Atrial fibrillation impairs cardiac sympathetic response to baroreceptor unloading in congestive heart failure

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Introduction

Congestive heart failure (CHF) is an increasingly common cardiovascular disorder, which is associated with high levels of morbidity and mortality. The pathophysiology of CHF is complex and is characterized by increased neurohormonal activation.1 In particular, spatially heterogeneous activation of the sympathetic nervous system has been well described, being most marked in the heart.2–4 Although the degree of cardiac sympathetic activation has been correlated with mortality,5,6 the specific afferent triggers that lead to increased sympathetic output to the heart is not well understood. Postulated mechanisms include disordered cardiopulmonary baroreflexes and elevated cardiac filling pressures.3,6–9 Arterial baroreflexes in humans have been shown to be blunted in CHF10,11 and similarly this has been correlated with mortality.12

Atrial fibrillation (AF) commonly accompanies CHF, and it is noted that patients with CHF and AF experience a greater risk of mortality than those with sinus rhythm (SR).13 The underlying mechanism for this observation is not understood, although we have previously shown that cardiac sympathetic tone is similar at rest in well-treated CHF, whether the patient is in SR or AF.6 In this context, several studies have shown that atrial fibrosis and remodelling are characteristic features of AF14–16 but the potential effect of this on cardiopulmonary baroreflexes is unknown.

In the present study, we sought to further understand the mechanism for the apparent adverse interaction between HF and AF. On the basis of previous evidence suggesting that the baroreceptors located in or around the left atrium may play a role in the reflex control of sympathetic drive to the heart, we hypothesized that this might be modified in the setting of AF. Specifically, such changes could be the result of alterations in atrial compliance by virtue of atrial fibrosis.

Methods

Patient characteristics

On the basis of our primary hypothesis that baroreceptor-induced cardiac adrenergic responses would differ between CHF patients, SR and AF patients, we determined that a sample size of nine patients would be required in each group based on our previous studies.8,17 Accordingly, we enrolled 18 CHF patients (nine patients in SR, nine patients in AF), mean age 59 ± 2 years, with left ventricular ejection fraction (LVEF) < 40% with NYHA class II–III symptoms, from the Heart Failure Clinic, Alfred Hospital. Other than these selection criteria and agreement to participate in the study, no other specific selection criteria were made, and no direct attempt to prospectively case-match for haemodynamic severity was made. There were 16 males (eight in each group) and two females.
(one in each group). The aetiology of CHF was idiopathic dilated cardiomyopathy in six patients (three in each group) and ischaemic cardiomyopathy in 12 patients (six in each group). 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 compensation. LVEF was assessed in each patient within 1 month of experimental procedure with Simpson’s biplane method on echocardiography or gated cardiac blood pool scanning. Left atrial diameter was measured by M-mode assessment of the left atrium from the parasternal long axis at the level of the aortic valve. All patients gave written informed consent, and the study was performed with the approval of the Alfred Hospital Ethics Review Committee. This study also complied with the Declaration of Helsinki.

Experimental procedures

We performed right heart catheterization and measured a ‘corrected transcardiac norepinephrine (NE) gradient’ to assess cardiac sympathetic activity [by coronary sinus (CS) catheterization]. Specifically, we measured the transcardiac veno-arterial gradient for NE and corrected this for the extent of fractional extraction of radiotracer NE across the heart.\(^\text{18,19}\) (CS flow cannot routinely be measured due to worldwide withdrawal of use of the Webster thermodilution flow catheters previously used for such purposes.) The corrected transcardiac NE gradient was performed at baseline, after 10 min of 20° and 30° of head up tilt (HUT).

On the day of the clinical study, under local anaesthesia, each patient underwent radial artery cannulation (3F, 5 cm, Cook, Brisbane, Australia) for arterial blood sampling and arterial pressure measurements. Venous introducer sheaths were placed in the antecubital fossae if two suitable veins were available or if not one sheath was positioned in the 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 (CO). Subsequently, a sampling catheter (6 Fr multipurpose coronary catheter) was advanced under fluoroscopic guidance to the CS for sampling, as previously described.\(^\text{3}\)

Once all catheters were positioned, baseline haemodynamic measurements including mean arterial pressure (MAP), heart rate (HR), pulmonary capillary wedge pressure (PCWP), and CO were performed, along with CS and arterial sampling for assessment of the corrected transcardiac NE gradient. Haemodynamic recordings for AF patients were performed over an average of five measurements.

The patient was then transferred to the tilt table and once stabilized underwent passive HUT to 20° for 10 min supporting their own weight, then haemodynamic data were recorded and samples were collected at the end of this 10-min period. Then, patients were further passively tilted to 30° for further 10 min and measurements repeated. After this, patients were returned to the supine position and monitored for 10 min.

