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Review Article

Electrophysiological Abnormalities of the Atrial Myocardium and the Rubenstein Clinical Classification of Patients with Sinus Node Dysfunction

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Abstract

Sinus node dysfunction (SND) may be due to an alteration in the generation of impulses within the sinus node and/or a disturbance of the conduction of impulses from the sinus node to the atrial myocardium. It is usually secondary to senescence of the sinus node and the surrounding atrial myocardium. Patients with this disorder are often elderly and generally have other comorbidities. Patients often seek medical attention with symptoms of stunning, pre-syncope, syncope and, in patients with alternating periods of bradycardia and tachycardia, palpitations or other symptoms associated with a rapid heart rate. Sometimes it may be difficult to establish a symptom-electrocardiographic alteration relationship because the symptoms may be variable in nature, non-specific and frequently transient. Typical electrocardiographic features correlating with clinical findings are one or more episodes of extreme sinus bradycardia (Rubenstein Type I), or sinus pauses, sinoatrial block and sinus arrest (Rubenstein Type II), or episodes of bradycardia and/or alternating pauses with atrial tachyarrhythmias (Rubenstein Type III). Investigations based on the recording of abnormally prolonged and fractionated atrial local electrograms during sinus rhythm atrial mapping and their characteristic distribution in the right atrium of patients with SND have provided important knowledge about the electrophysiological properties of the pathological atrium. The abnormal atrial electrogram results in an irregular atrial conduction characterized by a non-homogeneous local electrical activity, related to an anisotropic, non-uniform and delayed conduction through a pathological atrial myocardium, in which arrhythmias due to re-entry may arise. There is a different distribution of the abnormally prolonged and fractionated atrial endocardial electrograms in SND patients depending on the type of Rubenstein classification. The detection of abnormal atrial electrograms in the SND identifies a group of patients with increased atrial vulnerability and a significantly higher incidence of spontaneous or induced episodes of atrial fibrillation.

Keywords: *Sinus Node Dysfunction; Paroxysmal Atrial Fibrillation; Atrial Vulnerability; Endocardial Atrial Electrograms*

Introduction

In 1972, Rubenstein., *et al.* [1] conducted a quite descriptive review from the clinical point of view of 56 patients with episodes of documented bradycardia. In order to classify patients according to the electrocardiographic (ECG) features and clinical findings, they were divided into 3 groups and were called sick sinus syndrome which we will discuss in detail below [1]. Currently, this nosological entity is called sinus node dysfunction (SND). Patients with this disorder are often elderly, although some publications describe a bimodal distribution of age and, generally have other comorbidities [2-10].

The electrocardiographic abnormalities observed correspond to bradycardia, sinus pauses, and sinus arrest. These bradycardia rhythms frequently alternate with paroxysmal episodes of supraventricular tachy-arrhythmias and paroxysmal atrial fibrillation (PAF) [2,8]. Patients often seek medical attention with symptoms of stunning, presyncope, syncope and, in patients with alternating periods of bradycardia and tachycardia, palpitations or other symptoms associated with a rapid heart rate [3-5]. Because the symptoms may be variable in nature, nonspecific and frequently transient, it can sometimes be difficult to establish this symptom-electrocardiographic alteration relationship [8-10]. Typical ECG findings are one or more episodes of extreme sinus bradycardia (Rubenstein Type I), or sinus pauses, sinoatrial block, and sinus arrest (Rubenstein Type II), or episodes of brady-arrhythmias and/or alternating sinoatrial pauses with atrial tachy-arrhythmias (Rubenstein Type III) [1]. It is precisely these findings that lead us to carry out this review and to analyze in detail in this manuscript certain current concepts about the clinical classification and the electrophysiological alterations of the atrial myocardium in patients with SND that leads us to try to individualize and determine who are the patients with SND that are more susceptible to develop sustained episodes of PAF.

Clinical classification and electrophysiological correlation with abnormalities of atrial myocardium

Two main mechanisms have been proposed to explain bradycardia in the SND. In the first place, it could be an alteration in the generation of impulses within the sinus node; second, a disturbance of the conduction of impulses from the sinus node to the surrounding atrial myocardium [3]. The causative factors could be intrinsic, namely, diseases that directly alter the sinus node or extrinsic. The most common cause is idiopathic degenerative fibrosis associated with advanced age [4]. The intrinsic causative factors are idiopathic degenerative fibrosis, myocardial ischemia, infiltrative disorders, Chagas disease, endocarditis, myocarditis, immuno-mediated diseases, and cardiac surgery. The extrinsic causative factors are pharmacological agents (beta-blockers, calcium antagonists, digoxin, antiarrhythmics), electrolyte alterations, hypothyroidism, sleep apnea and increased vagal tone.

