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Case Report

Role of Pulmonary Vein in Atrial Fibrillation

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Background. Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, occurring in1–2% of the general population and likely to increase in next 50 years. The prevalence of AF increases with age, from 0.5% at 40–50 years, to 5–15% at 80 years. Precise mechanisms that lead to the onset and persistence of AF have not completely been elucidated. The key role of ectopic foci in pulmonary veins as a trigger of AF has been recognized. Depending on disease progression, 60 to 95% of triggers responsible for AF induction originate within the pulmonary veins (PV). Because of the clinical importance of the PVs in the initiation of AF, it makes the increasingly widespread application of catheter ablation techniques in these veins as a treatment for AF. Restoration and maintenance of sinus rhythm is of potential benefit if it can be achieved without the use of anti arrhythmic drugs, and this fact underscores the need to strive for the development of non pharmacological treatments to achieve and maintain sinus rhythm.
Objective. The aim of the presentation is to discuss about role of pulmonary vein potential isolation on treatment of atrial fibrillation.
Summary. A 64 year old man with diagnosis of paroxysmal atrial fibrillation was reported. The patient was then underwent catheter ablation using CARTO 3D electroanatomic mapping system. He underwent pulmonary vein isolation and had successful result. In paroxysmal AF, PV electrical isolation remains a pivotal strategy. It is associated with arrhythmia suppression without the use of anti arrhythmic agents. The clinical outcome of ablation can further improved.

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Keywords: atrial fibrillation, pulmonary vein isolation, catheter ablation

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Laporan Kasus

Peranan Vena Pulmonalis pada Fibrilasi Atrium

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Latar belakang. Fibrilasi atrium(FA) merupakan penyebab tersering dari aritmia jantung. Pada populasi umum terjadi pada 1-2% dan cenderung untuk meningkat pada 50 tahun kedepan. Prevalensi FA akan meningkat seiring dengan usia, sekitar 0,5% pada usia 40-50 tahun, dan 5-15% pada usia 80 tahun. Mekanisme yang tepat mengenai terjadinya FA belum sepenuhnya diketahui. Salah satu mekanismenya antara lain fokus ektopik pada vena pulmonalis sebagai suatu pencetus. Berdasar kan prograsifitas penyakitnya, 60-95% pencetus pada FA berasal dari dalam vena pulmonalis. Karena pentingnya peranan vena-vena pulmonalis tersebut pada inisiasi FA, maka teknik-teknik ablasi FA yang dikembangkan pada lokasi tersebut menjadi target tatalaksana pada FA. Kembalinya irama menjadi sinus serta pemeliharaannya merupakan suatu keuntungan sebagai tata laksana non-medikamentosa.
Tujuan. Mendiskusikan peranan isolasi potensial dari vena-vena pulmonalis pada tata laksana fibrilasi atrium.
Ringkasan. Telah dilaporkan kasus pada seorang laki-laki, 64 tahun dengan diagnosis fibrilasi atrium paroksismal yang dilakukan ablasi kateter dengan CARTO 3D *mapping system.* Prosedur yang dilakukan antara lain isoloasi potensial pada vena-vena pulmonalis dan berhasil baik. Pada FA paroksismal, Isolasi elektris dari vena pulmonalis merupakan strategi utama, yaitu tata laksana dalam supresi aritmia tanpa medika mentosa. Keberhasilan klinis dari prosedur ini memiliki hasil yang baik.

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Kata kunci: fibrilasi atrium, isolasi vena pulmonalis, ablasikateter

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, occurring in1–2% of the general population and likely to increase in next 50 years.[1] The clinically apparent manifestations of this condition result from thromboembolic complications, loss of atrial systole, and tachycardia mediated atrial and ventricular cardiomyopathy.[2] Precise mechanisms that lead tothe onset and persistence of AF have not completely been elucidated. The key role of ectopic foci in pulmonary veins as a trigger of AF has been recognized.[3] Depending on disease progression, 60 to 95% of triggers responsible for AF induction originate within the pulmonary veins (PV).[4]

Because of the clinical importance of the PVs in the initiation of AF, it makes the increasingly widespread application of catheter ablation techniques in these veins as a treatment for AF.[2] The aim of the report is to discuss about role of pulmonary vein potential isolationon treatment of atrial fibrillation.

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Case Report

MrK, a 64 years old man came to hospital with chief complaint of history of recurrent palpitation. He had uncontrolled hypertension. But, there were no other risk factors such as diabetes mellitus, or dyslipidemia. There was also no history of family with cardiac disease.

