Original article

Effect of spironolactone on ventricular arrhythmias in patients with left ventricular systolic dysfunction and implantable cardioverter defibrillators

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KEY WORDS

Aldosterone antagonists
ICD shocks
Implantable cardioverter defibrillators (ICDs)
Spironolactone
Ventricular tachycardia (VT)

A B S T R A C T

Aims/objectives: Patients with implantable cardioverter defibrillators (ICD) often receive an adjunctive anti-arrhythmic therapy. We propose that an addition of spironolactone will reduce the number of clinically significant ventricular arrhythmias and ICD-related therapies.

Methods and results: In a multicentre retrospective study, 64 patients with ischaemic and non-ischaemic dilated cardiomyopathy whose left ventricular ejection fraction (LVEF) was <35% and with ICD were selected. Amongst these patients, 28 patients were on spironolactone and 36 were not taking spironolactone. The ICD interrogation data were analysed for a maximum of 12 months. Wilcoxon Rank Sum test was used to compare the study and control groups. The outcomes were: (1) the number of shocks/anti-tachycardia pacing (ATP) episodes and (2) the number of episodes of ventricular tachycardia (VT) requiring ATP, non-sustained VT (NSVT), and ventricular fibrillation (VF) over the study period. The spironolactone group had fewer monthly, VTs ($P=0.027$) (requiring ATP). The two groups did not differ in the number of NSVT or VF per month.

Conclusion: Addition of spironolactone as an adjunct to ICD therapy in patients with congestive heart failure (CHF) reduces VT requiring ATP, but does not affect NSVT or VF per month.

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Introduction

The addition of aldosterone receptor antagonists to standard therapy for congestive heart failure (CHF) in ischaemic or non-ischaemic cardiomyopathy (CMP) is a Class I recommendation (as per the ACC/AHA guidelines) in patients with moderately severe to severe heart failure (HF) symptoms (New York Heart Association [NYHA] III/IV) and left ventricular ejection fraction (LVEF) <35% in the absence of renal failure and hyperkalaemia.¹ The addition of aldosterone antagonists [AA] to standard therapy reduced morbidity and mortality in the HF population.^{2,3} It is also known that spironolactone reduces the number of ventricular arrhythmias in patients with CHF secondary to idiopathic dilated, or to ischaemic CMP.^{4,5} The incidence of

sudden cardiac death decreased in the patients receiving AA in large randomised prospective multicentre trials (Randomised Aldactone Evaluation Study [RALES], Eplerenone Post-AMI Heart failure Efficacy and Survival Study [EPHESUS]).^{2,3} The addition of AA in EPHESUS proved to be a cost saving strategy due to a significant decrease in mortality.⁶ In a subgroup of patients in the EPHESUS trial with LVEF <30%, the relative risk reduction for sudden cardiac death and all-cause mortality was significantly incremental with the use of a selective AA (Eplerenone).⁷ Systematic reviews of clinical trials studying the efficacy of AA in HF revealed a significant reduction in all-cause mortality and sudden cardiac death.^{8,9} Mortality and morbidity was improved in a randomised clinical trial among patients with mild chronic systolic HF (NYHA Class II) and LV dysfunction.¹⁰

Implanted cardioverter defibrillators (ICDs) effectively treat sustained ventricular arrhythmias and thereby prolong

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life compared with anti-arrhythmic drug therapy (or no anti-arrhythmic drug therapy) in patients at risk for sustained ventricular tachyarrhythmias.^{11–15} However, many patients with an ICD have ventricular tachyarrhythmias that may cause transiently disabling symptoms and may lead to painful ICD shocks. In patients implanted with defibrillators after sustained ventricular tachyarrhythmias, quality of life improves in many but not in those who require multiple ICD therapies. Frequent shocks are associated with a higher mortality and frequent, expensive hospitalisations.¹⁶ Over time, 30–50% of ICD recipients receive anti-arrhythmic drug therapy to prevent symptomatic tachyarrhythmias and to reduce the number of device therapies. Moreover, defibrillator therapies often occur in clusters which suggest that recurrences of ventricular tachyarrhythmias do not occur randomly.

