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Effects of acute autonomic modulation on atrial conduction delay and local electrograms duration in paroxysmal atrial fibrillation

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ABSTRACT

Slowed atrial conduction may contribute to reentry circuits and vulnerability for atrial fibrillation (AF). The autonomic nervous system (ANS) has modulating effects on electrophysiological properties. However, complex interactions of the ANS with the arrhythmogenic substrate make it difficult to understand the mechanisms underlying induction and maintenance of AF.

Aim: To determine the effect of acute ANS modulation in atrial activation times in patients (P) with paroxysmal AF (PAF).

Methods and results: 16P (9 men; 59 ± 14 years) with PAF, who underwent electrophysiological study before AF ablation, and 15P (7 men; 58 ± 11 years) with atrioventricular nodal reentry tachycardia, without documentation or induction of AF (control group). Each group included 7P with arterial hypertension but without underlying structural heart disease. The study was performed while off drugs. Multipolar catheters were placed at the high right atrium (HRA), right atrial appendage (RAA), coronary sinus (CS) and His bundle area (His). At baseline and with HRA pacing (600 ms, shortest propagated S2) we measured: i) *intra-atrial conduction time* (IACT, between RAA and atrial deflection in the distal His), ii) *inter-atrial conduction time* (interACT, between RAA and distal CS), iii) *left atrial activation time* (LAAT, between atrial deflection in the distal His and distal CS), iv) *bipolar electrogram duration at four atrial sites* (RAA, His, proximal and distal CS). In the PAF group, measurements were also determined during handgrip and carotid sinus massage (CSM), and after pharmacological blockade of the ANS (ANSB). AF was induced by HRA programmed stimulation in 56% (self-limited – 6; sustained – 3), 68.8% (self-limited – 6; sustained – 5), and 50% (self-limited – 5; sustained – 3) of the P, in basal, during ANS maneuvers, and after ANSB, respectively ($p = \text{NS}$). IACT, interACT and LAAT significantly lengthened during HRA pacing in both groups (600 ms, S2). P with PAF have longer IACT ($p < 0.05$), a higher increase in both IACT, interACT ($p < 0.01$) and electrograms duration ($p < 0.05$) with S2, and more fragmented activity, compared with the control group. Atrial conduction times and electrograms duration were not significantly changed during ANS stimulation. Nevertheless, ANS maneuvers increased heterogeneity of the local electrograms duration. Also, P with sustained AF showed longer interACT and LAAT during CSM.

Conclusion: Atrial conduction times, electrograms duration and fractionated activity are increased in PAF, suggesting a role for conduction delays in the arrhythmogenic substrate. Acute vagal stimulation is associated with prolonged interACT and LAAT in P with inducible sustained AF and ANS modulation may influence the heterogeneity of atrial electrograms duration.

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1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in clinical practice. It has been recognized as a growing problem, with a prevalence ranging from 1% in the general population to more than 5% over the age of 65 [1,2]. The complex pathophysiology of AF has not been

clearly elucidated, due to limitations in studying the mechanisms that lead to the initiation and maintenance of this arrhythmia. Clinical and experimental works have provided new insights into a better understanding of AF, suggesting an important contribution of multiple depolarization wavelets, single dominant reentry circuits, focal sources of electrical activity, and different forms of atrial remodeling to the creation of electrophysiologic substrate for both the recurrence and progression to sustained AF [3–5]. Patients with established AF have regions of slowed conduction facilitating the functional substrate for the occurrence of reentry circuits within the atria [6].

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Furthermore, atrial remodeling causes changes in atrial refractoriness and atrial conduction that may promote AF [7]. Autonomic nervous system (ANS) activity is believed to play an important role in AF pathogenesis [8,9]. The onset of AF is often preceded by fluctuations in autonomic balance that are recognized as modulators in mediating AF [10,11]. Also, a number of electrophysiological properties related with vulnerability for AF may change as a result of vagal or sympathetic activation [12,13]. Vagal stimulation reduces velocity of the conduction in the atrial tissue and shortens the atrial effective refractory periods (ERP) heterogeneously, whereas sympathetic stimulation can increase atrial conduction velocity, favor trigger activity and uniformly reduce atrial refractoriness. However, complex interactions of the ANS with the arrhythmogenic substrate make it difficult to understand its influence in the mechanisms underlying induction and maintenance of AF. The present study was performed to assess the effects of acute ANS modulation in atrial conduction times and the duration of atrial local electrograms in patients with paroxysmal AF (PAF).

