Atrial Fibrillation: Pathogenetic Mechanisms and Electrophysiologic Peculiarities of the Heart Conduction System

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Summary

Due to a better understanding of its clinical complications and recent technical progress in medical technology, cardiologic research interests have been increasingly focusing on atrial fibrillation (AF). Sixty-six patients (47 male, 19 female, mean age 44.2 ± 9.5 years, range 23 to 64 years) with documented AF underwent electrophysiologic measurements at sinus rhythm, including accelerated and programmed pacing in both the right atrium (RA) and the coronary sinus (CS). Intracardiac electrograms (EGM) were recorded to evaluate several electrophysiologic parameters, such as interatrial conduction time (IACT) in the antegrade (from RA to CS) and the retrograde (from CS to RA) direction, effective refractory periods (ERP) of the RA, of the left atrium (LA), and of the atrioventricular (AV) node. The IACT analysis at sinus rhythm in paroxysmal AF patients and chronic AF patients after sinus rhythm restoration revealed conduction slowing between RA and CS, with a mean IACT of 84.3 ± 12.8 ms. Increases in IACT were detected during programmed stimulation; the IACT exceeded 100 ms and reached a mean of 124.3 ± 12.5 ms. The IACT progressively increased to 213.2 ± 14.7 ms as the extrastimulus delay approached the ERP of the RA. The ERP of the RA was 180.5 ± 20.4 ms on average, and the ERP of the LA was 220.2 ± 10.6 ms. Significant ERP dispersion of the RA and of the CS was detected in 47 patients (mean dispersion 40.4 ± 8.9 ms). Longitudinal AV node dissociation was observed in 18 patients (27%). It was characterized by an abrupt A2-H2 interval increase (more than 50 ms) in the differential His bundle EGM. We observed that AF aggravates not only the functional state of the atria in patients, but also causes electrophysiologic changes in the heart conduction system as a whole, manifesting themselves in AV conduction disturbances at all levels.

Key Words

Atrial fibrillation, electrophysiologic measurements, interatrial conduction, programmed stimulation, effective refractory period, vulnerable period

Introduction

Pathogenetic and electrophysiologic mechanisms of atrial fibrillation (AF) have been gaining increasing interest in the field of cardiac arrhythmia research during the last 40 years especially due to the introduction of esophageal and intracardiac investigation methods and computer data processing in practical cardiology. These methods have revealed the intimate mechanisms of most cardiac arrhythmias.

There are two main reasons for cardiologists to be interested in AF:

- Several implemented clinical trials have shown that AF is not the benign cardiac rhythm disturbance it was once thought to be, but is associated with significant morbidity and mortality [1-7].
- Technical progress in medical technology due to computer information processing allows detailed analysis of electrophysiologic processes during AF.

Decisive progress in explaining the AF mechanism was made by Allessie et al. in their studies on dogs [8]. Their wave model clarified the understanding of AF development and maintenance mechanisms and interrelated the roles of refractory period shortening and atrial conduction slowing in making reentry possible.

The early experimental reentry models of Mines [9]

and Rosenblueth [10] were based on a very "long" circle, where reentry is possible at almost normal conduction velocities (macro-reentry) because of the large circle size. Spach's [11] publications showed that macro-reentry conduction velocity might be altered. Even in the case of a very long circle, zones of slowed conduction with different pathologies of the myocardium can be localized [12-13]. The conduction velocity may decrease during the activation of not completely repolarized myocardium [14].

Moe et al. [15] included a time-dependent conduction delay in their AF computer model. This delay played a critical role in AF maintenance. Later, in experiments on rabbit atrial myocardium, Allesie [14] recorded a significant conduction delay. It was induced by extrastimuli delivered with less than 200 ms delay within shortened refractory periods, which had been caused by stimulating the vagal nerve. These research results indicated the possibility of reentry circuits in small myocardium areas. There, high-speed depolarization led to constant circular activation within a zone of only 6 mm in diameter. Slow conduction resulted due to the continuous activation of not completely regenerated myocardium ("step by step" activation on the tail of the refractory period induced by the previous circle wave). That led to the acceptance of functional conduction delay as a basis for short reentrant waves or micro-reentry [16].