The anti-arrhythmic drugs availability for these patients is limited largely due to their proarrhythmic effects. Drugs with Class I actions are contraindicated in patients with coronary artery disease (CAD) or left ventricular (LV) dysfunction. Sotalol a Vaughn Williams Class III anti-arrhythmic drug, a potassium channel-blocking agent with β -blocking properties it has been shown to be effective as an adjunctive therapy in patients with an ICD.¹⁷ It can cause *Torsade des pointes* and complicates concomitant therapy with β -blockers for many ICD patients who also have CHF. Similarly, azimilide, which is a pure K channel blocker, in a randomised placebo-control trial has shown to reduce the number of total appropriate therapies (both ventricular tachycardia [VT] and ventricular fibrillation [VF]),¹⁸ (hazard ratio=0.52, 95% confidence interval [CI] 0.30–0.89, $P=0.017$). About 1% patients developed TdP related to azimilide use and the incidence was not increased among those with diminished LVEF or women. One patient developed neutropenia. In a post hoc analysis, azimilide has also shown to be effective in reducing emergency room visits as well as hospitalisation amongst patients with ICD. Unfortunately, the drug did not get Food and Drug Administration (FDA) approval. The use of amiodarone is similarly limited by multiple serious adverse effects which include irreversible and sometimes fatal pulmonary toxicity, hypothyroidism, hyperthyroidism, and neurologic side effects such as tremors, ataxia, and hepatic toxicity. Amiodarone use may also increase the defibrillation thresholds. Additionally, amiodarone usage may also cause drug-drug interaction with many cardiac and non-cardiac drugs due to its effect on cytochrome P 450 system.

Aldosterone has an important role in the pathophysiology of HF.⁴ It promotes the retention of sodium, loss of magnesium and potassium, sympathetic activation, parasympathetic inhibition, myocardial fibrosis, baroreceptor dysfunction, and vascular damage and impairs arterial compliance. It also prevents the uptake of norepinephrine by myocardium.^{19–22} Spironolactone is a non-selective aldosterone receptor blocker. The effect of aldosterone receptor blockers on plasma volume and electrolyte balance is well-known. In addition, the aldosterone receptor blockade decreases sympathetic drive and improves norepinephrine uptake in patients with HF and heart rate variability. It improves ventricular remodelling by decreasing myocardial fibrosis. Aldosterone receptor blockers also reduce coronary vascular inflammation, reduce oxidative

stress, improve endothelial dysfunction, attenuate platelet aggregation, decrease activation of matrix metalloproteinases, and improve ventricular remodelling.

We propose that the addition of AAs to the standard therapy for CHF in patients with ICDs will reduce the number of clinically significant ventricular arrhythmias, thereby reducing the number of times anti-tachycardia pacing (ATP) and shocks delivered, as detected by ICD interrogation.

Methods

Patient sample

This was a retrospective study. Patients were enrolled from three different medical centres. The study group consisted of patients with ICDs with an ejection fraction (EF) <35% and receiving spironolactone. The control group consisted of patients with ICDs and an EF <35% who were not on spironolactone therapy. The aetiology of ventricular dysfunction could be ischaemic, non-ischaemic, or idiopathic dilated CMP. The enrollment period was from January 2000 through December 2002. To be eligible for inclusion, the ICD had to be placed for at least 12 months.

Study baseline characteristics and outcomes

Baseline demographic and clinical characteristics were collected for the two groups. Patients in the treatment group were followed from the time they started receiving spironolactone. Control group patients were followed from the time of ICD placement. The outcomes were (1) the monthly shocks/ATP episodes and (2) monthly episodes of VT, non-sustained VT (NSVT), and VF.

Statistical analysis

Fisher's exact test was used for comparisons involving categorical variables while the independent sample *t*-test was used for continuous variables. Inferences were made at the 0.05 level of significance with no adjustment for multiple comparisons.