2. Methods

2.1. Patient groups

The study included a group of 16 patients (9 men and 7 women with a mean age of 59 ± 14 years) with ≥ 1 year duration of clinical history of PAF, documented with electrocardiograms and/or Holter recordings, despite antiarrhythmic therapy, referred to our institution for AF ablation, and a control group of 15 patients (7 men and 8 women with a mean age of 58 ± 11 years), with clinically documented supraventricular tachycardia (all with electrophysiological diagnosis of atrioventricular nodal reentry tachycardia). None of these patients had a history of AF or induction of AF during the electrophysiological study (EPS) performed before ablation. Each group included 7 patients with arterial hypertension, but without underlying structural heart disease assessed with transthoracic echocardiography.

Patients with previous myocardial infarction or angina, heart failure, evidence of sick sinus syndrome, failure to remain in stable sinus rhythm while in-hospital monitoring before the EPS, permanent pacemaker implanted, bronchopulmonary disease, sleep apnea, and pregnancy or thyroid dysfunction were excluded. Prior to the EPS, all antiarrhythmic drugs were withdrawn for at least 5 half-life times. Patients under amiodarone stopped treatment 2 months before the EPS. The study protocol was approved by the local ethics and performed according to the ethical guidelines of the Declaration of Helsinki. All subjects were required to give written informed consent.

2.2. Electrophysiological protocol

All patients underwent EPS in a non-sedated post-absorptive state. No serum electrolyte disturbances were found. Atrial electrical stimulation and recording of electrograms were performed by using 6F bipolar catheter electrodes inserted percutaneously into the femoral and internal jugular veins. Quadripolar electrode catheters (2-mm-spaced; DaigCo) were positioned in the high anterior wall of the right atrium (HRA), right atrial appendage (RAA), His bundle area (HBE), and a decapolar catheter with 2 mm interelectrode distance and 5 mm space between each electrode pair was advanced into the coronary sinus (CS) as distal as possible. Stability of the electrode catheters was maintained by fluoroscopic monitoring. Surface ECG leads I, II, V1, and V5 and four intracardiac electrograms (RAA, HBE, CS proximal and CS distal) were displayed on an oscilloscope and a multichannel electrophysiological recorder (Bard Lab System) with a frequency response of 50–500 Hz used onto optical disks for later analysis.

Intra-atrial conduction time (IACT), the interval from the RAA to the atrial electrogram at the HBE, interatrial conduction time (interACT), the interval from the RAA to the atrial electrogram at the distal part of the CS, left atrial activation time (LAAT), the interval from the atrial electrogram at the HBE to the atrial electrogram at distal CS, and local wave duration from different atrial sites (RAA, HBE, proximal and distal CS) were obtained during sinus rhythm, at baseline drive-train stimulation (S1–S1, cycle length of 600 ms) and at the earliest propagated extra-stimulus (S2) during S1 pacing at the HRA. The maximal prolongation of the atrial electrograms during S2 was represented by the % of increase compared to baseline at each recording site.

Stimulation was performed with impulses of 2 ms duration at twice the diastolic threshold. All atrial electrograms were recorded at a fixed gain setting (accompanied by a 0.2 mV = 0.3 mm calibration signal) and remained almost consistent and reproducible at each recording site in each patient. The duration of the local electrograms was measured from the beginning of the earliest electrical activity that deviated from the stable baseline value to the last point of the atrial electrogram at which the baseline value was crossed [14]. Fragmented activity was defined as a disorganized atrial electrogram, with multiple deflections, resulting in a prolonged duration of the activation complex greater than or equal to 150% of the electrogram duration of basic beats [15].

Table 1
Baseline patient clinical characteristics and left atrial size.

