Chronic atrial fibrillation does not influence the magnitude of sympathetic overactivity in patients with heart failure

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Aims In this study we sought to assess the influence of atrial fibrillation (AF) on sympathetic nervous system overactivity in congestive heart failure (CHF) patients.

Methods and results We studied 133 consecutive patients with moderate to severe CHF. Subjects underwent haemodynamic assessment (right heart catheterization) and assessment of total systemic and cardiac sympathetic activity by the norepinephrine (NE) spillover method. The study population included 108 patients in sinus rhythm (SR) and 25 in AF. While AF patients had a lower cardiac output (CO) (SR vs AF: 4.2 ± 0.1 vs 3.7 ± 0.2 l/min, P < 0.05), the groups were otherwise matched for systemic blood pressure (BP), heart rate and filling pressures. In conjunction, total body NE spillover (SR vs AF: 5.8 ± 0.4 vs 4.9 ± 0.5 nmol/min, P > 0.05) and cardiac NE spillover (SR vs AF: 339 ± 21 vs 393 ± 49 pmol/min, P > 0.05) were not significantly different between the two groups, while the systemic clearance rate for NE was lower in the AF group (SR vs AF: 2.2 ± 0.1 vs 1.6 ± 0.1 l/min, P < 0.05).

Conclusion Congestive heart failure patients in AF do not appear to have heightened sympathetic tone compared to CHF patients in SR.

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KEYWORDS
Heart failure; atrial fibrillation; sympathetic activity

Introduction
Congestive heart failure (CHF) and atrial fibrillation (AF) are both increasing in prevalence internationally and are individually associated with high rates of morbidity.1-4 Atrial fibrillation itself, has been shown to be associated with an increased mortality independent of other cardiac risk factors.5 When AF is present in conjunction with CHF however, CHF mortality increases further.6-9 In addition, independent of the aetiology of CHF, it is known that poor control of the ventricular rate in atrial fibrillation can promote the progression or lead to the development of CHF.

The exact mechanism(s) by which the presence of AF in CHF adversely influences disease progression and outcome is unknown. It is well known that there is loss of coordinated atrial pumping which is deleterious to cardiac output, however the detrimental effect appears greater than would be expected from this haemodynamic effect alone. Of those therapies which have been shown to favourably influence outcome in CHF, pharmacological interventions that counteract the effects of maladaptive increases in the activity of the renin-angiotensin system and sympathetic nervous system have perhaps been the most effective to date.10-13 In conjunction, biochemical and electrophysiological techniques have clearly demonstrated a relationship between CHF severity and the degree of sympathetic activation.14-16 Moreover, it has been shown that the level of sympathetic activation can be directly correlated with prognosis in CHF and other arrhythmic complications such as ventricular arrhythmias.17-19 We therefore sought to test the hypothesis that further excess sympathetic activation is present in CHF patients with AF, to account for the adverse affect atrial fibrillation confers on the prognosis of CHF patients.
Methods

We performed right heart catheterization and employed the norepinephrine (NE) spillover method\textsuperscript{20,21} to measure total systemic and cardiac sympathetic activity (by coronary sinus catheterization) in 133 patients undergoing evaluation for heart failure at our institution.

Patient characteristics

The measurement of cardiac and systemic sympathetic activity occurred in a consecutive series of 133 CHF patients (age 53.7±7.9 years). There were 108 patients in the sinus rhythm (SR) group (90 male, 18 female, age 51.9±8.6 years), and the AF group included 25 patients (22 male, 3 female, age 55.5±7.3 years). Patients in the AF group had persistent AF of at least 3 months duration. All patients were haemodynamically stable at the time of evaluation, but all remained on anti-failure pharmacotherapy to avoid potential haemodynamic decompensation. All patients gave written informed consent and the study was performed with the approval of the Alfred Hospital Ethics Review Committee.

