Effects of spironolactone on endothelial function, vascular angiotensin converting enzyme activity, and other prognostic markers in patients with mild heart failure already taking optimal treatment

J E Macdonald, N Kennedy, A D Struthers

Objectives: To examine whether the favourable effects on endothelial function, vascular angiotensin converting enzyme (ACE) activity, cardiac remodelling, autonomic function, and QT intervals of spironolactone in combination with ACE inhibitor also occur in patients with New York Heart Association class I–II congestive heart failure (CHF) taking optimal treatment (including β blockers).

Methods: Double blind, crossover study comparing 12.5–50 mg/24 hours spironolactone (three months) with placebo in 43 patients with class I–II CHF taking ACE inhibitors and β blockers.

Results: Acetylcholine induced vasodilatation improved with spironolactone (p = 0.044). Vascular ACE activity fell (p = 0.006). QTc and QTd fell (mean (SD) QTc 473 (43.1) ms with placebo, 455 (35.4) ms with spironolactone, p = 0.002; QTd 84.5 (41.3) ms with placebo, 72.1 (32.3) ms with spironolactone, p = 0.037). β-Type natriuretic peptide (BNP) and procollagen III N-terminal peptide (PIIIINP) concentrations were also reduced by spironolactone (mean (SD) BNP 48.5 (29.6) pg/ml with placebo, 36.8 (28.5) pg/ml with spironolactone, p = 0.039; PIIINP 3.767 (1.157) μg/ml with placebo, 3.156 (1.123) μg/ml with spironolactone, p = 0.000).

Conclusions: Spironolactone improves vascular function (endothelial function, vascular ACE activity) and other markers of prognosis (BNP, collagen markers, and QT interval length) in asymptomatic or mild CHF when added to optimal treatment including β blockade. This gives support to the hypothesis that the prognostic benefit seen in RALES (randomised aldactone evaluation study) and EPHESUS (eplerenone postacute myocardial infarction heart failure efficacy and survival study) may also occur in patients with milder CHF already taking standard optimal treatment.

R ALES (randomised aldactone evaluation study) showed a 30% mortality reduction in severe congestive heart failure (CHF) with the addition of spironolactone.1 The recent EPHESUS (eplerenone postacute myocardial infarction heart failure efficacy and survival study) confirms this, although as in RALES, the EPHESUS patients had moderate to severe disease.2 These two studies now raise the question of whether spironolactone would produce the same benefit in patients with mild or asymptomatic CHF. Indeed the editorial accompanying the EPHESUS paper said that “trials are now needed to determine whether these drugs will be efficacious in less severe patients”. A second question is that despite EPHESUS there is still some uncertainty over whether the RALES benefit would occur in CHF in the presence of optimal treatment including concomitant β blockade. This uncertainty arises because of the adverse effects of triple neuroendocrine blockade in ValHeFt (valsartan heart failure trial), because the RALES trial predated the use of β blockers in CHF, and because the EPHESUS data arise from a different population—that is, patients immediately after a myocardial infarction. To answer both questions posed above, we have now studied the effect of spironolactone in patients with mild (New York Heart Association (NYHA) functional class I–II) CHF taking optimal treatment, including β blockers unless contraindicated. A third rationale for our study is to give some practical guidance as to whether doctors would be justified in extrapolating the RALES and EPHESUS results to using spironolactone in patients with mild or asymptomatic CHF.

The main mechanism now thought by most experts to explain why aldosterone blockade reduces mortality in CHF is that aldosterone blockade improves endothelial vascular function.3 This has been shown directly only in severe CHF so far, but in agreement is the observation that infused aldosterone causes endothelial dysfunction in normal humans and the observation that aldosterone blockade is antiatherosclerotic in animal studies.4–7 Other factors that also contribute to the overall benefit are the beneficial effects of aldosterone blockade on cardiac remodelling, vascular angiotensin converting enzyme (ACE), QT interval, and heart rate variability.4 8–14 To address the question posed in the EPHESUS editorial, we have now conducted a study to determine whether spironolactone improves endothelial function and other prognostic markers in patients with NYHA class I–II CHF taking optimal treatment including β blockers (unless contraindicated). The final answer as to whether aldosterone blockade reduces mortality in this setting can be obtained

