SPIRONOLACTONE ADDED-ON STANDARD ANTIARRHYTHMIC PHARMACOLOGICAL THERAPY DECREASES THE ATRIAL FIBRILLATION RECURRENCES

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Keywords: *spironolactone, antiarrhythmics, atrial fibrillation recurrences*

Abstract: *The alterations of atrial structure induced by the iterative atrial fibrillation (AFib) include renin-angiotensin-aldosterone system (RAAS) overexpression which could have a dominant role, aldosterone being involved in inflammation, fibrosis, remodeling. The objective of our study is the direct comparison of two therapeutic regimens (each one including other three subregimens), in order to assess the benefit of mineralocorticoid receptor blockers with spironolactone (S) in repetitive AFib patients (pts). Method. The study considered retrospectively 1008 pts with AFib during the last seven years, structured into two comparative groups, demographically balanced (slight male and 6th decade pts predominance, respectively, in both groups). The pts within the first group were treated with antiarrhythmics [Amiodarone (A), Propafenone (P) or Sotalol (So)] + S, while the pts within the comparative group were treated with antiarrhythmics (A, P, So) + exogenous potassium supplement (K^+). We compared the occurrence of AFib episodes 24 months before and, respectively, after the initiation of treatment with S. Among the exclusion criteria we notice the pts previously treated with betablockers (indirect antireninic effect), and ACE-inhibitors or ARB's (K^+ suppliers), respectively. Results. In the therapeutic arm with antiarrhythmic + S, the AFib episodes decreased dramatically over two times within the two time intervals taken into consideration. In contrast, within the therapeutic arm with antiarrhythmic + K^+, the AFib episodes slightly increased. Conclusions. According to our results, S seems to be a valuable additional therapeutic tool in prevention AFib recurrences. Beyond, S reduces RAAS activity and could also reduce the fibrosis involved in structural remodelling. These beneficial effects were independent of blood pressure lowering and are probably connected to the antiinflammatory effects of S.*

Cuvinte cheie: *spironolactonă, antiaritmice, recurenţe de fibrilaţie atrială*

Rezumat: *Alterările atriale structurale induse de fibrilaţia atrială (FibA) iterativă includ hiperfuncţia sistemului renină-angiotensină-aldosteron (SRAA) care poate avea un rol decisiv, aldosteronul fiind implicat în inflamaţie, fibroză, remodelare. Obiectivul studiului nostru a fost compararea directă a două regimuri terapeutice (fiecare incluzând alte trei subregimuri), în scopul de a evalua beneficiul blocării receptorilor mineralocorticoizi cu spironolactonă (S) la pacienţii (pts) cu FibA repetitivă. Metodă. Am studiat 1008 pts cu FibA retrospectiv pe ultimii şapte ani, structuraţi în două grupuri comparative, echilibrate demografic (uşoare predominenţe masculină şi, respectiv, decada a VI-a, la ambele grupuri). Pts din primul grup au fost trataţi cu antiaritmice [Amiodaronă (A), Propafenonă (P) sau Sotalol (So)] + S, în timp ce pts din al doilea grup au fost trataţi cu antiaritmice (A, P, So) + supliment exogen de potasiu (K^+). Am comparat episoadele de FibA înregistrate cu 24 luni înainte cu cele înregistrate după iniţierea tratamentului cu S. Printre criteriile de excludere menţionăm pts trataţi anterior cu betablocante (efect antireninic indirect), respectiv IECA şi sartani (ofertanţi de K^+). Rezultate. În braţul terapeutic cu antiaritmic + S, episoadele de FibA au scăzut dramatic de peste două ori în cele două intervale de timp considerate. În contrast, în braţul terapeutic cu antiaritmic + K^+, episoadele de FibA au crescut uşor.Concluzii. Potrivit rezultatelor noastre, S pare a fi un instrument terapeutic adiţional valoros în prevenţia recurenţelor de FibA. În plus, S reduce activitatea SRAA şi ar putea reduce fibroza implicată în remodelarea structurală. Acest efecte benefice au fost independente de presiunea sanguină şi se datorează, probabil, efectelor antiinflamatorii ale S.*

INTRODUCTION

Atrial fibrillation (AFib) is such a common arrhythmia that it is often wrongly regarded as an acceptable alternative to normal sinus rhythm. Its first onset may present with rapid and uncomfortable palpitations, breathlessness, dyspnoea, chest pain, and anxiety. Often it is entirely asymptomatic and discovered incidentally. Paroxysmal and persistent recurrences may eventually lapse into permanent AFib.