Characteristic	PAF group (n = 16)	Control group (n = 15)
Age, years	59 ± 14	58 ± 11
Male gender	56%	47%
Body mass index	27 ± 5	28 ± 6
History of hypertension	44%	47%
Heart rate, bpm	65 ± 9	63 ± 8
Systolic blood pressure, mm Hg	132 ± 20	126 ± 21
Diastolic blood pressure, mm Hg	85 ± 11	81 ± 12
LA M-mode, mm	43 ± 3	40 ± 3
History of palpitations; years	2.5 ± 2.0	3.0 ± 2.0

PAF = paroxysmal atrial fibrillation; LA = left atrium (M-mode measurements in parasternal view).

None of the variables differed significantly between the groups.

In the PAF group, measurements were made also during ANS stimulation maneuvers and after pharmacological ANS blockade (atropine 0.04 mg/kg + propranolol 0.15 mg/kg). Sympathetic stimulation was achieved by 3 min of static, intermittent handgrip (HG) of submaximal intensity until fatigue set in, and vagal activity was induced by right carotid sinus massage (CSM), with pressure applied at the point of strongest pulse at the level of the cricoid cartilage (for 10 s at 10-s intervals in 3-min periods). In the absence of a response, CSM was repeated on the left side. Continuous ECG and blood pressure monitoring, together with spectral analysis of RR intervals in the frequency domain (Task Force Monitor 3040; CNSystems), were used to confirm ANS stimulation or blockade. The frequency spectrum was divided into three components: very low frequency (VLF) (0–0.04 Hz), low frequency (LF) (0.04–0.15 Hz) and high frequency (HF) (0.15–0.4 Hz). HF values, attributed to vagal modulation, are affected by mechanical stimulation of the carotid sinus, while LF values mainly reflect sympathetic activity and increase during HG. Intravenous administration of propranolol and atropine resulted in total suppression of HF and LF activity, thus enabling assessment of the intrinsic electrophysiological properties [16].

All patients underwent programmed bipolar stimulation (drive-train cycle length of 600 ms using S2–S3 extra-stimuli delivered after eight paced beats) and incremental pacing protocols (short-term of burst pacing range from 600 to 300 ms) during sinus rhythm, by pacing from the distal electrode pair positioned at the HRA. AF was defined as a rapid atrial rhythm (rate > 350 beats/min) characterized by variability of the beat-to-beat cycle length, polarity, configuration and amplitude of the recorded atrial electrograms and lasting more than 5 cycles [17]. AF was considered not inducible; inducible, self-limited (< 60 s) or inducible, sustained, terminated by therapeutic intervention [18].

2.3. Statistical analysis

Categorical variables are expressed as frequencies and percentages. Continuous variables were expressed as means ± standard. Student's *t* test was used to compare all paired data in the same group. Comparisons between groups were made using the unpaired Student's *t* test, repeated ANOVA for continuous variables (overall comparison) or Mann–Whitney's test as appropriate. The chi-square test with Yates correction was used for categorical variables. A value of *p* < 0.05 was considered statistically significant. Data were analyzed using GraphPad Instruments version 3.05 (GraphPad Software, Inc., California, USA).

3. Results

Table 1 shows the clinical characteristics and the left atrial size (evaluated by M-mode echocardiography) of the patients with and without PAF. There were no significant differences between the groups.

Table 2
Comparison of the atrial conduction times between groups.

	SR	600 ms	S2
IACT (ms)			
PAF group	ψ34 ± 15	52 ± 19*	§102 ± 45**
Control group	24 ± 13	50 ± 22*	63 ± 19*
InterACT (ms)			
PAF group	82 ± 19	118 ± 22**	§176 ± 52**
Control group	73 ± 20	115 ± 20**	126 ± 22**
LAAT (ms)			
PAF group	53 ± 15	68 ± 17*	77 ± 58*
Control group	49 ± 18	58 ± 19*	70 ± 18*