Abbreviations: ACE, angiotensin converting enzyme; BNP, β-type natriuretic peptide; EPHESUS, eplerenone postacute myocardial infarction heart failure efficacy and survival study; FBFR, forearm blood flow ratio; HAD, hospital anxiety and depression; L-NMMA, N-monomethyl-l-arginine; MLWHF, Minnesota living with heart failure; NYHA, New York Heart Association; PIIINP, procollagen III N-terminal peptide; QTc, corrected QT interval; QTd, QT dispersion; RALES, randomised aldactone evaluation study; SDNN, standard deviation of all NN intervals; ValHeFt, valsartan heart failure trial
only by an expensive mega-trial. Funding for such a mega-
trial is only likely to become available if positive results are
seen in a study such as this, which measured important
surrogates for cardiac death.

**METHODS**

**Study population**

Fifty seven patients with stable NYHA class I–II CHF were
recruited after giving full, informed consent. At diagnosis,
their CHF had all been at least class II but optimising their
treatment had improved patients substantially into a stable,
less symptomatic state. The Tayside committee on medical
research ethics approved the study and it complies with the
Declaration of Helsinki. Left ventricular systolic dysfunction
on echocardiographic, angiographic, or nuclear imaging was
mandatory and taken as a left ventricular ejection fraction
< 50% or fractional shortening < 25% at some time in the
recent past. All participants were taking ACE inhibitors or
angiotensin II receptor blockers and their individually
titrated β blocker dose (all for at least six months). All
patients had been assessed for β blocker treatment so that
the subgroup not taking β blockers either had a contraindication
or were unable to tolerate them. In this way, the whole group
was regarded as taking optimal treatment for them. Patients
with serum sodium concentration < 130 mmol/l, potassium
> 5.0 mmol/l, urea > 10.0 mmol/l, or creatinine > 221 μmol/l
were excluded.

**Randomisation and drug titration**

Patients were randomly assigned in double blind, crossover
fashion to spironolactone (three months) or placebo (three
months). After three months, they were crossed over to the
opposite treatment for three months. The starting dose of
spironolactone was 25 mg/day. After two weeks this was
doubled to the same maximum dose (50 mg) as in RALES. If
side effects occurred or plasma urea and electrolytes became
deranged (criteria above) the dose was halved. Patients
unable to tolerate the minimum dose (12.5 mg/24 hours)
were withdrawn.

**Assessments after each treatment period**

The assessments were comprehensive and hence we made
them only at the end of each randomised treatment period
and not at baseline. This is especially because assessment of
endothelial function and vascular ACE require arterial
puncture. Therefore, for ethical reasons, we limited assess-
ments to the minimum necessary. Hence, we compared them
directly, rather than subtracting baseline values from both,
since baselines for each treatment would have then required
four rather than two arterial puncture studies.15 16

**Endothelial function**

Studies were conducted in quiet, temperature controlled
(24–
26°C) surroundings at 9 am. Patients fasted from midnight.
Prescribed medication was taken, except diuretics. After 20
minutes’ supine rest a 27 gauge steel needle (mounted on a
16 gauge epidural catheter) was positioned in the non-
dominant brachial artery. After 10 minutes of saline infusion
baseline forearm blood flow ratio (FBFR)17 was assessed by
forearm venous occlusion plethysmography as described in
detail elsewhere.4 Drugs were serially infused at increasing
concentrations and FBFR was assessed during the final two
minutes of each concentration. Between each infusion, the
infusion set was flushed with saline until FBFR had returned
to baseline levels.

**Intra-arterial infusions**

The endothelium dependent vasodilator acetylcholine
(CIBAVision) was administered at 25, 50, and 100 nmol/min,
each for five minutes. Then angiotensin I (Clinalfa) was
infused at 64.256 and 1024 pmol/min for seven minutes
each. In this model, vasoconstriction elicited by angiotensin
I relies entirely on its conversion to angiotensin II. Next
angiotensin II (Clinalfa) was infused at 16 and 64 pmol/
min for seven minutes each. The competitive nitric oxide
synthase inhibitor N-monomethyl-L-arginine (L-NMMA,
Clinalfa) was then infused at 4 μmol/min for five minutes.
After this, acetylcholine was co-infused with L-NMMA at
50 and 100 nmol/min, each for five minutes. Finally, the
endothelium independent vasodilator sodium nitroprusside
(David Bull Laboratories) was given at 37.8 μmol/min for five
minutes.