Compromised myocardial structure integrity, as it can develop in the course of various pathologic processes, and a functional time-dependant conduction delay result in AF. The combination of enlarged atria size and a structure disturbance is responsible for a conduction delay, which promotes complicated reentry initiation and AF onset [17]. The closer the heart size is to a critical value, the easier is the AF induction, and the longer lasts the fibrillation [18]. Large variability of AF paroxysm duration can be observed in one and the same heart. Thus, a pathologic AF substrate should provide, first, higher AF inducibility, and/or, second, less chances for a spontaneous arrhythmia suspension. Electrical mapping of atrial excitation during AF is one of the most useful methods to study AF pathogenic mechanisms. Moe's multiple reentry wavelet hypothesis [19] based on the non-dampening extension of separate waves in the atria was experimentally confirmed for cholinergic AF on isolated dog hearts in 1985 [20]. The critical number of waves necessary for AF maintenance has been determined to be not less than three.

There are less publications concerning AF mapping in man [21, 22]. Cox and et al. [21] have examined Wolff-Parkinson-White patients during surgery on accessory atrioventricular (AV) pathways. Atrial fibrillation was triggered in the patients by electrical pulse discharge. Mapping of induced AF showed that the heart activation was associated with reentry in the right atrium in half of the cases; along with that the left atrium was activated inhomogeneously by excitation wave fronts exiting the right atrium reentry circuits or the accessory AV paths. These studies documented multiple waves around natural anatomic obstructions and also functional conduction blocks if the waves occurred to be the result of simple reentry circuits.

As mentioned above, the intracardiac electrophysiologic study is the alternative method to investigate electrophysiologic processes in the heart during AF. This method provides a tool to study characteristic changes of intracardiac conductivity in AF patients.

The protocol used by the majority of authors [23-25] is based on stimulation of the sinoatrial zone, the right atrium (RA) septal area, and the coronary sinus (CS). Programmed stimulation shows intracardiac conduction slowing as evidenced by a progressive St2-A2 interval increase when the St1-St2 intervals approach the atrial effective refractory period (ERP) during both the RA and CS stimulation [23-25].

Another result of programmed stimulation was the detection of an atrial electrogram (EGM) fragmentation that showed the atrial potential to become multiphasic or widened.

In our study, we tried to estimate not only the intracardiac conductivity in AF patients but also electrophysiologic peculiarities of the conduction system as a whole.

Materials and Methods

Sixty-six patients (47 male, 19 female) with documented AF (mean age was 44.2 ± 9.5 years, ranging from 23 to 64 years) were investigated. Thirty-six patients suffered from coronary artery disease, 17 from myocardial cardiosclerosis, 3 from cardiomyopathy, and 3 from rheumatism. Thyroiditis was diagnosed in one patient. No internal organ damages were revealed in 5 of the patients whose heart rate disturbances were considered as idiopathic. Paroxysmal AF was detected in 53 patients. They had been suffering from the arrhythmia for 3 months to 10 years, 2.3 ± 1.7 years on