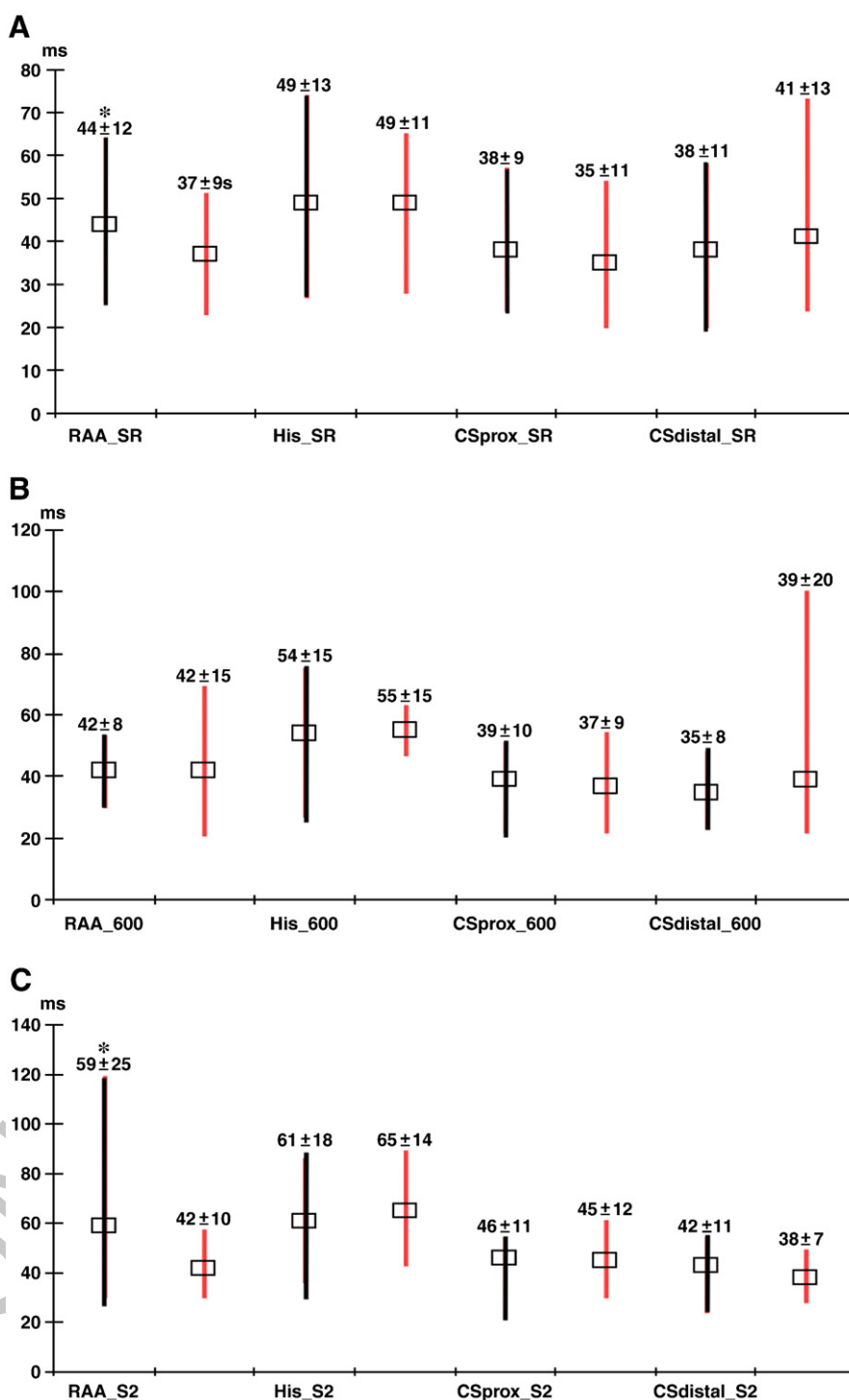
SR = sinus rhythm; 600 ms = drive-train stimulation with a cycle length of 600 ms; S2 = the earliest propagated extra-stimulus; IACT = intra-atrial conduction time; interACT = interatrial conduction time; LAAT = left atrial activation time; PAF = paroxysmal atrial fibrillation; control = no clinical history of atrial fibrillation nor induction of atrial fibrillation. **p* < 0.05 (vs. measurement in SR); ***p* < 0.01 (vs. measurement in SR); ψ*p* < 0.05 (between groups); §*p* < 0.01 (between groups).

179 AF was induced during programmed stimulation in 56% (self-limited – 6;
180 sustained – 3), 68.8% (self-limited – 6; sustained – 5), and 50% (self-limited – 5;
181 sustained – 3) of the PAF group in basal, during ANS maneuvers, and after ANS
182 blockade, respectively ($p = \text{NS}$).