**Blood samples**

Samples were collected between 11 am and 1 pm after 30
minutes’ supine rest and centrifuged. Plasma was stored at
−70°C (peptides) or −20°C (other samples). Blinded oper-
tors performed assays in batches. Plasma β-type natriuretic
peptide (BNP) samples were collected into EDTA and
aprotinin and measured by radioimmunoassay (Bachem, St
Helens, Merseyside, UK). Serum procollagen III N-terminal
peptide (PIIINP) concentrations were assessed by an intact
radioimmunoassay (Quidel, UK).

**QT parameters**

Standard 12 lead ECGs were recorded with a 4700A machine
(Hevlett Packard, Palo Alto, California, USA). For each lead,
the QT intervals of three consecutive non-ectopic complexes
were measured and averaged. A digitising tablet (Calcomp,
Anaheim, California, USA) with in-house software was used.
The QT interval was measured from QRS onset to T wave
cessation. If U waves were present, the end of the QT interval
was taken at the nadir between the T and the U waves. The
corrected QT (QTc) interval was calculated by Bazett’s
method (QTc = QT/RR). QT dispersion (QTd) was calcu-
lated as the difference between the longest and shortest QT
intervals. Measurements were performed by one blinded
investigator (JEM). Any lead omitted on a patient’s first ECG
was omitted on the second.

**Heart rate variability**

Twenty four hour ambulatory Holter monitoring was under-
taken. Patients with pacemakers, atrial fibrillation, or
intermittent bundle branch block were excluded. A two
channel Tracker II analogue tape recorder (Reynolds Medical,
Hertford, Hertfordshire, UK) was used with CM1 and CM5
leads. Data were processed with the Pathfinder 600 Analyser
(Reynolds Medical) and manually edited29 for both time
domain (mean RR interval, standard deviation of all NN
intervals) and frequency domain parameters (total power, ultralow
frequency, very low frequency, low frequency, and high
frequency).30

**Six minute walk**

Subjects were asked to walk briskly between two markers
spaced 20 m apart.

**Questionnaire data**

The Minnesota living with heart failure (MLWHF) and
hospital anxiety and depression (HAD) questionnaires were
administered.20 21

**Statistical analysis**

Forearm blood flow (ml/min/100 ml forearm volume) rates
were converted to ratios between forearm blood flow in the
infused arm and that in the control arm. Percentage change in FBFR from the baseline immediately preceding each infusion was calculated. FBFR measurements were analysed by a general linear model with treatment and dose as fixed factors and patient number as a random factor. The interaction between dose and treatment was non-significant in all cases. Other data were compared between treatments by Student’s paired *t* tests. A probability value of *p* < 0.05 was considered significant. Results are expressed as mean (SEM) in the figures.

RESULTS

Fourteen patients did not complete the study, of whom eight were taking spironolactone (two had cramps and two had hyperkalaemia) and six were given placebo (one experienced lethargy and one died). Six developed intercurrent illness. Two patients withdrew without giving reasons. Forty three patients completed the study (mean (SD) spironolactone dose of 40.1 (2.02) mg).

Clinical characteristics

Weight and NYHA class were unchanged (table 1). Systolic and diastolic blood pressures were significantly lower among patients taking spironolactone (*p* = 0.004 and *p* = 0.005, respectively).

Endothelial function

Endothelial function and vascular ACE was measured in only 40 patients, since those taking warfarin (*n* = 3) obviously cannot undergo arterial puncture studies. Blood pressure was unchanged during studies (table 4). Spironolactone significantly improved acetylcholine induced endothelium dependent vasodilatation (*p* = 0.045) (fig 1), blunted angiotensin I induced vasoconstriction (*p* = 0.006) (fig 2), and augmented angiotensin II induced vasoconstriction (*p* = 0.044) (fig 3). Responses to sodium nitroprusside, L-NMMA, and co-infusion of L-NMMA and acetylcholine were unaltered (fig 4). Mean (SD) sodium nitroprusside responses were 340 (156)% with placebo and 369 (189)% with spironolactone (*p* = 0.399, *t* test).