Rubenstein., *et al*. [1] conducted a nice descriptive review from the clinical point of view in 56 patients with episodes of documented bradycardia. The series included 31 women and 25 men between the ages of 26 and 90, with an average age of 65 years. In order to classify the patients according to the ECG features and clinical findings, they were divided into 3 types as depicted in the table.

Type I: Patients with unexplained extreme sinus bradycardia (less than 50 beats/minute, and often less than 40).
Type II: Patients with at least 1 documented episode of sinus arrest or sinoatrial block and with junction or ventricular escape beats.
Type III: Patients with bradycardia-tachycardia syndrome (alternating bradycardia and paroxysmal atrial tachy-arrhythmias). The most frequent tachy-arrhythmias were atrial fibrillation, atrial flutter and paroxysmal atrial tachycardia although many patients exhibited a combination of these atrial arrhythmias, that is, more than one type of tachyarrhythmia at different times of their clinical evolution [2].

Table: *Rubenstein clinical classification of the sinus node dysfunction.*

Sometimes the conventional ECG is not sufficient to make a clear diagnosis of the symptoms that present the patients. Therefore, additional diagnostic tests may be required. In addition, the SND should not be diagnosed until potentially reversible causes have been identified and treated, including the use of drugs, myocardial ischemia, hypothyroidism, and autonomic imbalance. Also, well-trained athletes have fairly low heart rates that must be taken into consideration. There are no standardized criteria to establish the SND diagnosis [10,11]. The key to arriving at the diagnosis of this entity is to establish a correlation between the clinical symptoms described by the patients and the electrocardiographic findings. A routine conventional ECG or a 24-hour Holter ECG monitoring can confirm the diagnosis of SND if the typical ECG findings can be correlated with symptoms. Typical electrocardiographic findings are one or more episodes of extreme sinus bradycardia (Rubenstein Type I), or sinus pauses, sinoatrial arrest and blockade (Rubenstein Type II), or episodes of bradycardia and/or alternating pauses with atrial tachyarrhythmias (Rubenstein Type III) [1]. If the electrocardiogram and repeated 24-hour Holter ECG monitoring fail to document the cause of a patient's symptoms, consideration should be given to using external event recording devices or an implantable continuous-loop, loop-recorder implantable heart monitor [5]. Stress tests can help identify the abnormal function of the sinus node, exclude myocardial ischemia, and can help guide device programming for patients who eventually receive a permanent pacemaker. Chronotropic incompetence, that is, a subnormal increase in heart rate after exercise, can help identify people with

abnormal sinus node function who may benefit from the implantation of a pacemaker [2]. Electrophysiological studies allow determine certain parameters that speak of the SND, such as the recovery time of the sinus node, and the sinus node conduction time. Therefore, this invasive study could be considered especially in those patients who persist symptomatic and in those who have not documented episodes of the electrocardiographic alterations described [7].

Clinical electrophysiological studies in SND patients with Rubenstein type III have certain limitations. Due to the ease with which these patients develop atrial fibrillation by programmed cardiac stimulation during the electrophysiological study in the laboratory [12-15]. A detailed analysis of the electrophysiological properties of the atrial myocardium cannot be performed since atrial fibrillation does not allow measurements to be made corresponding. Under these circumstances, the electrophysiological data obtained by atrial endocardial catheter mapping during sinus rhythm acquire an unquestionable importance in the knowledge of the electrophysiological substrate of the atrium [16-19]. Endocardial catheter mapping with a right atrial catheter allows recording the endocardial bipolar electrograms of the anterior, posterior, lateral and medial walls of the upper, middle and lower areas of the right atrium (Figure 1). Clinical electrophysiological investigations based on the recording of abnormally prolonged and fractionated atrial local electrograms during sinus rhythm by catheter mapping and their characteristic distribution within the right atrium of patients with SND have provided important knowledge about the electrophysiological properties of the pathological atrium (Figure 2) [20-23].