183 In baseline, mean P-wave duration was 108 ± 14 ms in patients with PAF and $96 \pm$
184 20 ms in patients without AF ($p = 0.05$). Baseline IACT, during sinus rhythm, was longer
185 in the PAF group, compared to the control group, without significant differences in
186 interACT and LAAT between groups (Table 2). IACT, interACT and LAAT significantly

187 lengthened in both groups during HRA pacing (drive-train with a cycle length of
188 600 ms and during premature stimulation). Patients with PAF showed a greater
189 prolongation in both IACT and interACT with the earliest propagated extra-stimulus
190 ($p < 0.01$) (Table 2).

191 Electrogram duration showed significant differences at the RAA, when comparing
192 both groups during baseline sinus rhythm and with S2 (Fig. 1). Also, patients with PAF
193 had greater prolongation of electrogram wave duration measured at the RAA and
194 distal CS during the earliest propagated S2 ($73 \pm 35\%$ vs. $11 \pm 8\%$ at the RAA and $13 \pm 3\%$



Q1

Fig. 1. Electrogram duration measured in sinus rhythm (SR) and during high right atrium pacing with a drive-train stimulation (600 ms) and with the earliest propagated extra-stimulus (S2). Comparison between the group with paroxysmal atrial fibrillation (black line) and the group without atrial fibrillation (red line). A: Baseline values during SR ($*p < 0.05$, at RAA site). B: Values during 600 ms cycle length pacing ($p = \text{NS}$). C: Values during the earliest propagated S2 ($*p < 0.05$, at RAA site). Values expressed in milliseconds, mean \pm standard deviation. The lines represent mean, maximum and minimum values. RAA = right atrial appendage; His = His position; CSprox = proximal coronary sinus; CSdistal = distal coronary sinus. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 3
Atrial conduction times during autonomic modulation in paroxysmal atrial fibrillation patients.

	PAF group (n = 16)	AF non-inducible (n = 5)	AF inducible (n = 11)	AF self-limited (n = 6)	AF sustained (n = 5)
IACT_baseline	34 ± 15	34 ± 18	35 ± 15	35 ± 19	35 ± 10
IACT_hand-grip	29 ± 11	32 ± 15	28 ± 10	27 ± 13	29 ± 7
IACT_carotid sinus massage	30 ± 14	29 ± 7	29 ± 11	30 ± 9	30 ± 13
IACT_ANS blockade	28 ± 13	25 ± 13	30 ± 14	29 ± 5	30 ± 13
interACT_baseline	82 ± 19	77 ± 24	83 ± 19	80 ± 20	86 ± 20
interACT_hand-grip	84 ± 20	83 ± 18	84 ± 22	80 ± 26	89 ± 17
interACT_carotid sinus massage	80 ± 21	76 ± 28	81 ± 18	71 ± 17*	95 ± 5*
interACT_ANS blockade	72 ± 14	64 ± 16	80 ± 8	74 ± 20	77 ± 9
LAAT_baseline	53 ± 15	44 ± 7	54 ± 19	53 ± 10	57 ± 19
LAAT_hand-grip	55 ± 17	51 ± 11	57 ± 19	52 ± 21	62 ± 16
LAAT_carotid sinus massage	52 ± 16	45 ± 7**	55 ± 14	47 ± 7**	65 ± 14**
LAAT_ANS blockade	44 ± 12	38 ± 11	42 ± 14	45 ± 13	48 ± 11

PAF = paroxysmal atrial fibrillation; AF = atrial fibrillation; IACT = intra-atrial conduction time; interACT = interatrial conduction time; LAAT = left atrial activation time; ANS = autonomic nervous system. Values expressed in milliseconds, mean ± standard deviation. *p<0.05; **p<0.01.

vs. 1 ± 6% ms at the distal CS, for PAF patients and control group, respectively; p<0.05).
Fragmented atrial activity was identified in 43.8% of the PAF group and in 6.7% of the control group (p=0.03).

3.1. Conduction parameters during acute autonomic modulation

Table 3 summarizes the results of the atrial conduction intervals during HG and CSM maneuvers, and after ANS blockade among patients with PAF. Atrial conduction

times were not significantly changed during ANS stimulation. However, patients with inducible sustained AF had longer interACT and LAAT during CSM.