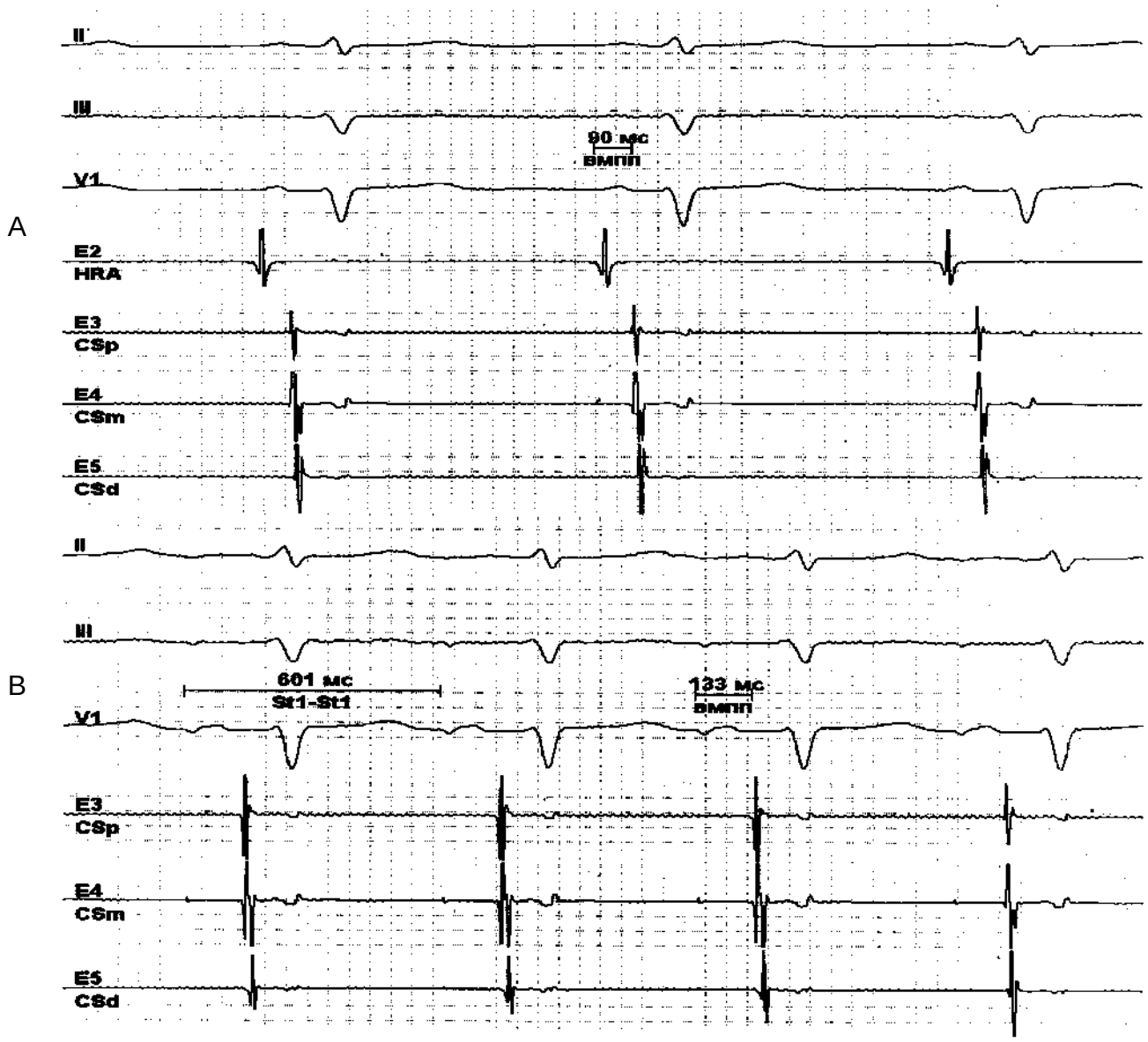

Figure 1. Fragments of electrophysiologic measurements (surface ECG and intracardiac EGMs): a) IACT at sinus rhythm is 90 ms; b) IACT during overpacing is 133 ms (basic pacing interval St1-St1 is 600 ms). II, III, V1 - standard leads, E2-E5 - intracardiac leads, HRA - high right atrium, CS - coronary sinus.

average. The frequency of AF attacks ranged from thrice a year to daily. The mean ventricular rate during tachyarrhythmia was 140.4 ± 35.9 bpm. The other 13 patients had been suffering from chronic AF for 3 months to 1 year.

Ultrasonic heart studies revealed left atrium dilatation in 49 patients, the mean left atrium size was 47.8 ± 5.4 mm.

An intracardiac electrophysiologic study was performed during sinus rhythm with the aid of the electrophysiologic system Elcart (Tomsk). In chronic AF patients, the sinus rhythm was restored by external cardioversion with 280 to 320 J prior to the investigation. Diagnostic pacing included accelerated and programmed stimulation of the RA (the sinoatrial zone and the lower third of the RA), of the CS, and of the

ventricles. The EGMs of the sinoatrial zone, CS, and His bundle were recorded.

The following parameters were evaluated:

- Wenckebach point
- interatrial conduction time (IACT) at sinus rhythm and during programmed stimulation both in the antegrade (from RA to CS) and the retrograde (from CS to RA) direction
- atrial potential amplitude
- ERP of the RA
- ERP of the LA
- ERP dispersion of the atria
- ERP of the AV node
- correlation of atrial and AV node ERP
- vulnerable zone
- changes in AV conduction (H2-V2 interval on the His bundle EGM).