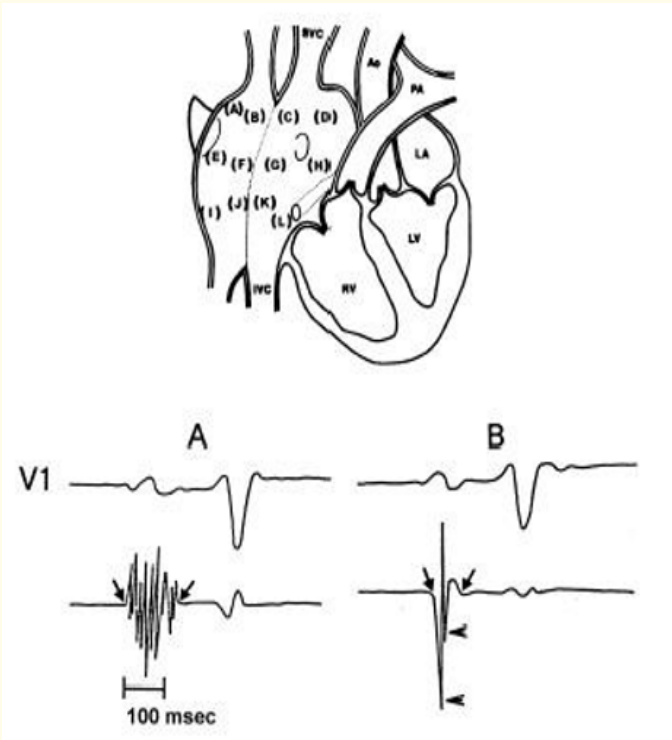

Figure 1: *Sites of endocardial catheter mapping of the right atrium are depicted. The atrial electrograms were recorded from 12 endocardial sites in each patient. The sites listed from A to D correspond to the upper part of the right atrium while the sites from E to H are from the middle part, and those from I to L are from the lower part of the right atrium. The sites marked A, E and I correspond to the anterior region, sites B, F and J to the lateral region, sites C, G and K to the posterior region, and sites D, H and L correspond to the medial region of the right atrium.*

SVC: Superior Vena Cava; IVC: Inferior Vena Cava; Ao: Aorta; PA: Pulmonary Artery; LA: Left Atrium; RV: Right Ventricle; LV: Left Ventricle.

In the lower part (A) there is an abnormal endocardial atrial electrogram with a duration of 130 ms and 10 fragmented deflections. (B) shows a normal endocardial atrial electrogram that lasts 80 ms in duration and has two fragmented deflections. Reprinted with permission from Centurion OA et al. Influence of advancing age on fractionated right atrial endocardic electrograms. Am J Cardiol 2005; 96: 239-242.