The causes of AFib are multiple and should be identified since many can be corrected, so the management of the arrhythmia can be simplified. The consequences of AFib may be terrible, like heart failure, stroke, sudden death, dilated cardiomyopathy (tachyarrythmic), with markedly reduced exercise capacity and degraded quality of life. Adequate rate control or successful rhythm control in suitable patients (pts), with appropriate thromboprophylaxis are essential. Appropriate and competent management can diminish stroke risk and heart failure occurrence, alleviate symptoms and ameliorate anxiety.

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PURPOSE

The alterations of atrial structure induced by the repetitive AFib includes renin-angiotensin-aldosterone system (RAAS) overexpression which could have a decisive role, aldosterone being involved in inflammation, fibrosis, remodeling. The purpose of our study was to test the hypothesis that Sp added-on to conventional drugs could add therapeutic value in repetitive AFib pts, by direct comparison of two therapeutic regimens (each one including other three subregimens), in order to assess the benefit of Sp in repetitive AFib pts. This idea is poorly represented in the literature at global level. That was the reason why we decided to perform this study in our centre.

METHODS

The study considered 1008 hospitalized informed consented pts with AFib in the last seven years (last pts last visit 05/05/2014), structured into two comparative groups, demographically balanced, slight male (57,8%) and 6th decade (26,7%) pts predominance, respectively in both groups (see figures 1 & 2). All investigations were performed in our clinic. The pts within the first group were treated with antiarrhythmics {Amiodarone (A) 68,85% (347 pts) or Propafenone (P) 22,22% (112 pts) or Sotalol (So) 8,93% (45 pts)} + exogenous potassium supplement (K^+), while the pts within the second group were treated with antiarrhythmics {A 68,85% (347 pts) or P 22,22% (112 pts) or So 8,93% (45 pts)} + Sp. We compared the occurrence of AFib episodes 24 months before and, respectively, after the initiation of treatment with Sp. The pts were trained that the AFib onset may present with rapid and uncomfortable palpitations, breathlessness, dyspnoea, chest pain, and anxiety, but often it is entirely asymptomatic and discovered incidentally. So, the pts have to be aware and call quickly the investigator in order to document the AFib episode. Among current inclusion/exclusion criteria, we have to mention two particular pharmacological exclusion criteria referred to the pts previously treated with betablockers (indirect antireninic effect), and ACE-inhibitors or ARB's (K^+ suppliers), respectively.

Inclusion criteria:

- pts men & women aged ≥ 18 ani
- pts with episodic AFib in permanent treatment with one of the following antiarrhythmic drugs: A, P or So

Exclusion criteria:

- pts with permanent AFib
- pts previously treated with spironolactone
- pts serum kallium values of < 3,5 mEq/L or > 5 mEq/L
- pts previously treated with betablockers (indirect antireninic effect)
- pts previously treated with ACE-inhibitors or angiotensin receptor blockers (K^+ providers)
- pts cu psychopathies which could influence the trial discipline
- pts with a survival horizon < 24 months

Figure no. 1. Gender distribution

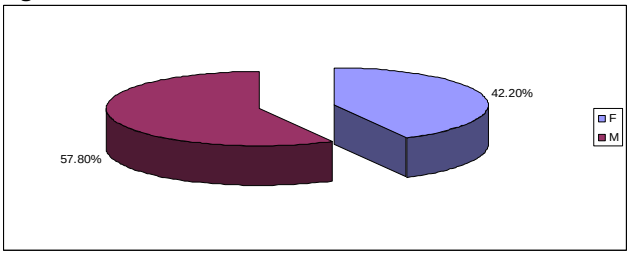
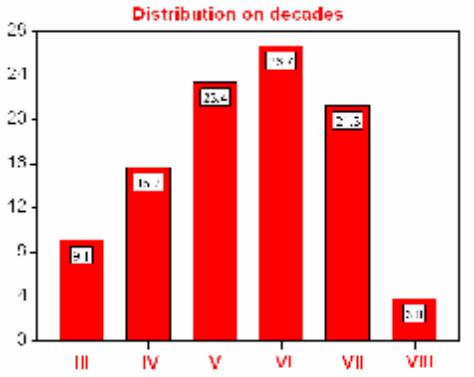