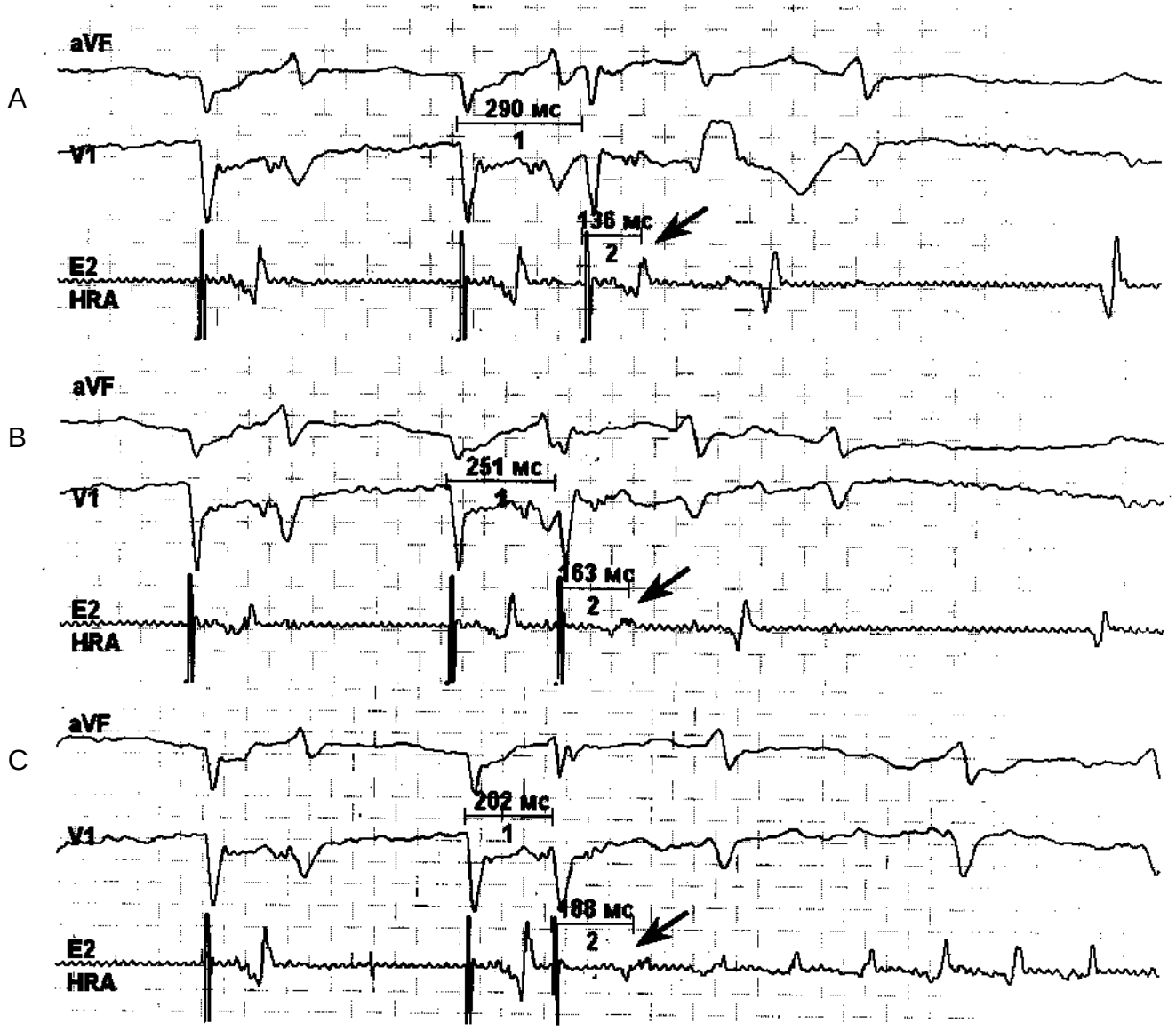

Figure 2. Intracardiac EGMs recorded during programmed CS pacing: HRA - high right atrium lead, 1 - programmed extrastimulus delay (St1-St2), 2 - intraatrial conduction time (IACT). As the programmed extrastimulus delay decreases (a - 290 ms, b - 251 ms, c - 202 ms), the retrograde IACT increases, and AF follows (c). Along with that, the atrial potential decreases and broadens.