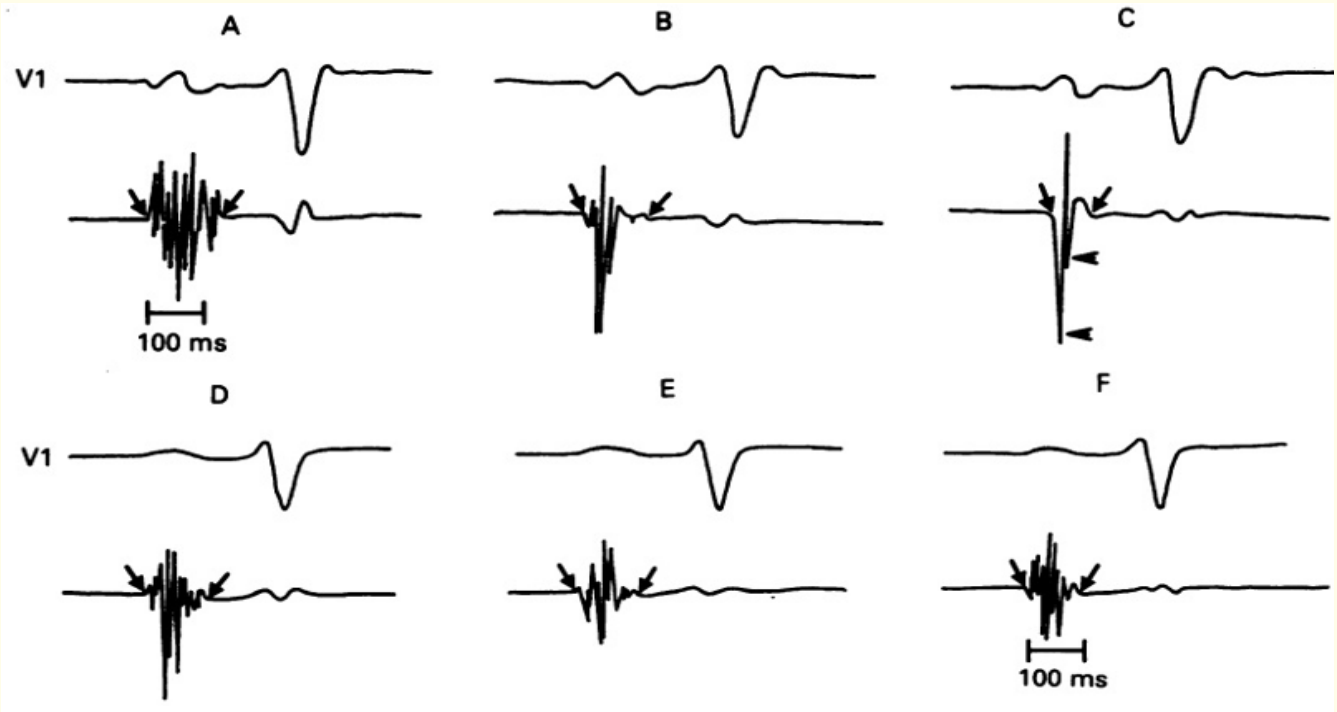

Figure 2: *Six atrial electrograms recorded at different right atrial sites in two patients with Sinus Node Dysfunction (A, B, and C in a SND patient with Rubenstein Type I and II; D, E, and F in a SND patient with Rubenstein Type III). Diagonal arrows represent the onset and offset of local electrical activity and horizontal arrows the downward deflections. Reprinted with permission from Centurión OA, Fukatani M, Konoe A, Tanigawa M, Shimizu A, Isomoto S y col. Different distribution of abnormal endocardial electrogram within the right atrium in patients with sick sinus syndrome. Br Heart J 1992;68:596-600.*

With atrial endocardial catheter mapping during sinus rhythm in SND patients, we have previously shown that abnormally prolonged and fractionated endocardial atrial electrograms recorded in the right atrium denote irregular atrial conduction and that they are frequently recorded in patients with Rubenstein type III SND [15-18]. We demonstrated in these Rubenstein type III SND patients, that the abnormal atrial electrograms were recorded from the entire right atrium. However, in SND patients from the Rubenstein Type I or Type II, the abnormal atrial electrograms were mainly recorded in the high zones of the right atrium [15] (Figure 3). Therefore, there is a different distribution of the abnormally prolonged and fractionated atrial endocardial electrograms in SND patients depending on the type of Rubenstein classification. Atrial endocardial mapping in patients with PAF has provided more knowledge about the electrophysiological substrate of this tachyarrhythmia. The detection of abnormal atrial electrograms identifies a group of SND patients with increased atrial vulnerability and a significantly higher incidence of spontaneous or induced PAF episodes. SND patients from the Rubenstein Type II and Type III have a greater abnormality of the atrial electrograms as depicted in figure 4.

Myocardial alterations of the right atrium in the endocardial mapping

Endocardial mapping of the right atrium during sinus rhythm has allowed the recording of abnormal atrial electrograms of certain pathological atrial zones in patients with SND [12-16]. From the beginning of the electrophysiological study as an invasive diagnostic procedure, the technique of atrial endocardial mapping has been used to perform a detailed analysis of myocardial activation sequence and has contributed to a better understanding of arrhythmogenic mechanisms in patients with supraventricular tachycardias. By means of