Blood analysis results

The most relevant differences between placebo and spironolactone administration were that both plasma BNP (*p* = 0.039) and plasma PIINP fell (*p* = 0.000) with spironolactone. The PIINP fall was greater when placebo PIINP was > 3 μg/l as in RALES.

QT parameters

QT indices were significantly reduced with spironolactone: QT (*p* = 0.009), QTc (*p* = 0.002), QTd (*p* = 0.037), and QTdc (*p* = 0.032) (table 2).

Heart rate variability data

Spironolactone significantly reduced ventricular extrasystoles (*p* = 0.030) (table 3). Couplets and triplets fell nonsignificantly. Heart rate variability measures did not improve, including early morning heart rate variability. The use of β blockers in this study appears to have negated the effect of spironolactone on heart rate variability seen in previous studies.

- **Figure 1** Forearm blood flow ratio (FBFR) response to acetylcholine after spironolactone (S) or placebo (P). *p* < 0.05.
- **Figure 2** Forearm blood flow ratio (FBFR) response to angiotensin I after spironolactone (S) or placebo (P). **p** < 0.01.
- **Figure 3** Forearm blood flow ratio (FBFR) response to angiotensin II after spironolactone (S) or placebo (P). *p* < 0.05.

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**Table 1** Baseline clinical data

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<tr>
<td>LVH</td>
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<tr>
<td>NIDDM</td>
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<tr>
<td>AF</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
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<tr>
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<td>Warfarin</td>
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<tr>
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<td>Statin</td>
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<td>β Blocker</td>
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<td>Digoxin</td>
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ACEI, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; DBP, diastolic blood pressure; DCM, dilated cardiomyopathy; HF, heart failure; IHD, ischaemic heart disease; LVH, left ventricular hypertrophy; NIDDM, non-insulin dependent diabetes mellitus; NYHA, New York Heart Association; SBP, systolic blood pressure.
arginine (L-NMMA) alone and co-infused with acetylcholine after endocrine blocking agent.

Six minute walk distance

Six minute walk distance was unaltered (table 2).

Questionnaire data

Total MLWHF questionnaire scores worsened significantly with spironolactone (p = 0.044) but there was no increase in physical dimension score (table 2). Total HAD and anxiety scores were also significantly worse after spironolactone (p = 0.035 and p = 0.021, respectively). These results were surprising but perhaps spironolactone produces subtle adverse effects that adversely influence quality of life. One possibility is the well known sexual side effects of spironolactone such as impotence and gynaecomastia.

Influence of β blockade

The improvements in PIIINP, BNP, endothelial function (acetylcholine), vascular ACE (angiotensin I vasoconstriction), and QTc were also seen when the analysis was limited to the smaller number of patients who were taking β blockers (p = 0.000, p = 0.016, p = 0.076, p = 0.025, and p = 0.002, respectively). This shows that spironolactone still has beneficial effects even when prescribed as a third neuroendocrine blocking agent.

DISCUSSION

Our main finding is that spironolactone improved our primary end point of endothelial function in patients with class I–II CHF taking optimal treatment. There are now seven separate studies showing that endothelial dysfunction is associated with future cardiovascular events.25–28 In addition, the two treatments that are known to improve prognosis in CHF also improve endothelial function—that is, ACE inhibitors and spironolactone.4,29 Thus, spontaneous abnormalities in endothelial function in general and treatment induced changes in endothelial function in CHF have so far always predicted prognosis. Indeed, a recent editorial in Circulation called endothelial function a “barometer of vascular health representing an orchestrated response to the many processes which contribute to atherosclerosis development and progression.”30