On first examination, patient was fully alert, mild ill, the resting blood pressure waselevated 160/90 mmHg with heart rate 65 x/minute. Other general examinations were within normal limit. The electrocardiogram (ECG) was recorded twice. First recording of ECG showed sinus rhythm with QRS rate 86 x/minute, QRS axis +60° (normal axis), P wave normal, PR interval 0,20 sec, QRS duration 0,08 sec with no ST or T wave changes. There is a single APC. The second ECG recording showed atrial fibrillation with normal ventricular response. QRS rate 95 x/minute, QRS axis +60° (normal axis). There are no ST or T wave changes. (Figure 1)

The radiologic and laboratory findings was within normal limit. The transthoracic echocardiography revealed normal systolic LV functionwith ejection fraction 68%. No thrombus was found. Coronary andiography showed no stenosis on coronary arteries.

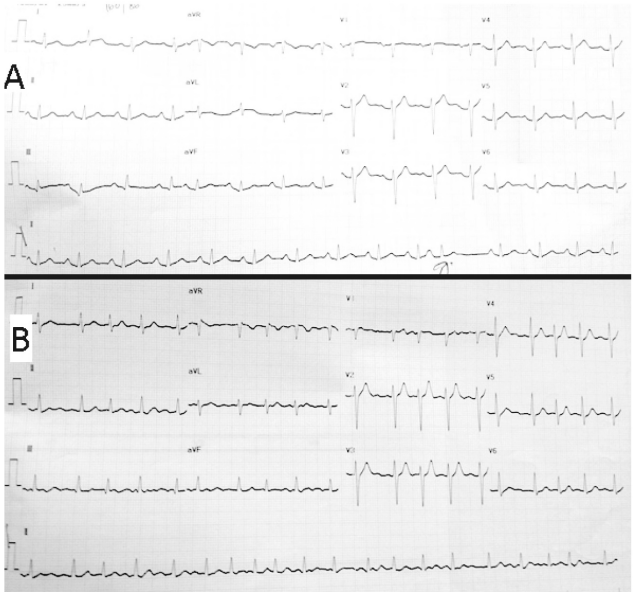

Figure 1. ECG recording on NCCHK. (A) Sinus rhythm; (B) Atrial Fibrillation

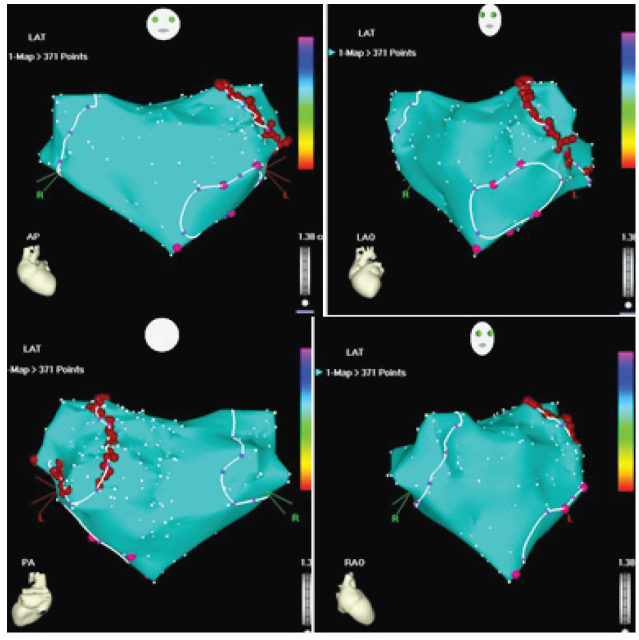

Figure 2. 3D-electroanatomic mapping using CARTO from different view. A) AP; B) LAO; C) PA; and D) RAO.

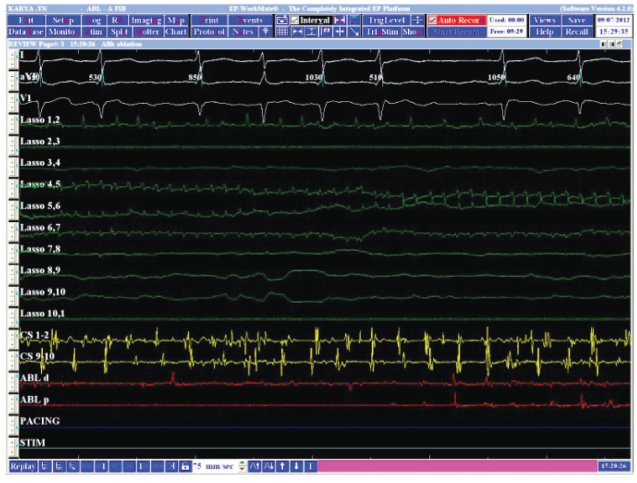

Figure 3. Intracardiacelectrogram-pulmonary potential rate on RSPV more than 600 bpm.