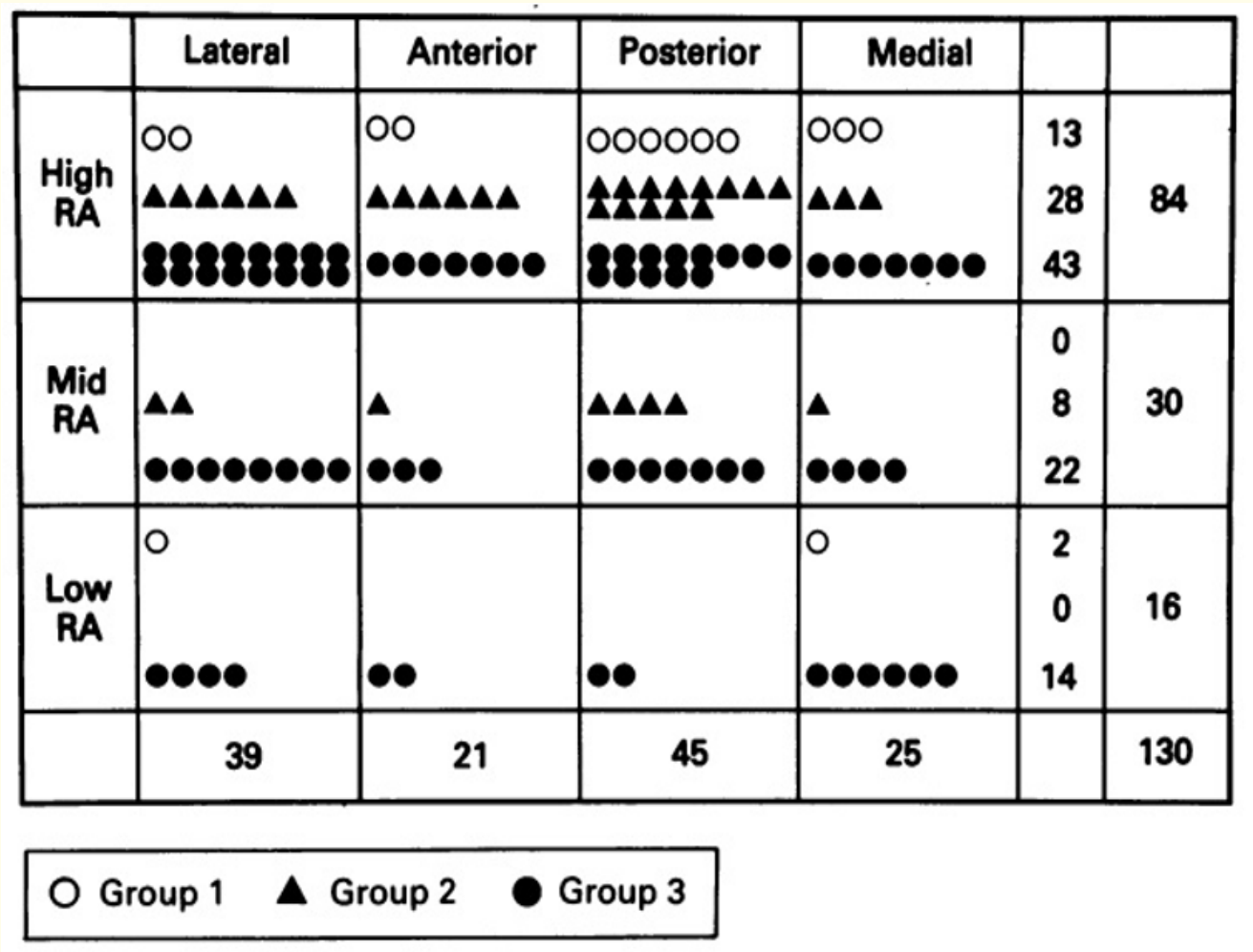

Figure 3: *Sites in the right atrium with abnormal atrial electrograms in SND patients from the three Rubenstein Types are depicted. One symbol represents one abnormal atrial electrogram. Reprinted with permission from Centurión OA, Fukatani M, Konoe A, Tanigawa M, Shimizu A, Isomoto S y col. Different distribution of abnormal endocardial electrogram within the right atrium in patients with sick sinus syndrome. Br Heart J 1992;68:596-600.*

Group I: Control group.

Group II: SND patients from Rubenstein Type I and II.

Group III: SND patients from Rubenstein Type III.

this technique, twelve endocardial electrograms can be recorded in the different sites of the right atrium and in each of them the duration and number of fragmented deflections can be measured quantitatively [17-23]. The definition of the duration of an atrial electrogram is the interval from the beginning of the earliest electrical activity that deviates from the baseline to the last deflection of the atrial electrogram where the baseline crosses the isoelectric line of atrial activity. The number of fragmented deflections is obtained by counting the deflections that point downwards as we can see in figure 2.