Angiotensin I induced vasconstriction was blunted by spironolactone, implying reduced angiotensin I to angiotensin II conversion and above that achieved with chronic ACE inhibitor treatment, as previously shown in patients with more severe CHF.4 This also agrees with data showing that aldosterone increases ACE mRNA 23-fold in tissue culture31 and with other experimental data.12 31 In our study this was despite spironolactone significantly increasing angiotensin II induced vasconstriction, which would have tended to mask the ability of our study to detect a spironolactone induced reduction in angiotensin I induced vasconstriction. We hypothesise that adding spironolactone produces additional blockade of angiotensin I to angiotensin II conversion, which results in reduced local angiotensin II. Such an effect has been seen before in patients with severe CHF.4 We speculate that this may then upregulate the vascular angiotensin II type I receptors, which manifests itself here as an amplified vasoconstrictive response to exogenous angiotensin II. Such upregulation of a receptor when its natural ligand is reduced is an accepted cornerstone of pharmacological theory even if it has not been studied before in this precise scenario. For that reason, our speculation here is the most likely explanation for our results. For clarity, we have used the term “vascular ACE” in earlier sections of this paper but, strictly speaking, we can only really say that spironolactone altered vascular angiotensin I to angiotensin II conversion, as we cannot know whether in our study spironolactone altered ACE, non-ACE pathways, or both.4

In this study, we used BNP as an index of intracardiac pressure/volume and left ventricular remodelling. We also used PIIINP as an index of ventricular collagen turnover. Use of these plasma markers in this way is well established. Furthermore, both such markers are prognostic markers in CHF.32–34 Consistent reductions in both suggest improved left ventricular remodelling. Our intention was to confirm this with echocardiography but good images were obtained for only 21 patients because smoking and obesity were

<table>
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<tr>
<th>Placebo</th>
<th>Spironolactone</th>
<th>p Value</th>
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<tr>
<td>Weight (kg)</td>
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<td>DBP (mm Hg)</td>
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<td>HR (beats/min)</td>
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<td>769 (361)</td>
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<td>82.8 (8.89)</td>
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<td>6 minute walk distance (m)</td>
<td>472 (81.1)</td>
<td>466 (13.9)</td>
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<td>465 (54.7)</td>
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<td>RSA (m/s)</td>
<td>1.93 (0.16)</td>
<td>1.92 (0.16)</td>
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<tr>
<td>LVIDd (cm)</td>
<td>5.40 (0.86)</td>
<td>5.06 (0.94)</td>
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<td>IVSd (cm)</td>
<td>1.15 (0.30)</td>
<td>1.12 (0.29)</td>
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<td>LVPWd (cm)</td>
<td>1.04 (0.26)</td>
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<td>235 (81.2)</td>
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<tr>
<td>LVM (g/m²)</td>
<td>122 (41.0)</td>
<td>112 (36.3)</td>
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Data are mean (SD). *p<0.05; **p<0.01.

BNP, β-type natriuretic peptide; BSA, body surface area; HAD, hospital anxiety and depression; HR, heart rate; IVSd, interventricular septum thickness; LVIDd, left ventricular end диastolic diameter; LVM, left ventricular mass; LVMi, left ventricular mass index; LVPWd, left ventricular posterior wall thickness; MLWHF, Minnesota living with heart failure; PIIINP, procollagen III N-terminal peptide; PWV, pulse wave velocity; QT, corrected QT interval; QTc, QT dispersion; QTdc, corrected QT dispersion.
common in our cohort. Even in these 21 patients, we did find significant confirmatory reductions in left ventricular internal diameter (5.40 (0.18) cm to 5.06 (0.19) cm, p = 0.006) and left ventricular mass index (122 (8) g/m² to 112 (7) g/m²; p = 0.036), but these echocardiographic results are bit unreliable because they refer to only a subset of patients. Nevertheless, changes in BNP and PIIINP are so well linked to prognosis and remodelling in CHF that favourable improvements in endothelial function and left ventricular mass index (122 (8) g/m² to 112 (7) g/m², p = 0.006) and left ventricular ejection fraction (38.4 (9.9) % to 41.1 (9.6) %, p = 0.016). It is possible that the blood pressure reduction caused the improvements in endothelial function and left ventricular remodelling. However, this appears unlikely, as blood pressure did not change in our previous study in severe CHF, which makes it unlikely that these effects occurred purely by chance in these mild to asymptomatic patients.