The patient was diagnosed as symptomatic paroxysmal atrial fibrillation. He was planned to perform pulmonary vein (PV) isolation with radiofrequency ablation by using3D-electroanatomic mapping system. Reconstruction of the geometry of left atrium was performed. (Figure 2)

After the reconstruction, decapolar lasso catheter was placed within each pulmonary vein to record pulmonary vein potential which appropriate as

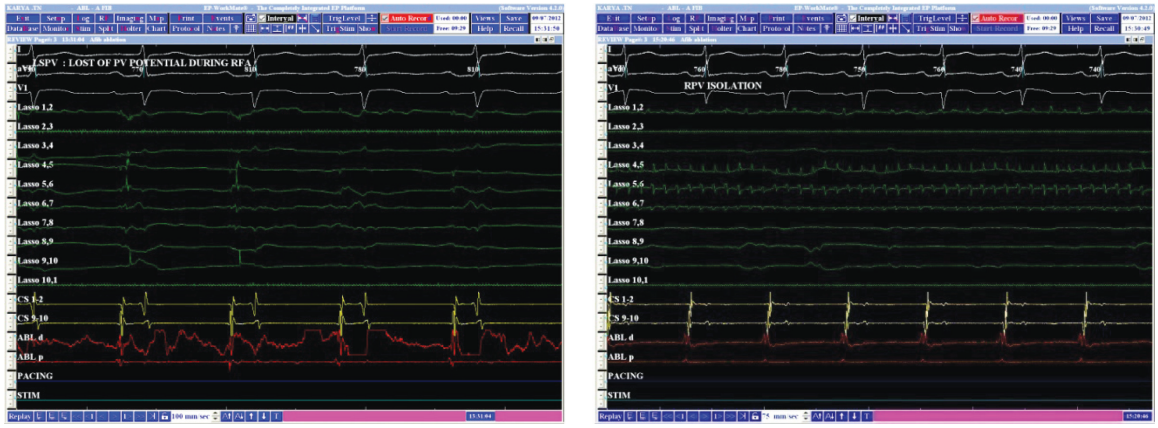

Figure 4. Intracardiac electrocardiogram after performing RFA. LSPV :Lost of PV potential after RFA (left panel); RSPV : complete CPVI with AF inside RSPV and normal SR outside (right panel).

the source of atrial fibrillation. The potential was recorded as intracardiacelectrogram which shown in Figure 3.

Lasso catheter was placed within LSPV and LIPV during RF delivery. After a complete circumferential PV isolation (CPVI) in left pulmonary vein, no PV potential was detected within ipsilateral PV (Figure 4). Following, lasso catheter was placed within RSPV and RFA was performed. After CPVI in RSPV, it is documented that the PV potential was still persisted, meanwhile surface ECG showed normal sinus rhythm. It can be concluded that the isolation of RSPV was also successful.

The procedure was stopped, and no complication occurred. During hospitalization, no arrhythmia reoccurred. The patient was still given amiodarone 1 x 200 mg, bisoprolol 1 x 5 mg, and aspirin 1 x 80 mg. On follow up, he did not feel any recurrent palpitation.

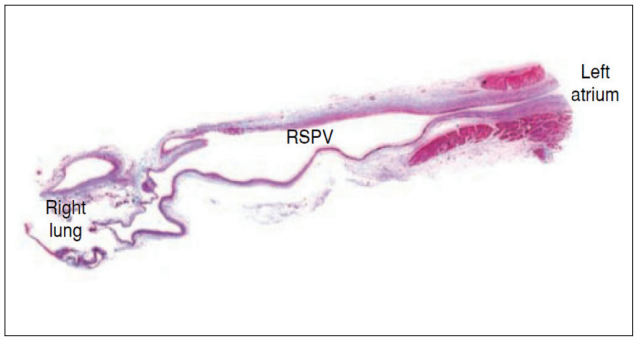

Figure 5. Histologic section through RSPV shows myocardium from LA continuing along the venous wall to form myocardial sleeve.