Despite longer electrograms in RAA and His during CSM when compared to baseline recordings, there were no significant differences in the mean duration of the measured electrograms during autonomic stimulation or after autonomic blockade (Fig. 2). Nevertheless, we observed an increased heterogeneity of the atrial wave duration, with significant differences between the recording sites, appearing during ANS maneuvers, and abolished after ANS blockade (Fig. 2). Representative intracardiac

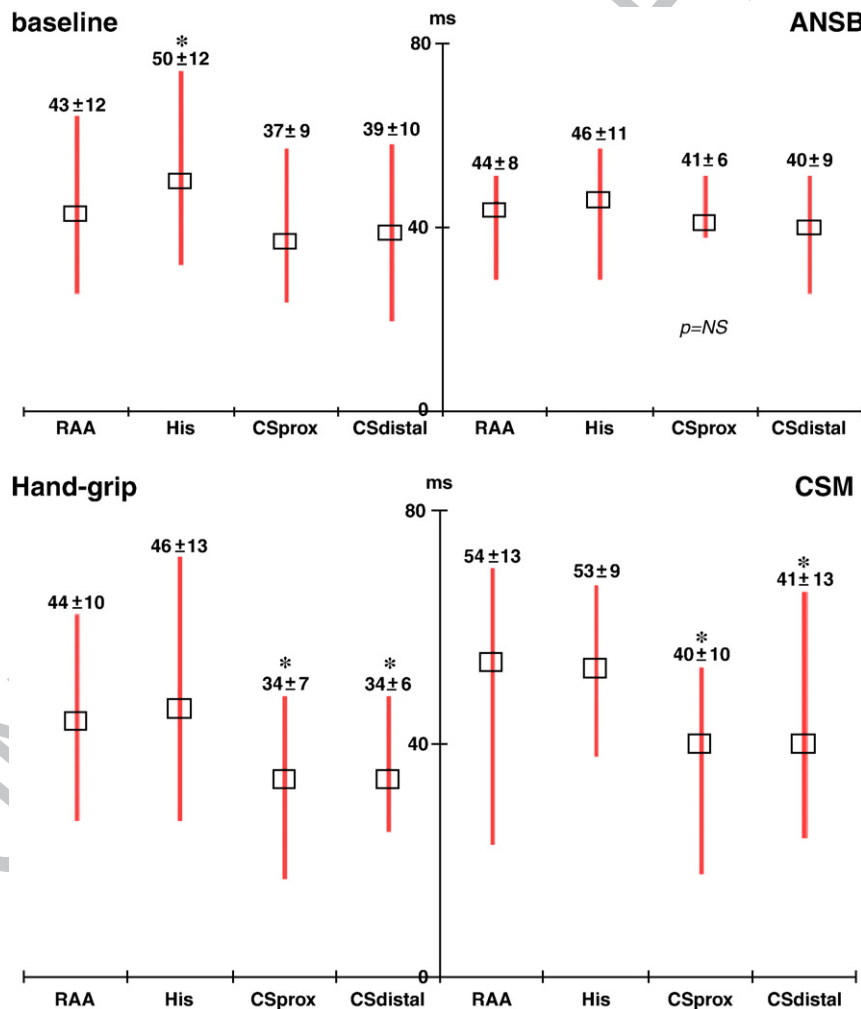


Fig. 2. Electrogram duration measured during sinus rhythm in baseline, with handgrip, carotid sinus massage (CSM) and after pharmacological blockade of autonomic activity (ANSB). *p<0.05 compared to other sites. Values expressed in milliseconds, mean ± standard deviation. The lines represent mean, maximum and minimum values. RAA = right atrial appendage; His = His position; CSprox = proximal coronary sinus; CSdistal = distal coronary sinus.

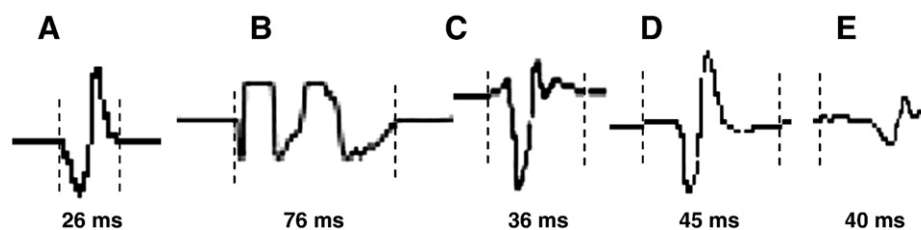


Fig. 3. Electrograms obtained from the right atrial appendage in a 72 years old woman with paroxysmal atrial fibrillation. Sinus rhythm (A), with the earliest propagated extra-stimulus (B), during handgrip (C) and carotid sinus massage (D), and after pharmacological autonomic blockade (E).

