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Contraction-Excitation Feedback in Human Atrial Fibrillation

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Summary

Background: Contraction-excitation feedback, that is, electrophysiologic changes that are caused or preceded by mechanical changes of the myocardium, has been extensively studied in the ventricles. The role of contraction-excitation feedback in the atria, and more particularly in the genesis and maintenance of atrial fibrillation, has been less adequately investigated.

Hypothesis: The aim of the present study was to determine whether increased right atrial pressure (RAP) facilitates the induction of atrial fibrillation (AF) in patients with a history of lone AF.

Methods: Sixteen patients with a history of paroxysmal AF but without structural heart disease were included in the study. All patients underwent electrophysiologic study at both a lower (3.1 ± 2.0 mmHg) and (in 13 cases) a higher (6.4 ± 2.5 mmHg) RAP. "Higher" was considered the pressure following rapid (in about 30 min) intravenous administration of normal saline or before the administration of a diuretic.

Results: Rapid atrial pacing induced AF in 19 of 29 attempts. At a lower pressure, rapid pacing induced brief (3 s to 3 min) AF in 3 of 16 patients, long-lasting (>3 min) AF in 3 of 16 patients, and no AF in 10 of 16 patients. At a higher pressure, brief AF was induced in 3 of 10 patients in whom no AF could be induced at a lower pressure, and long-lasting AF in 10 patients in whom either brief AF (3 cases) or no AF (7 cases) was induced at a lower pressure. In 11 patients, in whom Wenckebach periodicity was determined at both higher and lower pressure, the critical cycle length at which atrioventricular block appeared was significantly ($p<0.001$, paired *t*-test) longer (349.1 ± 44.4 ms, i.e., +15.5 ± 11.3 ms) at higher than at lower atrial pressure (333.6 ± 41.0 ms). In nine patients, in whom Wenckebach periodicity was determined and two rhythms occurred at different pressures, the critical cycle length was 332.2 ± 45.8 ms when associated with sinus rhythm, and significantly ($p<0.01$) longer (344.4 ± 48.0 ms, i.e., +12.2 ± 8.3 ms) when associated with induction of AF.

Conclusion: In patients with lone atrial fibrillation, modest increases in atrial pressure may facilitate the induction of atrial fibrillation.

Key words: contraction-excitation feedback, atrial fibrillation, atrial refractoriness, Wenckebach periodicity

Introduction

Contraction-excitation feedback, that is, electrophysiologic changes that are caused or preceded by mechanical changes of the myocardium, has been extensively studied in the ventricles.[1–4] The role of contraction-excitation feedback in the atria, and more particularly in the genesis and maintenance of atrial fibrillation, has been less adequately investigated.[5] Previous investigators[6,7] have confirmed that a change in the mechanical properties of the atrial myocardium may cause a change in atrial refractoriness. In healthy canine atria, an elevation of the atrial pressure is associated with an increase in the propensity of the atria to fibrillate.[8] If atrial fibrillation (AF) may be induced more easily with extreme pressure increases in normal canine atria,[8] the same might occur with only modest pressure increases in atria of patients who fibrillate easily for some reason, as in lone fibrillation. The purpose of this study was to investigate the hypothesis that increased atrial pressure may facilitate the induction of AF in patients with lone AF (or in susceptible patients) and to study the effect of atrial pressure on atrial refractoriness. If this hypothesis proves valid, patients with lone AF might benefit by keeping their atrial pressure at low levels.

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Methods

Patient Population

Sixteen patients with lone AF aged 54.7 ± 7.0 years (mean ± SD), were studied. All patients had at least three paroxysms of AF and none had structural heart disease as assessed by clinical examination, electrocardiogram (ECG), chest x-ray, and echocardiography. In all patients, the size of the left atrium was ≤40 mm. The thyroid function was normal. No patient was receiving diuretics. All antiarrhythmic drugs and digitalis had been discontinued for ≥5 half lives.

All patients had given informed consent and the study protocol had been approved by the Central Council of Health of the Ministry of Health. The ethical aspects of the protocol were considered by the Central Council of Health, which is constituted by both medical doctors and laymen.