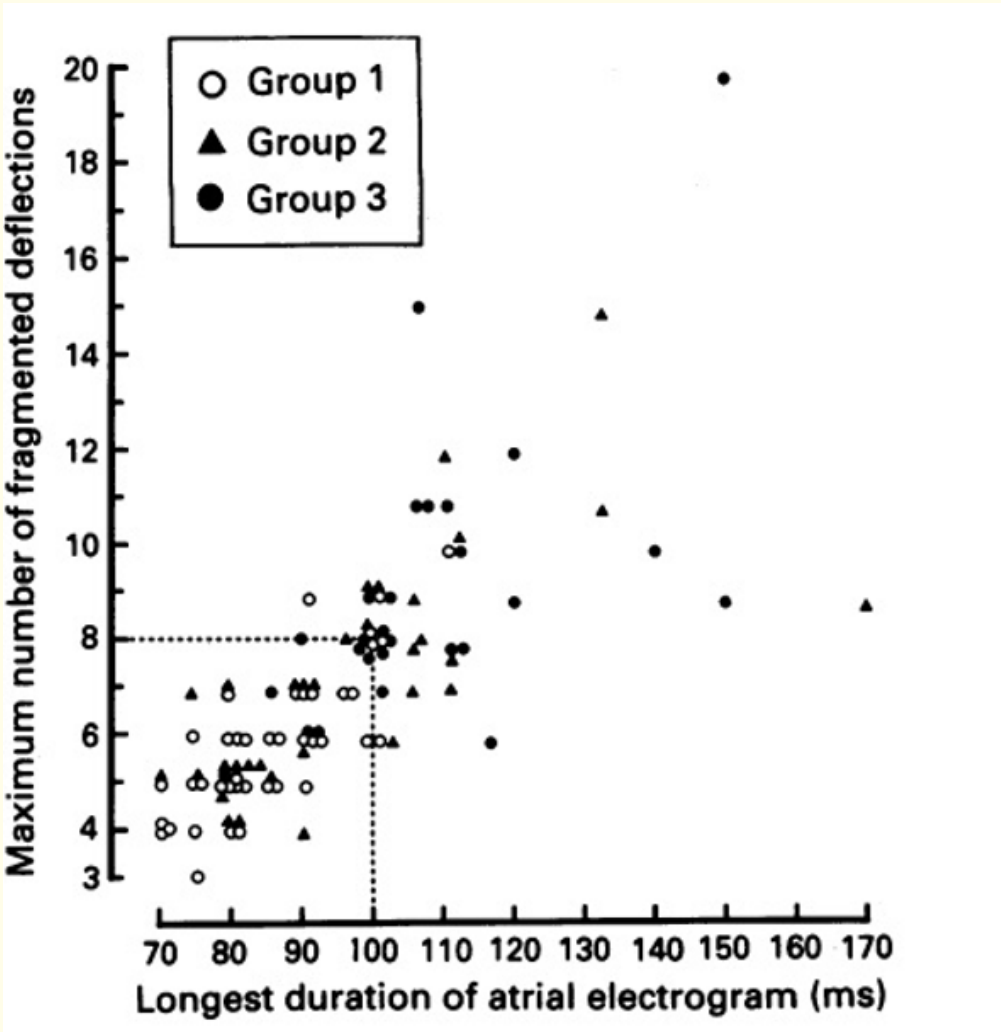

Figure 4: *Longest duration and the maximal number of fragmented deflections of atrial electrograms at 12 sites in the right atrium in each patient in the three groups are depicted. One symbol represents one patient. The broken lines indicate the limits of normality. Symbols on the lines or outside the square formed by the lines are abnormal results. As it is shown, SND patients from the Rubenstein Type II and Type III have a greater abnormality of the atrial electrograms. Reprinted with permission from Centurión OA, Fukatani M, Konoe A, Tanigawa M, Shimizu A, Isomoto S y col. Different distribution of abnormal endocardial electrogram within the right atrium in patients with sick sinus syndrome. Br Heart J 1992;68:596-600.*

In a pioneer study, Tanigawa M., *et al*. [18] defined the normal values of endocardial atrial electrograms based on the quantitative and qualitative measurements of 516 endocardial electrograms in 43 subjects with normal sinus node function and without PAF. The average duration and the average number of fragmented deflections of the endocardial atrial electrograms of these patients were 74 ± 11 ms and 3.9 ± 1.3, respectively. Therefore, with these average values obtained in normal subjects, values greater than 2 standard deviations were defined as abnormal values [18]. Therefore, an abnormal endocardial atrial electrogram was defined as having duration equal to or greater than 100 ms and/or eight or more fragmented deflections.

During the conduction of an electrical impulse, the axial current flows from one myocardial cell to the adjacent one through the intercalated discs, which normally have a relatively low resistance [24]. Under normal tissue conditions some mild disturbances in conduction of cardiac impulses may occur. The conduction perpendicular to the longitudinal axis of the atrial muscle fibers can be delayed because in that direction the effective axial resistance is greater [24]. This greater axial strength results in part from the scarce amount and short length of the intercalated discs in the lateral-lateral direction of the muscle fibers, compared to the terminal-terminal direction. When the atrial muscle fibers are separated by connective tissue, the conduction properties can be altered due to the effects on the axial resistance, creating a discontinuous and anisotropic propagation [24-31]. In this regard, Spach and colleagues have shown that the slowing of the conduction velocity causes a decrease in the amplitude and an increase in the duration of the extracellular electrogram of the canine Purkinje system [26]. To investigate the cause of the increase in the duration and deflections of the electrogram, it has been studied and demonstrated in a computerized model of electrogram generation that the decreased conduction velocity was responsible for the increase in electrogram duration, while intracellular resistance increased, was responsible for the fractional nature of the electrogram [30].