Results

Twenty-eight patients were in the study group, ICD patients with an LVEF <35% and receiving spironolactone while 36 patients composed the control group, ICD patients with an LVEF <35% but not taking spironolactone. Table 1 shows the baseline characteristics of the two groups. The two groups differed only on digoxin, with 71% of treatment patients versus 36% of control patients using this medication ($P=0.006$).

Table 2 shows that the control group was followed for a longer period than the treatment group (mean=17.5 months

Table 1
Baseline characteristics of the treatment and control groups.

Characteristics	Treatment group (n=28) (%)	Control group (n=36) (%)	P value*
Age			
Mean	64.61	67.54	0.29
SD	11.37	10.57	
Gender			
Male	22 (78.6)	30 (83.3)	0.75
Female	6 (21.4)	6 (16.7)	
Institution			
Good Sam	12 (42.9)	36 (100)	NA
Dayton Card	7 (25)	0	
DCEP	9 (32.1)	0	
Beta-blockers			
Yes	24 (85.7)	23 (63.9)	0.09
No	4 (14.3)	13 (36.1)	
ACEIs			
Yes	21 (75)	22 (61.1)	0.29
No	7 (25)	14 (38.9)	
ARBs			
Yes	3 (10.7)	4 (11.1)	1.00
No	25 (89.3)	32 (88.9)	
CAD			
Yes	23 (82.1)	34 (94.4)	0.22
No	5 (17.9)	2 (5.6)	
Diabetes mellitus			
Yes	8 (28.6)	11 (30.6)	1.00
No	20 (71.4)	25 (69.4)	
Amiodarone			
Yes	6 (21.4)	11 (30.6)	0.57
No	22 (78.6)	25 (69.4)	
Sotalol			
Yes	1 (3.6)	1 (2.8)	1.00
No	27 (96.4)	35 (97.2)	
Digoxin			
Yes	20 (71.4)	13 (36.1)	0.006
No	8 (28.6)	23 (63.9)	
Ejection fraction			
Mean	21.32	24.75	0.063
SD	7.64	6.81	

*Independent sample *t*-test for age and ejection fraction; all others: Fisher's exact test. ACEI: angiotensin-converting enzyme inhibitor, ARB: angiotensin receptor blockade, CAD: coronary artery disease, Dayton Card: Dayton Cardiology, Dayton, Ohio, DCEP: dayton cardiac electrophysiology, Good Sam: Good Samaritan Hospital, Dayton, Ohio, SD: standard deviation, NA: not available.

and median=16 months for the control group versus mean=11 months and median=7 months for the treatment group, $P=0.026$). The two groups did not differ on monthly shocks for any cause ($P=0.83$), monthly NSVTs ($P=0.33$), or monthly VFs ($P=0.24$), but the treatment group has fewer monthly VTs ($P=0.027$) requiring ATP.

Discussion

The beneficial effects of aldosterone receptor blockers are well-known in patients with CHF both due to ischaemic or secondary to non-ischaemic CMP. It is also known that sudden cardiac death is significantly higher in patients with LV dysfunction

Table 2
Comparison of outcomes between treatment and control groups.

Outcomes	Treatment group	Control group	P value*
No. of follow-up months			
Mean	11.04	17.50	0.026
SD	10.81	11.57	
Median	7	16	
Shocks (per month)**			
Mean	0.24	0.29	0.83
SD	1.14	0.66	
VT (per month)†			
Mean	0.0020	0.1957	0.027
SD	0.0108	0.4523	
NSVT (per month)‡			
Mean	0.3539	5.5938	0.33
SD	1.2432	28.3622	
VF (per month)#			
Mean	0.2393	0.0139	0.24
SD	1.1360	0.0833	

*Independent sample *t*-test. **Shock for any cause (excluding inappropriate shocks). †VT episodes per month (requiring anti-tachycardia pacing). ‡NSVT (requiring no therapy). #VF requiring shock. NSVT: non-sustained ventricular tachycardia, SD: standard deviation, VF: ventricular fibrillation, VT: ventricular tachycardia.