Electrophysiologic Testing

All studies were performed during sinus rhythm in the fasting, unsedated state under local anesthesia with lidocaine. Two quadripolar electrode catheters were inserted percutaneously from the right femoral vein and positioned under fluoroscopic guidance in the high right atrium and the His-bundle region. A central lumen Swan-Ganz catheter was positioned in the mid right atrium via the left femoral vein for recording right atrial pressure. Lead I or II of the surface ECG, the two intracardiac recordings, and the right atrial pressure were simultaneously displayed on a PPG Hellige EVR 12 recorder.

Pacing Protocol

Pacing was performed using the Medronic Stimulator with pulses 2 ms in duration at twice stimulation threshold, while the right atrial and His electrogram were recorded. The effective refractory period of the right atrium was determined using two pacing drive cycle lengths of 600 and 500 ms. A premature stimulus was introduced after a regular sequence of eight paced beats and the coupling interval was reduced in decrements of 10 ms. The effective refractory period of the right atrial myocardium was considered as the longest coupling interval of the stimulus that did not result in a propagated atrial response. The critical pacing rate for Wenckebach periodicity of the atrioventricular node was determined using incremental right atrial pacing.

Burst atrial pacing was performed at different cycle lengths starting at 600 ms and progressively reduced in decrements of 50 to 200 ms. Rapid stimulation was performed at each cycle length for 10 s, followed by a 10-s cessation of pacing. If long-lasting (>3 min) AF could not be induced by this protocol, a rapid intravenous infusion of up to 1000 ml normal saline was given within about 30 min, aiming at doubling the right atrial pressure. The protocol was then repeated for determination of right atrial effective refractory period and burst atrial pacing. If, on the other hand, AF could be initiated at baseline state, furosemide 40 mg was given intravenously to reduce right atrial pressure and the patient was observed for 30 min. If sinus rhythm was restored, the pacing protocol was repeated. If, according to the protocol, AF persisted for over 6 h, electrical cardioversion would have needed to be performed; in fact, this was not necessary in any case.

In the following, atrial pressures are considered as "higher" after the intravenous saline infusion or before furosemide administration, or "lower" before the saline infusion or after administration of diuretics.

Atrial fibrillation was considered to exist when spontaneous irregular atrial activity at a mean rate of ≥300/min was present on the atrial electrogram for at least 3 s.

Statistics

All results are given as mean ± standard deviation. The Student's independent *t*-test was used to compare mean values of the two groups. The mean change of one parameter in one group is expressed as mean change with the + or −sign, respectively; ± standard deviation of the difference and its significance was evaluated using the paired *t*-test. The incidence of AF inducibility was analyzed using the chi-square test. A p value of < 0.05 was considered significant.

Results

The baseline mean atrial pressure was 3.2 ± 2.1 mmHg. In four patients, the baseline rapid pacing caused long-lasting AF, in three others brief (3 s to 3 min) AF, and in the remaining nine patients the baseline pacing left the atria in sinus rhythm (Table I). In one of the patients (No. 16, Table I), in whom long-lasting AF occurred in the baseline test, brief AF had occurred twice while trying to measure the effective refractory period. Normal saline was given to all 12 patients in whom the initial pacing did not cause long-lasting AF. Overall, the change in pressure in these patients was +3.5 ± 1.00 mmHg. Furosemide was given to three of the remaining four patients and resulted in a diminution of the pressure by 2.5 ± 2.8 mmHg.

Table I shows the rhythm effect of rapid atrial pacing on the 16 patients. In one of the four patients (No. 13, Table I) with long-lasting AF before any volume intervention, right atrial pressure was reduced from 6 to 4 mmHg in about 25 min following the administration of intravenous furosemide, and sinus rhythm was restored spontaneously. Rapid atrial pacing at a pressure of 4 mmHg failed to cause AF in this patient. In the remaining three patients, AF persisted for over 30 min.

The atrial pressure in the three patients with brief AF (1.0 ± 1.0 mmHg) was increased by +2.7 ± 1.1 mmHg following the fluid infusion. Long-lasting AF occurred in all three patients during pacing after the atrial pressure elevation. In two of these patients, arrhythmia was initiated while trying to determine the pacing rate for the appearance of Wenckebach periodicity.