Results and Discussion

The IACT analysis during sinus rhythm in paroxysmal AF patients as well as in chronic AF patients after sinus rhythm restoration showed slowing of the impulse conduction time between RA and CS; the average was 84.3 ± 12.8 ms. Even larger IACT increases were detected during programmed stimulation where the IACT exceeded 100 ms, with a mean value of 124.3 ± 12.5 ms (Figure 1). During programmed stimulation, the St2-A2 interval was stable, but the IACT progressively increased to 213.2 ± 14.7 ms as the extrastimulus delay approached the ERP of the RA.

The same conduction changes were detected in the case of CS stimulation. Sometimes one or several echo-answers were observed indicating occurrence of unstable local reentry circuits (vulnerable zone) [14,26], or AF paroxysm was induced (Figure 2). It should be noted that vulnerable zones were observed in

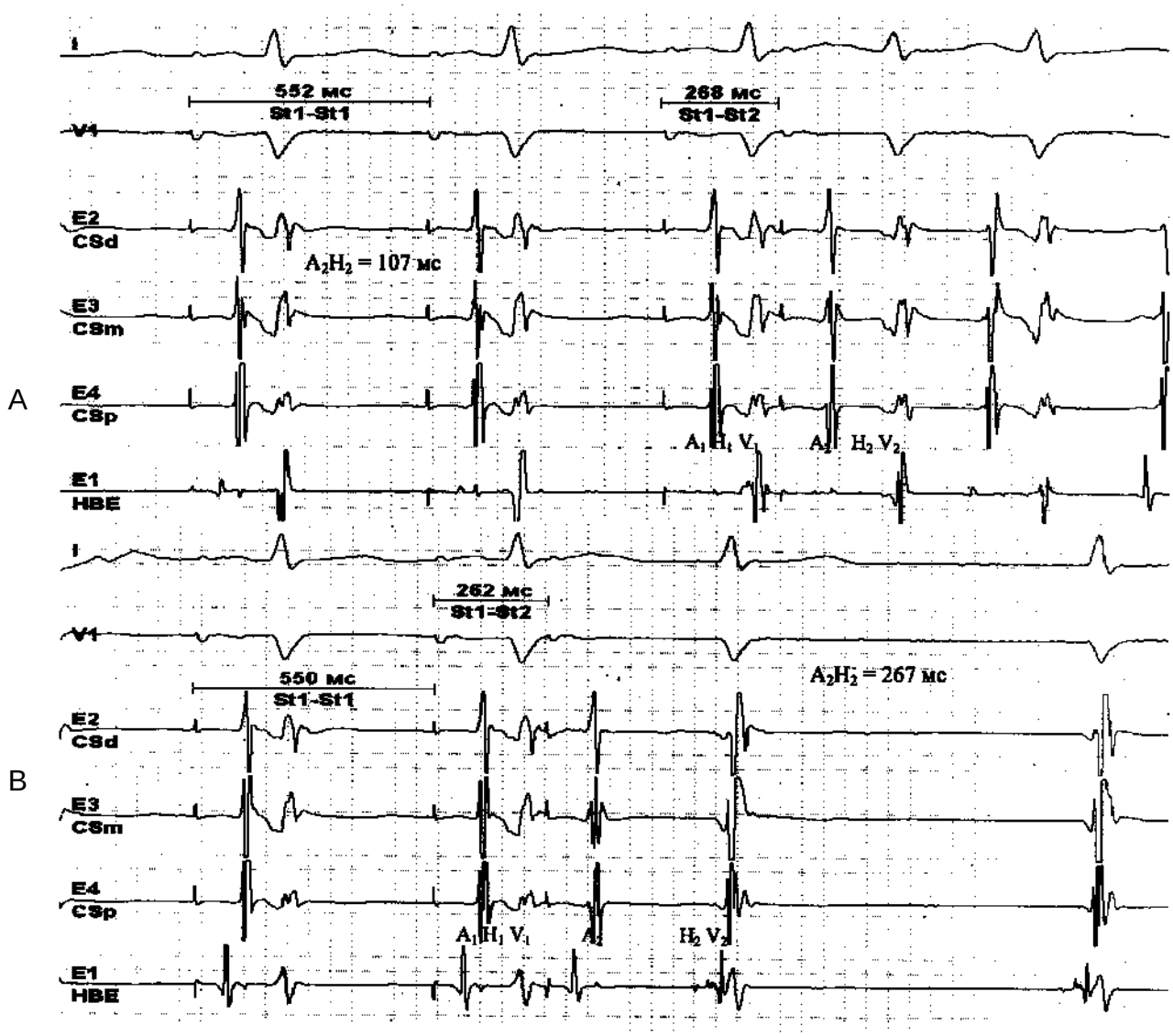

Figure 3. Fragment of electrophysiologic measurement. I, V1 - standard leads, E1-E4 - intracardiac leads, CS - coronary sinus, HBE - His bundle EGM. As the programmed extrastimulus delay decreases, the A2-H2 interval abruptly increases: a) St1-St2 = 268 ms, A2-H2 = 107 ms; b) St1-St2 = 262 ms, A2-H2 = 267 ms;