Detailed and quantitative pathological studies performed in patients with Rubenstein type SND have demonstrated extensive atrial myocardial fibrosis in the vicinity of the sinus node and internodal tracts [32-36]. Therefore, an abnormally prolonged and fractionated atrial endocardial electrogram recorded in these patients by mapping the right atrium during sinus rhythm, could translate a localized and non-homogeneous electrical activity related to a delayed, non-uniform and anisotropic conduction through a pathological atrial myocardium [14-17]. In addition, it has been demonstrated histologically that the tissues where the abnormally prolonged and fractionated electrograms originate present fibro-degenerative processes [24-26]. When the atrial walls are markedly altered by fibrosis, the depolarization wave must frequently change direction with respect to the longitudinal orientation of the myocardial fiber. This would cause unidirectional block, slow conduction and dispersion of the refractory periods in certain places, generating the fundamental elements of the re-entry mechanism [24,37-42].

Centurión OA., *et al.* designed a study to evaluate the relationship between certain electrophysiological parameters that indicate increased atrial vulnerability and abnormal atrial electrograms in patients with SND [43]. Among the electrophysiological indicators of increased atrial vulnerability were studied the fragmented atrial activity, atrial conduction delay, repetitive atrial firing and sustained atrial fibrillation, all induced by programmed atrial stimulation with single extra-stimulus (Figure 5). In this work, an attempt was made to clarify the importance and significance of the recording of abnormal atrial electrograms during sinus rhythm in patients with SND susceptible to developing atrial fibrillation. They showed that patients who had abnormal atrial electrograms had a significantly increased atrial vulnerability, compared to those with normal electrograms. Abnormal atrial electrograms showed a very good specificity and positive predictive value when evaluating the induction of sustained AF. The specificity demonstrated was 94% with a positive predictive value of 93% [43].

Although there are several factors that influence to a greater or lesser degree the appearance of AF in these patients with SND, abnormal atrial electrograms recorded during sinus rhythm in patients with electrophysiological alterations of the atrial myocardium could be considered as indicators of an increased atrial vulnerability [44-49]. We have demonstrated that there is a direct relationship between abnormal electrograms and age. There was a progressive increment in the extension of the electrophysiologically altered atrial myocardium with advancing age [19]. Considering that abnormal atrial electrograms increase with advancing age these electrophysiological changes may account for the ease to develop AF in elderly patients. In a study with 3D electroanatomic mapping, it was also found an age-related evidence of generalized conduction slowing in the atria [50]. They also found development of increasing numbers of fractionated signals and double potentials in the atrium but particularly along the crista terminalis with advancing age in patients with SND [51] (Figure 6). This fact may be important because functional conduction delay at this structure has been implicated in the development of a range of atrial arrhythmias.

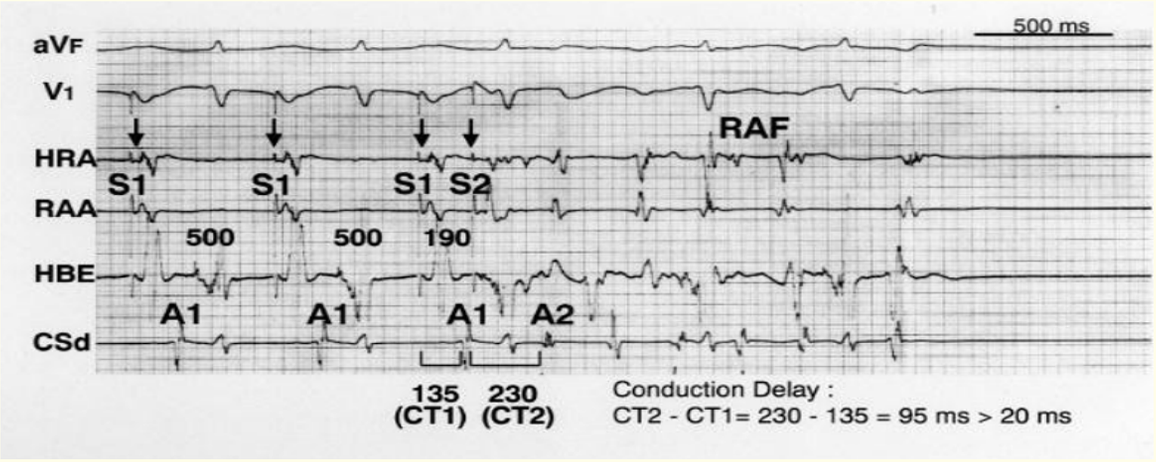

Figure 5: *Programmed atrial stimulation with single extra-stimulus at a coupling interval of 190 ms with a basic cycle interval of 500 ms that generates repetitive atrial activity (RAF) and a delay in interatrial conduction (CD) are depicted. S1 and A1 refer to the artifact of the stimulus and the atrial electrogram, respectively, of the beat of the basic cycle. S2 and A2 refer to the artifact of the stimulus and the atrial electrogram, respectively, of the extra-stimulus. The interval S1-A1 at the level of the distal coronary sinus (CSd) measures 135 ms (CT1). However, the S2-A2 interval is prolonged to 230 ms (CT2) with the extra-stimulus. Therefore, the maximum delay in interatrial conduction is 95 ms (CT2-CT1) (230-135 = 95).*