Discussion

Triggered AF episode sinitiated by 'focal firing' from within the PV sled to the strategy of electrically isolating these triggers from the atrial substrate. Understanding anatomy and embryological development of PV is important in the development of balloon-based ablation technologies.[5]

Anatomy of left atrium (LA) and pulmonary vein (PV)

At embryologic phase, specialized conduction tissue that is derived from the heart tube and is destined to have pacemaker activity has been shown to be located within the myocardial sleeves of the PVs. Perez-Lugones demonstrated the presence of P cells, transitional cells, and Purkinje cells in the human PVs. These observations help provide an understanding for why the PVs are commonly identified as the location of rapidly electrical activity which triggers the development of AF.[5]

The presence of myocardial muscle extensions ("sleeves") covering the outside of PVs in mammals and in humans has been recognized for many year, and myocardial muscle fibers extend from the LA into all the PVs at a length of 1–3 cm; muscular sleeve is thickest at the proximal end of the veins (1–1.5 mm) and it then gradually tapers distally. The sleeve is thickest at the inferior wall of the superior PVs and at the superior wall of the inferior PVs. (Figure 5)

In a study published by Hassink et al, myocardial sleeves were recognized in 89% of population. The

prevalence of sleeves was comparable between patients with and those without AF in their study. Itwas found a statistically significant higher frequency of atrial myocardium in the PVs of patients with AF. The distances of the myocardial extension into the PVs were more extensive in the superior than in the inferior PVs.[6]Tagawa et al. also reported longer myocardial sleeves in the superior PVs compared with the inferior PVs as well. The distances of the sleeves in both inferior PVs reached a statistically significant difference comparing veins of patients with and without AF, being longer in the subjects with the arrhythmia.[7]

Frequently, the sleeve was composed of circularly and longitudinally oriented bundles of cardiomyocytes. But the peripheral end of the myocardial sleeve was irregular.[8] Another study also found less uniform myocytes and some fibrosis.[7] The longest myocardial sleeves were found in the superior veins and were longitudinally oriented. At the PV-atrial junction, the circular bundles were not often circumferential. PV myocardial architecture confirmed the possibility of initiating AF. This fact is important for therapeutic radiofrequency ablation and explains why PV disconnection is essential.[8]

In addition, there are abundant adrenergic and cholinergic nerves in the ganglionated plexi in the vicinity [20]. Preferential location of these structures includes the left superior PV at the junction with the atrial roof, the posteroinferior junction of the inferior PVs, and the anterior border of the right superior PV.[5]

Mechanism of arrhythmogenic activity of pulmonary veins

The electrophysiological mechanism of AF remains elusive. The thoracic vein hypothesis suggests that AF is maintained by interactions between the LA and PVs, due to the complex orientation of the myocardial fibers.[9]The premature depolarizations that arise within the muscle sleeves of the pulmonary veins often are multifocal and may not be manifest during an electrophysiology procedure.[5]

1. **Atrial Fibrillation Initiation**
   - *Triggers*
     Spontaneous AF is usually initiated by atrial premature complexes (APCs) that couple with a short interval to the preceding beat. Although clinical AF may begin apparently *de novo*, a great number of episodes seen clinically are started by a single APC. Previous study showed that the earliest atrial activation during initiation of spontaneous AF wasclose to the site of spontaneous APCs within LA and the right atrium (RA)observed during electrophysiological study. The authors attributed this to a possible initial spiral-wave/ rotor mechanism triggering AF by generation of multiple daughter wavelets. LA onset of AF was more common among patients without heart disease, whereas patients with hypertension or coronary artery disease had more frequent initiation from the RA.

The myocardial sleeves of PVs are a particularly important locus of AF initiation. Haissaguerre *et al*. reported that the onset of AF is frequently triggered by APBs that originate from the sleeves of the atrial muscle that extend into the PVs. Others have reported that focal firing within the PVs is responsible for sustained AF.[10]PV foci trigger a high percentage of clinical AF episodes in patients without structural heart disease. The mechanism leading to PV ectopic activity appears to be non-re-entrant, as the arrhythmia could not be induced by programmed stimulation. Some experimental studies have shown abnormal automaticity and triggered activity in PV preparations. The architecture of the PVs may facilitate micro-re-entry by virtue of structural complexities, leading to heterogeneous impulse propagation with marked slowing at regions of directional discontinuity [15]. Optical mapping suggests that re-entry may be the predominant arrhythmia mechanism within normal PV myocardium.[11]