The atrial pressure in the nine patients who remained in sinus rhythm at baseline study was 3.4 ± 2.0 mmHg. One of these patients (No. 1, Table I) with an atrial pressure of 1

TABLE I Atrial pressure, electrophysiologic parameters, and associated rhythm before and after intervention (fluid infusion or furosemide)

Patient	Before				After			
No.	RAP	ERP	Wenc	Rht	RAP	ERP	Wenc	Rht
1	1	270	340	SR	5	270	360	SR
2	3	230	380	SR	6	240	390	SAF
3	3	250	300	SR	7	270	300	SAF
4	8	240	330	SR	12	230	340	SAF
5	2	240	400	SR	5	230	410	LAF
6	3	180	280	SR	6	180	300	LAF
7	3	260	380	SR	7	270	400	LAF
8	3	270	340	SR	8	270	360	LAF
9	5	240	300	SR	10	230	320	LAF
10	0	180	340	SAF	4	190	380	LAF
11	1	200	220	SAF	3	220	LAF	—
12	2	240	240	SAF	4	220	LAF	—
13	6	210	280	LAF	4	210	280	SR
14	1	180	340	LAF	—	—	—	—
15	5	270	280	LAF	—	—	—	—
16	5	SAF	340	LAF	—	—	—	—
Mean	3.2	230.7	318.1		6.2	233.1	349.1	
SD	2.1	33.1	50.1		2.6	30.4	44.4	
N	16	15	16		13	13	11	

Abbreviations: RAP = right atrial pressure (mmHg), ERP = effective refractory period (ms), Wenc = cycle length at which Wenckebach atrioventricular block occurred (ms), Rht = rhythm induced, SR = sinus rhythm, SAF = atrial fibrillation of short duration, LAF = long-lasting atrial fibrillation, SD = standard deviation, N = number.

mmHg, remained in sinus rhythm after pacing at a higher (+4 mmHg) pressure. In three of nine patients (atrial pressure 4.7 ± 2.9 mmHg), brief AF occurred by rapid pacing at higher (+3.7 ± .6 mmHg) pressure. Finally, in five of nine patients with a mean right atrial pressure of 3.2 ± 1.1 mmHg, an increase in pressure by +4.0 ± 1.0 mmHg was associated with induction of long-lasting AF after rapid pacing. In summary, in 13 patients an attempt was made to induce AF at both lower and higher atrial pressure. Sinus rhythm and brief and long-lasting AF were induced in 10, 3, and 0 patients, respectively, at a lower pressure and in 1, 3, and 9 patients, respectively, at a higher pressure (X^2= 16.36, $p<0.0005$ for 2 degrees of freedom). In the remaining three patients, long-lasting AF was induced on the first attempt.

The right atrial refractory period in the 15 patients in whom it was measured (i.e., excepting the patient in whom AF occurred while determining refractoriness) was 230.7 ± 33.1 ms. In 13 patients, in whom it was measured at both lower (231.5 ± 30.5 ms at a pressure of 2.9 ± 2.0 mmHg) and higher pressure, the difference was not significant (+1.5 ± 12.1 ms at +3.5 ± 1.1 mmHg higher pressure). In 10 patients in whom two pacing runs resulted in sinus rhythm and AF (long-lasting and brief), respectively, the effective refractory period was 230.0 ± 30.9 ms when the sinus rhythm remained, and +2.0 ± 10.3 ms longer (nonsignificant difference) when pacing caused AF.

Wenckebach periodicity occurred at a baseline pacing interval of 318.1 ± 50.1 ms. In the 11 patients in whom it was determined at both a lower (333.6 ± 41.0 ms at a pressure of 3.2 ± 2.1 mmHg) and a higher (349.1 ±144.4 ms at 6.7 ± 2.5 mmHg) pressure, it was found significantly ($p<0.001$) longer (+15.5 ± 11.3 ms) at higher than at lower pressure. In nine patients in whom two pacing runs resulted in sinus rhythm and AF, respectively, and Wenckebach periodicity was determined, the critical cycle length at which Wenckebach atrioventricular block occurred was 332.2 ± 45.8 ms when associated with sinus rhythm at a pressure of 3.8 ± 1.8 mmHg and significantly ($p<0.01$) longer (344.4 ± 48.0 ms, i.e., +12.2 ± 8.3 ms) when associated with the induction of AF ($p<0.01$).