Experimental procedures

Under local anaesthesia, the radial artery was cannulated (3F, 5 cm, Cook, Brisbane, Australia) for arterial blood sampling and arterial pressure measurements. Venous introducer sheaths were placed in the antecubital fossae or right internal jugular vein. A pulmonary artery thermodilution catheter (7F, Arrow, Arrow International) was passed to the pulmonary circulation to measure right heart pressures and cardiac output. Subsequently a coronary sinus thermodilution catheter (Webster CCS 7/8U 90A, Webster Laboratories) was advanced under fluoroscopic guidance to the coronary sinus for sampling and measurement of coronary sinus plasma flow, as previously described.\textsuperscript{15}

All studies were performed in the morning after a light breakfast and a 24-h caffeine-free period. The NE isotope-dilution technique was employed as previously developed by our institution to measure cardiac and total body NE spillover.\textsuperscript{20,21} The technique in brief, involves infusion of levo-(7-\textsuperscript{3}H)-norepinephrine (New England Nuclear, Boston, Massachusetts) at a rate of 0.5 to 1 uCi/min through a peripheral vein for 30 min to achieve steady state plasma concentrations. Once steady state was achieved blood sampling for cardiac and total body NE spillover was performed.

Analysis of plasma catecholamines

Blood samples were collected into ice-chilled tubes containing an anticoagulant, ethyleneglycol-bis (beta-amino-ethyl ether) N,N\textsuperscript{#}tetraacetic acid (EGTA) and reduced glutathione to prevent oxidation. After centrifugation at 4 °C, plasma samples were stored at −70 °C until assayed. NE plasma concentration was determined by high performance liquid chromatography with electrochemical detection as previously described.\textsuperscript{22} The plasma [\textsuperscript{3}H]-NE concentration was determined by liquid scintillation spectroscopy after collection of eluant from the electrochemical detector cell using a fraction collector. The total systemic and cardiac NE spillover rates were calculated as previously described:

\[
\text{Total Systemic NE spillover} = \frac{[\text{H}]\text{NE infusion rate}}{\text{Arterial NE specific activity}}
\]

Cardiac NE Spillover = [(Cv − Ca) + Ca \times (NEext)] \times (PF)

Where Cv is the plasma NE concentration in the coronary sinus and Ca is the NE concentration in the arterial plasma and NEext is the fractional extraction of radio-labelled NE across the heart and PF is coronary sinus plasma flow.

Statistical analysis

Data were presented as mean value±SEM, unless otherwise stated. Statistical analysis and graphical presentation was performed using statistical software (SigmaStat, version 2.03, Chicago, Illinois). Between group data were compared using an unpaired t-test for normally distributed data, and non-normal data were analysed by a Mann–Whitney test. Nominal or categorical data was compared using a Chi-squared test, or Fisher’s exact test where appropriate. Correlation between data was assessed using a Pearson correlation. A P value of <0.05 was considered statistically significant.

Results

There were 108 patients in the sinus rhythm group and 25 patients in the AF group. Demographic data are presented in Table 1. The only significantly different haemodynamic variable measured between the two groups was cardiac output (SR vs AF: 4.2±0.1 vs 3.7±0.2 l/min, \(P=0.04\)). The comparison of haemodynamic data between the two groups is presented graphically (in Fig. 1). The

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SR (n=108)</th>
<th>AF (n=25)</th>
<th>(P) value</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52±1</td>
<td>56±1</td>
<td>0.04</td>
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<td>Aetiology (ischaemic %/non-ischaemic %)</td>
<td>57/51 (53%/47%)</td>
<td>11/14 (44%/56%)</td>
<td>0.57</td>
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<td>NYHA class</td>
<td>2.8±0.1</td>
<td>2.8±0.1</td>
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<td>LVEF (%)</td>
<td>21±1</td>
<td>19±2</td>
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<td>Heart rate (bpm)</td>
<td>85±4</td>
<td>72±2</td>
<td>0.22</td>
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usage of anti-failure and antiarrhythmic medication between the two groups is presented in Table 2. The only significant difference between the groups was with digoxin usage (SR 78%, AF 96%; P<0.05).