209 electrograms, obtained from the RAA during sinus rhythm, with S2, HG and CSM, and
210 after ANSB are shown in Fig. 3.

211 4. Discussion

212 Although the triggers for AF initiation appear to be located in the
213 pulmonary veins, established AF has been associated with conduction
214 disturbances and heterogeneous reduction of ERP, that facilitate the
215 occurrence of multiple reentry circuits within the atria, probably
216 contributing to the electrophysiological substrate required for the
217 presence of AF [3,6,18].

218 While prolongation of atrial conduction is a frequent finding in
219 patients with AF [19,20], the influence of autonomic activity in the
220 atrial conduction intervals and local wave duration is incompletely
221 explored. The present study characterized the IACT, the interACT and
222 electrogram duration measured in different atrial recording sites in
223 response to an extra-stimulus with a short coupling interval and
224 during acute modulation of the ANS. There were no differences
225 between the baseline characteristics of PAF patients and controls.
226 However, the group with history of PAF showed longer IACT and RAA
227 electrograms in baseline, compared with control patients. Further-
228 more, they showed significant atrial conduction delays and greater
229 prolongation of atrial wave duration during early premature impulses
230 delivered at the HRA. Also, fragmented atrial activity was identified in
231 more patients with PAF than in control patients. These findings are
232 consistent with previous studies who demonstrated greater delays in
233 intra-atrial or inter-atrial conduction, and a higher incidence of atrial
234 fragmentation in patients with PAF [6,20–22]. In fact, the presence of
235 marked conduction delay during an atrial premature beat with a short
236 coupling interval, combined with longer and fractionated electro-
237 grams is an important electrophysiological finding, compatible with
238 the necessary conditions for the occurrence and maintenance of local
239 reentry circuits. Focal repetitive activity, most frequently originated
240 from pulmonary veins, plays an important role in the initiation of AF,
241 particularly when combined with abnormal atrial impulse conduc-
242 tion, which appears to be pre-requisite for the maintenance of AF
243 [23,24]. Heterogeneity of atrial conduction delay and the presence of
244 local fragmented potentials have long been associated with the
245 substrate for AF [25–27]. The greater prolongation of atrial activation
246 times and of local wave duration with the earliest propagated extra-
247 stimulus, showed in our results, might contribute to explain why the
248 mean coupling interval was significantly shorter for pulmonary veins
249 discharges initiating AF than for discharges that did not in a recent
250 study by Arentz et al. [28]. Therefore, a combination of atrial
251 premature complexes with short coupling intervals and delayed
252 activation of the atria may act as one component of the arrhythmo-
253 genic substrate for the vulnerability to PAF.

254 4.1. Autonomic modulation of conduction parameters in PAF patients

255 The supporting evidence of the impact of ANS activity in the
256 electrophysiological properties of the atria and its role in the initiation
257 and maintenance of AF has been mostly studied in experimental
258 preparations. Little is known about the effects of acute stimulation or

259 blockade of the ANS in atrial conduction and electrogram duration
260 during electrophysiological evaluation of patients with PAF. In our
261 data, obtained from patients with clinical history of PAF, the interACT
262 and LAAT were significantly prolonged during CSM in the group with
263 inducible sustained AF, supporting the notion that the substrate of AF
264 is associated with conduction abnormalities of the atria, which can be
265 more pronounced during vagal stimulation and contribute to the
266 maintenance of AF. Although conduction abnormalities in PAF have
267 been associated with increased age, atrial dilation and stretch, fibrosis,
268 changes in the expression levels of connexins and electrophysiological
269 remodeling [2,3,5–7,24], acute autonomic modulation seems to
270 influence atrial conduction properties in patients with PAF.