The specific cellular mechanisms underlying the formation of special clinical triggering regions are poorly understood. Triggered activity may result from delayed or early after depolarizations. Diastolic cellular depolarization, primarily through electrogenic Na+/Ca2+ exchange in the presence of intracellular Ca2+ overload, underlie delayed after depolarizations. Reactivation of L-type calcium channels during prolonged action potentials may underlie early after depolarizations. Abnormal automaticity may also be relevant in the genesis of AF, if

phase 4 depolarization is accelerated, causing threshold to be reached prematurely and APCs to be initiated. Focal cellular activity that could trigger AF has been reported in PV myocytes, even from healthy canine hearts. However, other laboratories were unable to demonstrate any spontaneous activity under control conditions.[11]

- *Substrate*

Besides triggering the arrhythmia, PVs may be an important part of the environment for the maintenance of AF. They play an important role in persistent AF, albeit not as critical as their role in triggering arrhythmia in paroxysmal AF without structural heart disease. An ideal substrate for re-entry thus would involve slowing of impulse propagation (e.g. due to decreased Na+ current, or passive conduction abnormalities like tissue fibrosis or abnormal cell-connecting connexin proteins) and would also shorten the RP (by decreasing action potential duration (APD), which is the most important cellular determinant of the RP). Furthermore, RP heterogeneity is also important in promoting re-entry.

PV muscle fascicles within the myocardial sleeves display a great degree of decremental conductionand significant heterogeneity in conduction properties and refractoriness. Together with their complex anatomical structure, PVs are a favorable site for re-entrant arrhythmias. Fibrillatory activation may be maintained and re-initiated in isolated PVs after electrophysiological disconnection from the LA. PVs may thus represent both triggers for AF initiation and a key part of the substrate for AF maintenance. (Figure 8).[11]

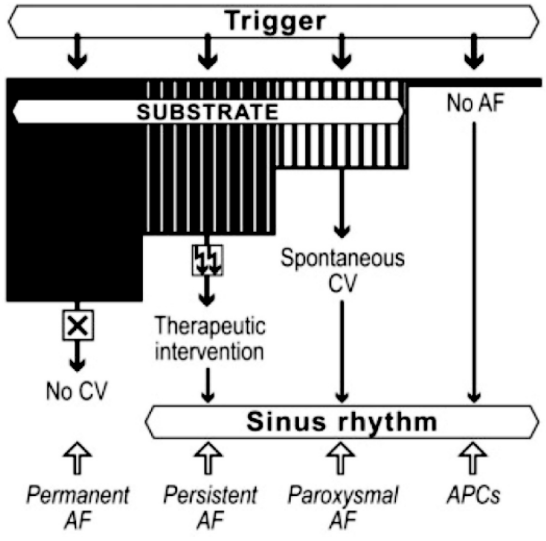

Figure 6. The relationship of different forms of atrial fibrillation (AF) encountered in clinical practice to the underlying substrate

2. **Atrial Fibrillation Sustenance**

Once AF occurs, the atria accommodate to the rapid activation rate by downregulatingICa, which protects the cell from Ca2+ overload but makes it easier for AF to become sustained. This electrical remodeling results from sustained rapid atrial activation, independent of the underlying mechanism.

AF remodeling leads to shorter atrial RP with increased RP heterogeneity and reduced RP rate adaptation. RP particularly decreases at slow heart rates, increasing vulnerability to ectopic beats. Longstanding AF may additionally reduce conduction velocity, by decreasing sodium current (INa) or causing spatially heterogeneous changes in connexin expression. These features – shortened RP and reduced conduction velocity – decrease wavelength and make sustained re-entrant activation via multiple wavelet re-entry more likely. A prominent reduction of ICa,L occurs in human AF. Along with Ca2+ current, the transient outward potassium current (Ito) is also downregulated by AT. Intracellular calcium-homeostasis is altered and Ca2+ overload may jeopardize cell vitality [63]. Slower and smaller Ca2+ transients caused by sustained rapid atrial rates decrease atrial myocyte contractility and underlie the atrial contractile dysfunction ('atrial stunning') observed in clinical AF.[11]

Catheter ablation of pulmonary vein

1. **History of pulmonary vein isolation ablation**

The use of catheter ablation techniques for the treatment of focally triggered AF arising from the PVs is growing rapidly. Specific therapeutic targets may be deduced from these insights into triggers and substrates.[12] Curative catheter ablation techniques initially attempted to mimic the lesions created by the surgical Maze procedure,

resulting in limited success with a substantial complication rate. Ablation approaches are effective for suppression of initiation, whereas pharmacological and surgical approaches play a central role in controlling sustenance.