Figure no. 2. Age groups distribution



RESULTS

This trial, as a particular feature, was performed on a population geographically defined as a zone arounded to our centre of cardiology.

The adjacent table structures the main outcomes of the study:

Table no. 1. Study results

Therapeutic Arm	AFib Episodes (24 mo. before)	AFib Episodes (24 mo. after)	*p* value
A + K^+	8,8+/-1,7	10,5+/-2,5	<0,01
P + K^+	9,1+/-2,4	10,3+/-1,7	<0,01
So + K^+	8,9+/-0,9	10,3+/-1,1	<0,05
Antiarrhythmic + K^+	*8,9+/-2,6*	*10,5+/-2,8*	*<0,005*
A + Sp	9,1+/-2,1	3,7+/-2,0	<0,01
P + Sp	9,0+/-2,5	3,9+/-2,3	<0,01
So + Sp	8,7+/-2,4	4,1+/-2,1	<0,05
Antiarrhythmic + Sp	*9,1+/-2,3*	*3,7+/-1,9*	*<0,005*

The therapeutic benefit is obvious in the group with added Sp vs. added K^+, totally and for any of three antiarrhythmics (A, P, and So) pts subgroups.

Appropriate thromboprophylaxis was essentially done in all pts. However, a rate of 2,9% ischaemic strokes occurred in Sp added group vs. 3,3% in K^+ added group.

Paroxysmal and persistent recurrences may eventually lapse into permanent AFib. In our study, we observed a progressive trend of permanentization proportional with age, number of recurrences, duration of crisis. Even dropped-out, we continued to follow-up these pts and perform adequate rate control.

The rates of pts dropouts, AFib permanentization, and strokes were quite similar and statistically insignificant in both groups.

Stroke risk was diminished by appropriate thromboprophylaxis. Heart failure was improved by competent management of underlying comorbid disease and proper rate control. Rhythm control was achieved with antiarrhythmic drugs; no pts from this study was remitted for left atrial ablation techniques.

As a morphologic substrate, AFib induces an increased expression of extracellular matrix proteins and increased atrial fibrosis, displayed by Masson's trichrome stain.

The limits of our investigator's driven trial are:

- small number of pts
- non-blinded design
- maybe too rare 24-hrs. ECGs
- retrospective data not anytime complete.

DISCUSSION AND CONCLUSIONS

Pathophysiologically, aldosterone is released from the adrenal cortex. Angiotensin II stimulates the zona glomerulosa

of the adrenal cortex to increase the synthesis and secretion of aldosterone, and augments responses to other stimuli, like ACTH and K^+. Increased output of aldosterone is elicited by concentrations of angiotensin II that have poor effect on blood pressure. Aldosterone acts on the distal and collecting tubules retaining Na^+ and excreting K^+ and H^+. The stimulant effect of angiotensin II on aldosterone synthesis and release is enhanced when hyponatremia and/or hyperkalemia, and respectively reduced when hypernatremia and/or hypokalemia occur.

This work is conceptually located at the interface of electrical remodeling, structural changes, focal activity, and left ventricular dysfunction. Thus, Sp seems to intervene inside the vicious circle formed by these four players.

Within the entity "upstream therapy", Sp appears in our pts as a valuable additional therapeutic tool in decreasing AFib recurrences. Thus, Sp brings an endogenous potassium, more metabolic friendly than K^+ exogenic uptake. Beyond, Sp reduces RAAS activity and could also reduce the fibrosis involved in structural remodelling. These beneficial effects were independent of BP lowering and are probably due to the antiinflammatory effects of Sp. A larger prospective study is needed to ascertain results.

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