who are not receiving aldosterone receptor blockers. The incidence of ventricular arrhythmias is lower in patients with CHF who received spironolactone. The VT rate was significantly lower among patients treated with AA in a small retrospective study by Dimas et al.²³

We postulated that ICD patients with CHF, LV dysfunction, and EF <35% would benefit from treatment with spironolactone. Ventricular tachycardia/month in the group on spironolactone were lower in patients who did not receive this drug. While NSVTs were notably lower in the treatment group and VF were notably lower in the control group, these differences did not reach the statistical significance due to small sample sizes, patient variability, and large standard deviations in relation to means. A slightly lower rate of monthly shocks was found in the treatment group, but this difference was also not significant.

There was a reason to believe that spironolactone would decrease the number of episodes of ventricular arrhythmias and possibly sudden cardiac death. The mechanism of action is due to anti-arrhythmic actions that include inhibition of electrical and structural cardiac remodelling, inhibition of neurohumoral activation, reduction of blood pressure and stabilisation of electrolyte disturbances.

Aldosterone receptor blockers work at different levels via different mechanisms to improve outcomes in patients with CHF. The most well-known mechanisms of these are through blockade of aldosterone thus promoting natriuresis, preserving potassium and magnesium in the body. Aldosterone blockers also decrease cardiac fibrosis and improve cardiac sympathetic activity, norepinephrine uptake, heart rate variability, and ventricular remodelling.

Ventricular arrhythmias are common in LV dysfunction and CHF. These are frequently associated with a poor prognosis in this population. Anti-arrhythmic drugs, such as Class I

drugs, have been tested in patients with CHF, and most were found not to be helpful and have increased arrhythmias. Primary prevention trials, MADIT I¹¹ and MADIT II¹² showed that in addition to conventional medical therapy when ICDs were placed in high-risk patients, they reduce mortality. Randomised prospective trials using eplerenone and spironolactone in the RALES³ and EPHESUS² trials respectively showed that sudden cardiac death improved in patients in the treatment groups. Ramires et al. and others also showed the treatment with spironolactone in patients with CHF decreases the number ventricular arrhythmia assessed by Holter monitoring and exercise stress tests.^{4,5} Animal studies have shown that chronic aldosterone-overload induces structural and electrical remodelling of the myocardium increasing the risk for malignant ventricular arrhythmia²⁴ and the use of AA attenuated electrical remodelling and suppressed the inducibility of ventricular arrhythmia.^{9,25,26} The use of AA causes a delay or reversal of myocardial fibrosis as noted by a decreased turnover of extracellular markers in the treatment arm of RALES trial.²⁷ Spironolactone has also been shown to reduce plasma levels of metalloproteinases in ischaemic HF indicating its role in reversing collagen dysregulation that plays a role in cardiac remodelling.²⁸ Other potential causes for decrease in arrhythmia could be due to reduction in heart rate, heart rate variability, alteration in QT dispersion, myocardial collagen turnover, magnesium efflux and an early morning rise in heart rate among heart failure patients.^{5,9,29,30} The selective aldosterone receptor blocker eplerenone has been shown to improve impulse propagation, reduce the incidence of cardiac arrhythmias and minimised myocardial fibrosis in the setting of CMP.³¹

Our study had some inherent shortcoming due to retrospective data analysis and small sample size. Unlike other monitoring modalities, ICDs were capable of storing all VT and VF events which could unequivocally demonstrate the beneficial effect of AA on suppression of VT/month.

We showed that the spironolactone is a useful and potent anti-arrhythmic drug for patients with LV dysfunction and CHF by decreasing VT episodes. However, further prospective, double-blind, placebo-controlled studies are needed among HF patients who are undergoing biventricular ICD implantation, where the arrhythmias and therapies delivered by ICDs can be retrieved and documented based on stored electrograms.

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