271 It has been known that vagal stimulation shortens the atrial ERP
272 and increases dispersion of atrial refractoriness [8,9,12,13]. Although
273 both vagal and sympathetic stimulations could produce significant
274 reductions on ERP, vagal stimulation appears more arrhythmogenic in
275 promoting AF [29]. One reason could be related with the lengthening
276 of atrial conduction time during vagal activity, that results in a
277 pronounced wavelength shortening (ERP x conduction velocity),
278 which would promote AF maintenance.

279 In the present study, we evaluated atrial electrograms duration
280 during autonomic stimulation and after pharmacological autonomic
281 blockade. Electrograms duration increased slightly in RAA and His
282 during CSM, but no significant differences were obtained during acute
283 autonomic modulation. However, when compared to baseline
284 recordings, differences in atrial wave duration between the recording
285 sites became more pronounced during ANS maneuvers and were
286 abolished after ANS blockade. Although the impact of autonomic
287 stimulation appears to be modest in the induction of AF (68.8% during
288 ANS maneuvers vs. 50% after ANS blockade), it is possible that the
289 electrogram duration heterogeneity and local conduction delay
290 produced by autonomic modulation contribute to the initiation and
291 maintenance of AF. Vagal stimulation has been found to result in a
292 large regional heterogeneity of atrial electrograms, and there is
293 evidence that the appearance of complex fractionated atrial electro-
294 grams during activation of the intrinsic cardiac autonomic neural
295 elements reflects a change in the local electrophysiological properties
296 [30,31]. In fact, differential areas of conduction velocity and dispersion
297 of electrogram characteristics may provide a substrate for functional
298 reentry, creating a suitable environment for AF [32,33].

299 All patients underwent programmed bipolar stimulation (drive-
300 train cycle length of 600 ms using S2–S3 extra-stimuli delivered after
301 eight paced beats) and incremental pacing protocols (short-term of
302 burst pacing range from 600 to 300 ms) during sinus rhythm, by
303 pacing from the distal electrode pair positioned at the HRA.

304 There have been limited data on autonomic influences in the
305 characteristics of electrograms during sinus rhythm. Guo et al., in a
306 canine model, found that vagal stimulation shortened the electrogram
307 duration in ischemic myocardium zone in the right atrium, whereas
308 sympathetic stimulation did not alter electrogram duration [34]. In a
309 previous analysis of atrial electrograms during sinus rhythm in
310 patients with PAF, electrograms with ≥ 4 deflections and duration
311 ≥ 40 ms were associated with a parasympathetic response during AF
312 ablation [35]. The explanation for this finding was related with local

effects of acetylcholine in atrial tissue, causing conduction block between adjacent fiber bundles. Recently, in a different study, complex fractionated atrial electrograms, representing slow conduction areas or pivoting points in reentry circuits, were induced by local application of varying concentrations of acetylcholine or by injecting acetylcholine into the anterior right ganglionated plexi, providing evidence that ANS activity may induce changes in local atrial conduction [36].

There is a great need for experimental and clinical studies to better understand the relationship between the dynamic changes in atrial electrogram morphology and autonomic innervation and its role in the maintenance of AF.

5. Study limitations

Although it was possible to identify slight changes in atrial activation times and wave duration during acute autonomic modulation, the study included a small number of patients. However, all patients acted as their own controls to enable comparison of the parameters during stimulation and after blockade of the ANS. Although obtaining high density recordings by using multipolar catheters with better spatial resolution from several simultaneous right and left atrial sites could give more precise results, allowing a better comprehension of the problem, transeptal punctures for the use of left atrial catheters were not justifiable in a preliminary investigative study in humans. Another concern is that despite the confirmation of HG and CSM effects based on frequency domain spectral analysis, direct stimulation of sympathetic and parasympathetic nerves would have improved the results.

6. Conclusions

The presented study demonstrated that atrial conduction times, electrograms duration and fractionated activity are increased in patients with PAF when compared with control patients, suggesting that conduction abnormalities in the atria contribute to the arrhythmogenic substrate for AF. Also, acute vagal stimulation prolonged interACT and LAAT in patients with inducible sustained AF and ANS modulation influenced the heterogeneity of atrial electrograms duration in the recording sites. These should be taken into consideration in future studies in order to better understand the dynamic phenomena involved in the onset and perpetuation of AF episodes.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [37].

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