two targets in typical atrial flutter ablation. Am J Cardiol 2000;85(11):1302–1307.

144. Lin YJ, Tai CT, Liu TY, et al. Electrophysiological mechanisms and catheter ablation of complex atrial arrhythmias from crista terminalis. Pacing Clin Electrophysiol 2004;27 (9):1231–1239.

145. Chen JY, Lin KH, Liou YM, et al. Usefulness of pre-procedure cavotricuspid isthmus imaging by modified transthoracic echocardiography for predicting outcome of isthmus-dependent atrial flutter ablation. J Am Soc Echocardiogr 2011;24(10):1148–1155.

146. Hightower JS, Taylor AG, Ursell PC, et al. The Chiari network: a rare cause of intracardiac guide wire entrapment. Journal of Vascular and Interventional Radiology 2015;26(4):604–606.

147. Schernthaner C, Haidinger B, Brandt MC, et al. Influence of cavotricuspid isthmus length on total radiofrequency energy to cure right atrial flutter. Kardiol Pol 2016;74(3): 237-243.

148. Da Costa A, Faure E, Thévenin J, et al. Effect of isthmus anatomy and ablation catheter on radiofrequency catheter ablation of the cavotricuspid isthmus. Circulation 2004;110(9):1030–1035.

149. Klimek-Piotrowska W, Holda MK, Koziej M, et al. Clinical Anatomy of the Cavotricuspid Isthmus and Terminal Crest. Plos One 2016;1(9):1-16.

150. Lee SH, Tai CT, Yu WC, et al. Effects of radiofrequency catheter ablation on quality of life in patients with atrial flutter. Am J Cardiol 1999;84:278–283.

151. Anselme F, Savouré A, Cribier A, et al. Catheter ablation of typical atrial flutter: a randomized comparison of 2 methods for determining complete bi-directional isthmus block. Circulation 2001;103:1434–1439.

152. Shah DC, Takahashi A, Jaïs P, et al. Local electrogram-based criteria of cavo-tricuspid isthmus block. J Cardiovasc Electrophysiol 1999;10:662–669.

153. Da Costa A, Romeyer-Bouchard C, Jamon Y, et al. Radiofrequency catheter selection based on cavotricuspid angiography compared with a control group with an externally cooled-tip catheter: a randomized pilot study. J Cardiovasc Electrophysiol 2009;20:492-498.

154. Da Costa A, Romeyer-Bouchard C, Dauphinot V, et al. Cavotricuspid isthmus angiography predicts atrial flutter ablation efficacy in 281 patients randomized between 8 mm- and externally irrigated-tip catheter. Eur Heart J 2006;27:1833-1840.

155. Chen J, De Chillou C, Basiouny T, et al. Cavotricuspid isthmus mapping to assess bi- directional block during common atrial flutter radiofrequency ablation. Circulation 1999;100:2507– 2513.

156. Klug D, Lacroix D, Marquie C, et al. Prospective evaluation of a simplified approach for common atrial flutter radio frequency ablation with only two catheters. Europace. 2001;3:208– 215.

157. Matsushita T, Chun S, Liem LB, et al. Unidirectional Conduction Block at Cavotricuspid Isthmus Created by Radiofrequency Catheter Ablation in Patients With Typical Atrial Flutter. Journal of Cardiovascular Electrophysiology. 2002;13:1098–1102.

158. Basso, C., Aguilera, B., Banner, J. et al. Guidelines for autopsy investigation of sudden cardiac death: 2017 update from the Association for European Cardiovascular Pathology. Virchows Arch. 2017; https://doi.org/10.1007/s00428-017-2221-0