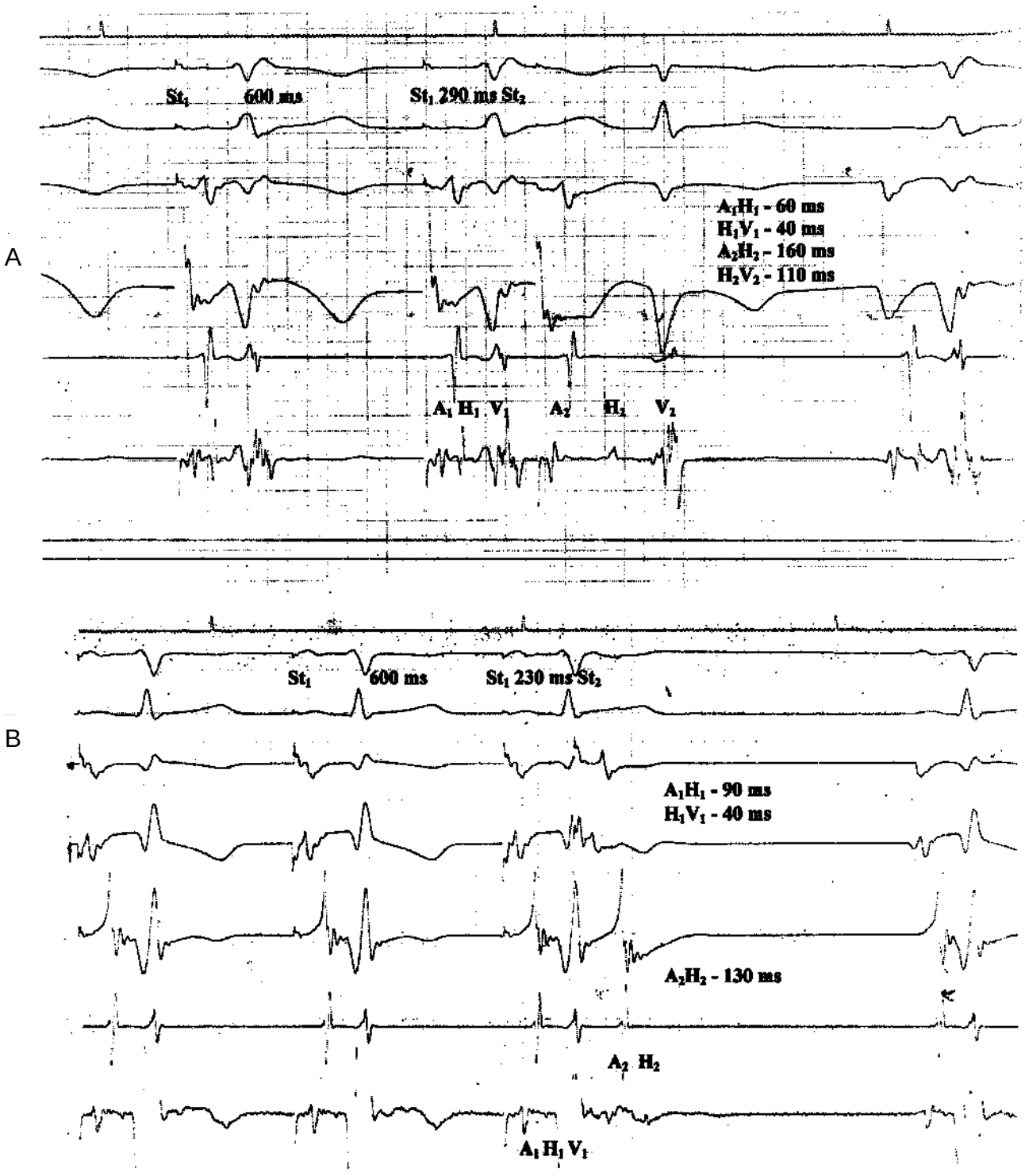

Figure 4. Fragment of electrophysiologic measurement: a) record of distal conduction disturbance (increased H2-V2 interval following the programmed extrastimulus) during programmed pacing; b) no additional ventricular signal follows the programmed extrastimulus.

48 patients during RA stimulation (the mean duration was 50.6 ± 10.8 ms). During CS stimulation, vulnerable zones were observed more often (in 57 patients) and existed longer (80.3 ± 20.5 ms).

In addition, during the programmed stimulation a modification in the atrial potential waveform was detected on differentiated EGMs. It was broadened, the amplitude decreased, and fragmentation occurred. These modifications affected the CS potential in 50% of the cases, and the RA potential in 90% of the cases during retrograde stimulation (Figure 2). This confirms the fact that interatrial conduction disturbances and differentiated EGM modifications are related to reentry and are the result of slow impulse propagation in the atria. These results indicate that AF onset is more often associated with the RA than with the LA. Slowing of the retrograde IACT more often revealed changes in the RA potential than in the CS potential, and the RA had a longer vulnerable period.

The ERP of the RA was 180.5 ± 20.4 ms on average, the ERP of the LA was 220.2 ± 10.6 ms. Significant differences in the ERP of the RA and of the CS were detected in 47 patients. The mean difference was 40.4 ± 8.9 ms. The presence of ERP dispersion and interatrial conduction disturbances with echo-answers can be generalized as "wave indices", which are the predictors of AF onset [27].

AV conduction disturbances were detected along with the above outlined changes. A longitudinal AV node dissociation was observed in 18 patients (27%). It was characterized by an abrupt A2-H2 interval increase (more than 50 ms) on the differential His bundle EGM (Figure 3).