- *Focal ablation of pulmonary vein triggers of atrial fibrillation*
  The identification of triggers that initiate AF within the PVs led to prevention of AF recurrence by catheter ablation at the site of origin of the trigger.In 1998, Haissaguerre et al. first demonstrated that pulmonary veins (PVs) provided focal firings triggering the occurrence of paroxysmal AF, so as the target ablation at the site of earliest activation during spontaneous ectopy.[2,10] They showed that as many as 94% of such triggers originated from the PVs and that the elimination of these foci by radiofrequency (RF) energy applications in the PVs could cure the paroxysmal form of AF, which became the cornerstone of curative ablation of AF.[10] RF ablation at this earliest site resulted in acute abolition of atrial ectopy.[2] However, it turned out that high recurrence rates of AF and late development of PV stenosis were often associated with this procedure. It is also became evident that, in many patient with AF, multiple PVs and multiple sites within given PV could give rise to spontaneous triggers.[2]
- *Pulmonary vein isolation*
  A further limitation of this approach is that multiple sites of triggering foci were commonly observed. To overcome these limitations, an ablation approach was introduced by Haissaguerre *et al* which was designed to electrically isolate the PV myocardium. This segmental PV isolation technique involved the sequential identification and ablation of the PV ostium close to the earliest sites of activation of the PV musculature.[13]Another approach introduced by Pappone was performed anatomically guided circumferential PV ablation encircling individual PVs. This approach was safe and effective due to no thromboembolic events or PV stenosis were observed.[14]

2. Radiofrequency ablation

Electrophysiologic features of PV potensialsare: 1) rapid, high frequency initial deflestion, 2) short duration (<50 ms), 3) follows farfield atrial electrogram during atrial pacing, 4) precedes farfield atrial electrogram during pulmonary vein pacing. By sequential ablation at sites of earliest activity, the PVs can be electrically isolated from LA. Ablation can be started in either right or left PVs and can be performed individually or en bloc, particularly if the ostias are coalescent. It is started at posterior wall and then continued around the venous perimeter.

Ablation is usually performed circumferentially, with longer application at critical sites of the PV to LA connection. These sites may be identified as those sites with earliest PV activity during antegrade conduction into vein or as sites at which a change in PV activation occur during ablation. The potential target sites for AF ablation are: 1) Ectopic activity triggering AF, 2) Earliest PV potential activation in PV, 3) all ostial PV potential, 4) sites of PV polarity reversal, 5) possible sites of dominant frequency or rapid activity during AF.

Although most groups agree that lesion around PV are sufficient to cure paroxysmal AF, there remains controversy as to whether complete electrical disconnection is superior to incomplete disconnection. End points for ablation of atrial fibrillation are: 1) entrance block electrical isolation of all PVs, 2) Exit block electrical isolation of all PVs, 3) Elimination of all atrial ectopic activity, 4) non inducible/non sustainable AF, 5) elimination of high frequency 'drivers' during AF, 6) elimination of fractionated electrograms, and 7) PV isolation plus completion of linear lesion (e.g. left atrial isthmus, roof line, anterior line).

This patient was diagnosed as lone AF and underwent pulmonary vein isolation ablation. This was appropriate with management recommended by AHA Guidelines 2006 and ESC Guideline 2011. For this case, we define successful PVI as an elimination of PVs potential in left pulmonary vein. Meanwhile ablation on right pulmonary vein showed that PV potential was still persisted from the intracardiac electrogram, meanwhile surface ECG showed normal sinus rhythm. This evidence proved that this procedure could isolate the PV potential, so it did not affect basic rhythm of his cardiac. This was also proved that electrical disconnection between PVs

and LA is the cornerstone stated that of AF ablation strategies.

Summary

We have reported a case of symptomatic paroxysmal atrial fibrillation which still persist with optimal antiarrhythmic drug. His risk factor was hypertension without any structural heart disease. The patient was then underwent catheter ablation using CARTO 3D electroanatomic mapping system. He underwent pulmonary vein isolation and had successful result. In paroxysmal AF, PV electrical isolation remains a pivotal strategy. It is associated with arrhythmia suppression without the use of anti arrhythmic agents. While acute results appear quite favorable, further study is warranted to determine long-term safety and efficacy of this innovative technology.

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