The norepinephrine kinetic and arterial norepinephrine data are presented in Table 3. In measuring sympathetic activity, the only significant difference between the groups related to systemic norepinephrine clearance (SR vs AF: 2.2±0.1 vs 1.6±0.1 l/min, P=0.02). No difference in total systemic or cardiac NE spillover was evident (see Table 3). To determine the basis for the reduction in systemic NE clearance in AF we examined the impact of the lower CO in this group. As shown in Fig. 2, CO was significantly related to systemic NE clearance for the group as a whole. In further analysis, the cardiac NE spillover was strongly related to pulmonary capillary wedge pressure (PCWP) and independent of rhythm (see Fig. 3).

Discussion

In the current study we examined the influence of AF on cardiac and total sympathetic activity in CHF using the norepinephrine spillover method, as established by our group.20,21 Our study did not demonstrate a difference between resting cardiac sympathetic tone in patients with CHF in SR as compared with those in AF. To our knowledge this is the first study to evaluate the effects of AF compared to SR, at rest, on cardiac and global sympathetic activation in CHF patients using the norepinephrine spillover method.

It has been well established that CHF is associated with marked neurohormonal activation.23,24 In particular, it appears that activation of the sympathetic nervous system is pivotal to the progression of CHF.14–16,18 The level of sympathetic activation is intimately related to prognosis in CHF17,19 and the pathophysiological mechanisms by which this association occurs include; promotion of ventricular arrhythmias,18 exacerbation of myocardial ischaemia25 and remodelling of the myocardium with fibrosis and myocyte necrosis.26 In addition to the increased frequency of AF in CHF, it has been shown that outcome in CHF is adversely influenced by AF.6,8,9,27 This has been attributed to progressive pump failure and not sudden cardiac death.6 Whilst it is well known that AF itself is associated with marked morbidity and mortality,5,28 the exact mode by which AF inflicts its deleterious effects in CHF is unknown. While it has solely been attributed to the haemodynamic effect of the loss of the contribution of the atrial pump to cardiac output, the specific impact of AF upon neurohormonal activation is unclear.

The present study showed that our cohort of AF patients were similar to their counterparts in terms of filling pressures, however in the setting of a lower cardiac output. Nevertheless our patients were also well matched in terms of their left ventricular ejection fraction and New York Heart Association class. We did not observe a difference in total systemic or cardiac NE spillover, while a significant decrease in the systemic NE clearance rate was observed in AF patients. This finding was explained by the apparent relationship between systemic NE clearance and cardiac output. Other demographic data was also not significantly different except for the age of the groups. It has previously been shown at

![Fig. 1](https://example.com/fig1.png)
older ages (60 to 75 years) that NE reuptake reduces which increases NE spillover when compared to younger subjects. However, these differences would be unlikely to bias our study as the age difference in the present study was negligible.

Consistent with previous studies of cardiac and systemic norepinephrine spillover in severe heart failure patients, both systemic and regional spillover levels were found to be elevated. In the present study we found that cardiac rhythm per se did not influence cardiac spillover but rather that cardiac filling pressures (PCWP) contribute significantly to cardiac sympathetic activation consistent with previous work. Systemic sympathetic activation however has been shown to vary independently of the cardiac sympathetic activation in CHF, perhaps dependent more on arterial blood pressure in addition to other factors.

There is currently evidence showing that the autonomic system significantly influences the genesis and chronicity of AF. It has been shown that vagal influences on myocardium can initiate atrial fibrillation by affecting atrial refractory periods and favouring macro re-entry. Increased vagal tone generally leads to paroxysmal lone AF, occurring commonly nocturnally, in males aged 40 to 50 years. Increased vagal reflex activity has also been associated with atrial fibrillation occurring during cardiac pacing. In addition, the sympathetic nervous system can promote and initiate AF by increasing automaticity and triggered activity. Symptomatically induced AF is generally observed in patients with underlying heart disease and is provoked by emotional or physical stress. These episodes occur during the day and tend to respond to beta-blockers, while vagally induced AF tends to respond to class I antiarrhythmics. Whether AF itself causes alteration to autonomic tone is less clear however studies in animal atrial pacing models of AF have shown evidence of atrial neural remodelling particularly sympathetic hyperinnervation. In this context a recent study demonstrated increased peripheral sympathetic activity in a heterogeneous group of patients during acutely induced AF.