Distal slowing of AV node conduction by up to 60 ms (H2-V2 interval) was observed in 39 patients (59%). During programmed stimulation, this disturbance was observed in all patients, the interval being 90 ± 15.6 ms on average. In some cases (9 patients), it was as long as 130 ms (Figure 4). It should be noted that distal conduction disturbance was associated with a His bundle conduction block of different grades (81%). In patients with very evident distal conduction disturbance (where an H2-V2 interval increase was recorded on the His bundle EGM without stimulation), the ventricular rate during AF paroxysms was significantly ($p < 0.05$) less (mean 126 ± 16.4 bpm) than in other patients (mean 168 ± 29.4 bpm). This should be taken into account when choosing a method to treat this pathology.

Conclusion

The results of our investigations support the AF wave model suggested by Moe [15] and supplemented by Allessie [8]. Interatrial conduction disturbance contributes significantly to AF. During programmed atrial stimulation, the IACT increases and a vulnerable zone appears due to local reentry loops. The changes in differentiated atrial potential EGMs and the atrial ERP dispersion also confirm the theory outlined above.

Structure changes and size enlargements in the LA are considered to play the main role in AF onset. However, Cox's research has shown that in half of the cases the AF onset is associated with the RA [21]. Our data support these results: Slowing of the retrograde IACT more often revealed changes in the RA potential than in the CS potential, and the RA had a longer vulnerable period.

As observed, AF in patients aggravates not only the functional state of the atria but also causes electrophysiologic changes in the heart conduction system as a whole, which are manifest in AV conduction disturbances at all levels.

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