Discussion

The present data indicate that a modest elevation of right atrial pressure increases the probability to induce AF patients with a history of paroxysmal AF but with no structural heart disease or hyperthyroidism. During elevated atrial pressure, rapid atrial stimulation resulted in a higher incidence of AF inducibility and in long-lasting arrhythmia in those in whom no arrhythmia or brief AF could be induced at a lower atrial pressure. These results are in accordance with experimental data in which a markedly elevated right (and left) atrial pressure was associated with an increased inducibility of AF in normal anesthetized open-chest dogs.[8] Furthermore, a close relationship seems to exist between atrial dilatation and the incidence of atrial arrhythmias in the elderly,[9] while the onset of AF, at least in mitral stenosis, contributes to further enlargement of both atria.[10] Acute studies suggest also that AF is associated with increased left atrial pressure[11–13] or with atrial dilatation produced by inflation of a balloon catheter.[14] The pressure elevations caused in these cases were within the limits of commonly occurring spontaneous pressure changes.

The mechanism of atrial fibrillation was not fully elucidated in this study. Shortened atrial refractoriness is a common mechanism that may cause AF[15] as, for example, in hypoglycemia.[16] An increase in atrial pressure may cause prolongation[5,6] or shortening[17,18] of the atrial refractoriness or action potential duration. In open-chest anesthetized dogs, a marked increase in atrial pressure was associated with significant prolongation of the right atrial effective refractory period,[19] but the change in refractoriness was not the electrophysiologic change that was associated with an increased inducibility of AF, although the latter was associated with elevated atrial pressure. Similarly, in the same study[19] atrial pressure elevation was associated with prolongation of the interatrial conduction time, but again this change was not the one associated with increased inducibility of AF. In this study, the effective refractory period of the right atrium was not significantly affected by pressure elevation, and induction of AF was not associated with a change in refractoriness. Therefore, right atrial refractoriness does not seem to be a major factor determining the inducibility of AF in susceptible subjects, although inhomogeneity in refractoriness, caused by acute atrial pressure el-

evation, cannot be excluded as a possible mechanism. Atrial conduction was not measured in this study.

A rather unexpected finding of this study was the appearance of Wenckebach periodicity at a longer cycle length when the atrial pressure was elevated rather than when it was lower. Marked increase in ventricular pressure may be associated with atrioventricular conduction disturbances.[20] The ventricular pressure was not measured in this study, but it may be assumed that the rapid fluid infusion might have increased ventricular pressure. A reflex vagal stimulation might be responsible for this effect, but there is no clear evidence for this. Even more unexpected was the more common appearance of Wenckebach periodicity at a longer cycle length when AF was induced than when it was not. The two phenomena (Wenckebach periodicity at a slower rate and easier AF inducibility) may be independent and unrelated observations. Any attempt to explain the statistically found association would be speculative at present.

The increases in atrial pressure in this study were modest, well within the range of commonly occurring spontaneous pressure changes. Although AF never occurred spontaneously in the patients in this study, it is conceivable that accidental pressure elevations in patients with lone AF might facilitate the genesis of a paroxysm in them. If this is true, individuals in whom increased atrial pressure is found to increase their susceptibility to induced AF might benefit by measures that prevent an increase in atrial pressure. This hypothesis needs validation. Furthermore, the findings of this study might explain the common occurrence of AF in conditions such as left ventricular hypertrophy with an otherwise normal heart in which the atrial size may reflect the degree of left ventricular dysfunction.[21,22]

Conclusion

In patients with paroxysmal atrial fibrillation without structural heart disease (lone atrial fibrillation), modest increases in right atrial pressure may facilitate the induction of atrial fibrillation. The enhanced inducibility of atrial fibrillation with higher atrial pressure and the longer Wenckebach cycle length, found to be statistically related, are likely independent and unrelated observations.

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