The use of anti-failure medications between the two groups was not significantly different, except for the use of digoxin, which was greater in the AF group (96% vs 78%). This is understandable as digoxin is often used to control ventricular rate in AF. Previously studies have shown that digoxin augments baroreceptor sensitivity in CHF and may enhance baroreceptor inhibition of sympathetic output during physical or chemical stimulation. This effect however has been shown not to affect cardiac sympathetic activation in CHF. A small number of patients were treated with carvedilol, which we have previously shown not to alter cardiac sympathetic tone, although this remains controversial. The rate of amiodarone usage was similar between the two groups (25% in SR vs 28% in AF). Amiodarone is often used as an antiarrhythmic in CHF and AF, but its effect on survival in CHF remains controversial.

<table>
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<th>Parameter</th>
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<th>AF (n=25)</th>
<th>P value</th>
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<tr>
<td>Arterial NE (pg/ml)</td>
<td>490±23</td>
<td>543±45</td>
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<tr>
<td>Systemic NE spillover (nmol/min)</td>
<td>5.8±0.4</td>
<td>4.9±0.5</td>
<td>0.40</td>
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<tr>
<td>Systemic NE clearance (l/min)</td>
<td>2.2±0.1</td>
<td>1.6±0.1</td>
<td>0.02</td>
</tr>
<tr>
<td>Cardiac NE spillover (pmol/min)</td>
<td>339±21</td>
<td>393±49</td>
<td>0.24</td>
</tr>
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Table 3 Systemic and cardiac norepinephrine spillover

Fig. 2 Scatterplot showing the relationship between cardiac output and norepinephrine clearance in sinus rhythm (SR) (closed circles) and atrial fibrillation (AF) (open circles) patients.

Fig. 3 Scatterplot showing the relationship between cardiac norepinephrine spillover rate and pulmonary capillary wedge pressure in sinus rhythm (SR) (closed circles) and atrial fibrillation (AF) (open circles) patients.
shown in previous studies that amiodarone may exert a cardioselective sympatholytic process in CHF and hence affect cardiac NE spillover measurements.

In the present study, we evaluated a relatively modest number of patients with atrial fibrillation in contrast to the sinus rhythm group. This may potentially have compromised the capacity of our study to detect small differences in sympathetic tone between the two groups. Furthermore, the study was only performed under resting conditions and the AF group displayed good rate control. However, it is well known that the haemodynamic response and rate control may be poor during exercise in AF patients. Thus it is possible that sympathetic tone in AF patients may rise substantially above that in SR during exercise. In this context, newer strategies for rate control such as atrioventricular node ablation and atrioventricular pacing have shown symptomatic benefit independent of left ventricular function. Furthermore, the AF arm of the MUSTIC trial showed benefit with the combination of biventricular pacing and atrioventricular node ablation for chronic AF in CHF, although the overall benefit with this strategy was less than that for SR. The effect of these new pacing approaches in CHF on neurohormonal activation compared with conventional management is an area for future research. It would also be important to investigate the effect of poor rate control on sympathetic tone and hence survival in CHF. In conjunction, the effectiveness beta-blockers on progression of CHF in patients with AF has not been widely studied, there is currently only retrospective data which indicates benefit for their use.

Conclusions

Our study indicates that AF in CHF patients is not accompanied by further increases in sympathetic tone, at least at rest. Further studies are required to evaluate the basis for the adverse effect of AF on CHF outcome.

References