HRA: High Lateral Right Atrium; RAA: Right Atrial Appendage; HBE: Electrogram of the His Bundle; CSd: Coronary Sinus Distal; CT: Conduction Time. Reprinted with permission from Isomoto S, Centurion OA, Shibata R, et al. The effects of aging on the refractoriness and conduction of the atrium in patients with lone paroxysmal atrial fibrillation revealed with programmed atrial stimulation. Rev Soc Parag Cardiol 2005; 3: 25-30.

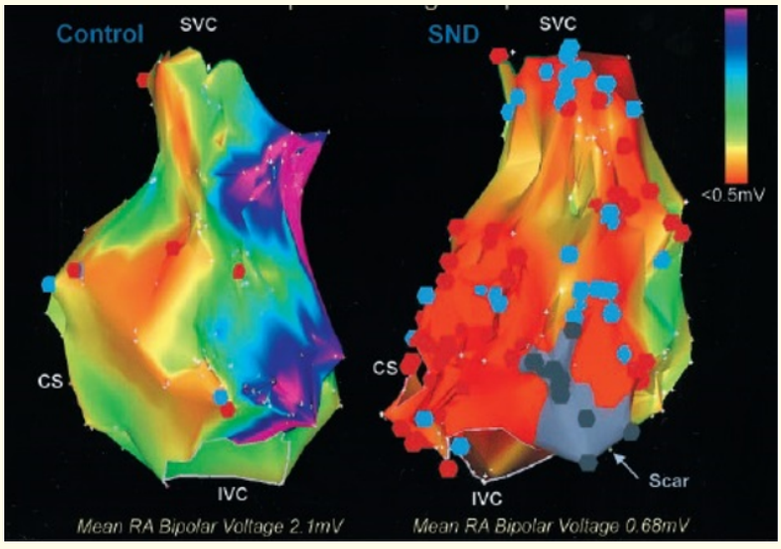

Figure 6: *Bipolar voltage mapping in a patient with SND (right) and an age matched control (left). Both atria are oriented such that posterior RA is in face. Areas of electrical silence (scar) are demonstrated in gray. Note, patient with SND demonstrates significantly greater number of points with DP (blue dots) and FS (brown dots). Reprinted with permission from Sanders P., Morton JB, Kistler PM, Spence SJ, Davidson NC, Hussin A, et al. Electrophysiological and electroanatomical characterization of the atria in sinus node disease: Evidence of diffuse atrial remodeling. Circulation 2004;109:1514-1522.*

DP: double potentials separated by an isoelectric interval; FS: fractionated signals-complex electrograms of long duration (≥ 50 ms).

The clinical implication demonstrated is that the detection of abnormal atrial electrograms during sinus rhythm in patients susceptible of developing AF, such as those with SND, can help to identify a group of patients with significantly increased atrial vulnerability and, a significantly higher incidence of spontaneous or induced episodes of PAF [52-57]. This could lead to taking the necessary preventive measures to avoid the disastrous consequences of this frightening tachyarrhythmia.

Conclusion

Typical electrocardiographic findings of SND are one or more episodes of extreme persistent sinus bradycardia (Rubenstein Type I), or sinus pauses, sinoatrial block or sinus arrest (Rubenstein Type II), or episodes of bradycardia and/or alternating pauses with atrial tachyarrhythmias (Rubenstein Type III). Investigations based on the recording of abnormally prolonged and fractionated atrial local electrograms during sinus rhythm and their characteristic distribution within the right atrium of patients with SND have provided important knowledge about the electrophysiological properties of the pathological atrial myocardium.

There is a different distribution of the abnormally prolonged and fractionated atrial endocardial electrograms in SND patients depending on the type of Rubenstein classification. Abnormal atrial electrograms were recorded diffusely from the entire right atrium in the Rubenstein type III SND patients. However, in SND patients from the Rubenstein Type I or Type II, the abnormal atrial electrograms were mainly recorded in the high zones of the right atrium.

The abnormal atrial electrogram results in an irregular atrial conduction characterized by a non-homogeneous local electrical activity, related to an anisotropic, non-uniform and delayed conduction through a pathological atrial myocardium, in which arrhythmias due to re-entry may arise. The detection of abnormal atrial electrograms in the SND identifies a group of patients with increased atrial vulnerability and a significantly higher incidence of spontaneous or induced episodes of atrial fibrillation.

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Volume 5 Issue 11 November 2018