Spironolactone did appear to worsen significantly one quality of life score and depression scores. Unlike the positive effects, such effects have not been seen before. These adverse scores may relate to adverse side effects of the drug, which were too subtle to lead to their being recognised as adverse drug effects as such. In addition, these patients had such mild CHF that it may have been difficult to improve their quality of life when it was fairly normal to start with. Obviously this is an important issue needing further study, since this finding may detract importantly from the beneficial effects seen in vascular and other prognostic markers.

**Conclusion**

Spironolactone improves endothelial nitric oxide bioactivity, vascular ACE activity, QT interval length, and other prognostic markers (BNP, PIIINP) when added to optimally treated patients with class I–II CHF. Although such effects have been seen before in moderate to severe CHF, the key point here is that we found them the first time ever in patients with mild CHF already taking optimal treatment. Most pertinent is that this is the first study to show beneficial effects in mild to asymptomatic CHF on the main mechanism that is thought to underlie its benefits—that is, endothelial function. A mega-trial should now be undertaken to obtain whether these improvements in surrogate markers translate into a significant prognostic benefit and in particular to see whether any putative benefit outweighs the not inconsiderable and unpredictable risks of hyperkalaemia when spironolactone and ACE inhibitors are given together in certain patients with CHF. Such mega-trials are so expensive that underpinning data such as these are essential before any funding body is going to be persuaded to release the necessary funds.

**ACKNOWLEDGEMENTS**

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**REFERENCES**


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### Table 3

<table>
<thead>
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<th>Parameter</th>
<th>Placebo</th>
<th>Spironolactone</th>
<th>p Value</th>
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<tr>
<td>Normal GRS</td>
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<td>1.548 (357.1)</td>
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<td>Extrasystoles</td>
<td>400 (832)</td>
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</tr>
<tr>
<td>Couplets</td>
<td>98.3 (370)</td>
<td>22.4 (57)</td>
<td>0.167</td>
</tr>
<tr>
<td>Triplets</td>
<td>12.7 (74.7)</td>
<td>0.62 (1.76)</td>
<td>0.317</td>
</tr>
<tr>
<td>Salvo</td>
<td>2.15 (11.7)</td>
<td>0.18 (0.45)</td>
<td>0.291</td>
</tr>
<tr>
<td>VT</td>
<td>0.08 (0.27)</td>
<td>0.10 (0.31)</td>
<td>0.661</td>
</tr>
<tr>
<td>Brachyarrhythmia</td>
<td>53.5 (151)</td>
<td>47.7 (139)</td>
<td>0.835</td>
</tr>
<tr>
<td>Dropped beat</td>
<td>3.03 (1.49)</td>
<td>0.69 (2.66)</td>
<td>0.251</td>
</tr>
<tr>
<td>Pausos</td>
<td>0.00 (0.00)</td>
<td>0.00 (0.00)</td>
<td>0.294</td>
</tr>
<tr>
<td>Maximum HR</td>
<td>100 (15.8)</td>
<td>98.5 (15.1)</td>
<td>0.241</td>
</tr>
</tbody>
</table>

**Table 4**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo Mean (SD)</th>
<th>Spironolactone Mean (SD)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total flow rates (ml/min)</td>
<td>2.74 (0.27)</td>
<td>2.74 (0.75)</td>
<td></td>
</tr>
<tr>
<td>Placebo control arm</td>
<td>2.66 (1.06)</td>
<td>2.67 (0.99)</td>
<td></td>
</tr>
<tr>
<td>Placebo infusion arm</td>
<td>2.67 (0.99)</td>
<td>2.71 (0.86)</td>
<td></td>
</tr>
<tr>
<td>Spironolactone control arm</td>
<td>2.71 (0.86)</td>
<td>2.74 (0.75)</td>
<td></td>
</tr>
<tr>
<td>Spironolactone infusion arm</td>
<td>2.74 (0.75)</td>
<td>2.74 (0.75)</td>
<td></td>
</tr>
</tbody>
</table>

There were no significant differences between the spironolactone and placebo basal flow rates (p = 0.78 for control arm and p = 0.65 for infusion arm).


Effects of spironolactone on endothelial function, vascular angiotensin converting enzyme activity, and other prognostic markers in patients with mild heart failure already taking optimal treatment

J E Macdonald, N Kennedy and A D Struthers

*Heart* 2004 90: 765-770
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