All studies were performed in the morning after a light breakfast and a 24-h caffeine-free period. The corrected NE isotope-dilution technique was employed, which is a modification of the NE isotope-dilution technique which was developed by our institution to measure cardiac NE spillover.\(^\text{18,19}\) The technique, in brief, involves infusion of levo-(7-\(^3\)H)-NE (New England Nuclear, Boston, MA, USA) at a rate of 0.5–1 µCi/min through a peripheral vein for 30 min to achieve steady state plasma concentrations. Simultaneous arterial and CS blood samples were obtained at baseline and at the end of each 10-min period of tilt at 20° and 30°. Total body NE spillover and NE clearance were calculated as previously described.\(^\text{18,19}\)

Analysis of plasma NE

Blood samples were collected into ice-chilled tubes containing an anti-coagulant, ethyleneglycol-bis(beta-amino-ethyl ether) N,N'-tetraacetic acid, 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.\(^\text{20}\) The plasma \(^{[3]}\)H-NE concentration was determined by liquid scintillation spectrometry after collection of eluant from the electrochemical detector cell using a fraction collector. The corrected transcardiac NE gradient was calculated:

\[
\text{Corrected transcardiac NE gradient} = \left[ \frac{C_C - C_A}{C_A} \right] + \left[ \frac{C_E \times (NE_{\text{extr}})}{C_A} \right]
\]

where \(C_C\) is the plasma NE concentration in the CS, \(C_A\) the NE concentration in the arterial plasma, and \(NE_{\text{extr}}\) the fractional extraction of radiolabelled NE across the heart.

Collection of right atrial appendages and assessment of atrial fibrosis

In a separate cohort, undergoing coronary artery bypass grafting for ischaemic heart disease, right atrial appendages were collected in 10% neutral buffered formalin (4% formaldehyde) and 5-µm serial sections made from paraffin blocks. These were subsequently stained with Sirius Red (0.1% Sirius Red F3BA in saturated aqueous picric acid). A single examiner (P.A.G.) performed quantitative analysis of total collagen content blindly, using a light microscope (Olympus BX 50) equipped with a JVC KY-F55B camera and analysed using OPTIMAS version 6.2 software. Variability between assessments of collagen content was avoided by using a specific routine to assess for the colour significance of the Sirius Red-stained collagen fibrils. Ten views were randomly selected and analysed at \(\times 10\) magnification for the per cent area of collagen, and the result was averaged for the slide. This approach has been previously used to assess cardiac interstitial collagen content.\(^\text{21,22}\)

Statistical analysis

Data are presented as mean value ± SEM, unless otherwise stated. Statistical analysis and graphical presentation were performed using statistical software (SigmaStat, version 2.03, Chicago, IL, USA). The sample size calculations were based on our previous studies on the influence of baroreceptor unloading on cardiac adrenergic tone.\(^\text{8,17}\) From these studies, we calculated that nine patients would be required per group to detect a difference of 20%, with a common standard deviation of 50 pg/mL and with a power of 80% to reject the null hypothesis at \(P < 0.05\). 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. Categorical data were compared using a \(\chi^2\) test or a Fisher’s exact test where appropriate. A two-way ANOVA with repeated measures was used to compare the sympathetic responses between the SR and AF groups during the tilt by investigating the interaction term between the level of tilt and group. One-way ANOVA with repeated measures was used to compare within-group variables with respect to the haemodynamic responses. Correlations within patients in each ANOVA model were performed using a random intercept. Post hoc testing was performed using the least-significant differences test. A two-sided, \(P\)-value of <0.05 was considered statistically significant.

Results

The demographic data for the patients undergoing cardiac catheterization are presented in Table 1. Of the 18 patients, all completed the first tilt at 20° and 14 patients (seven AF and seven SR patients) completed the 30° tilt. Four patients did not complete the 30° tilt because of prolonged study time due to difficulties with venous access. In comparison, the two groups were well matched with respect to the use of anti-failure and anti-arrhythmic medications. The LVEF
and left atrial diameter were also not significantly different between the SR and AF groups. The AF group tended to be older; however, this did not reach significance \((P = 0.06)\).

Within-group haemodynamic data for SR and AF are presented in Table 2. At baseline, there was a borderline significantly increased MAP (AF 91 ± 6 mmHg, SR 75 ± 4 mmHg, \(P = 0.05\)) and significantly increased diastolic blood pressure (DBP) (AF 73 ± 6 mmHg, SR 61 ± 5 mmHg, \(P = 0.04\)) in the current AF group; however, all other baseline haemodynamic data were not significantly different between groups.

From baseline to 30° HUT, there were significant decreases in PCWP (AF, \(P = 0.002\); SR, \(P < 0.001\)) and RAP (AF, \(P = 0.04\); SR, \(P = 0.009\)) within each group. A comparison of the other haemodynamic parameters between the groups during HUT found no significant difference.

Cardiac sympathetic response differed significantly between the two groups during HUT (Figure 1A and B). Specifically, the corrected transcardiac NE gradient during HUT was significantly different between AF and SR groups (\(P = 0.014\)), and CS NE during HUT between AF and SR groups was also significantly different (\(P < 0.001\)). There was a significant increase from baseline to 30° HUT in corrected transcardiac NE gradient (\(P = 0.013\)) and CS NE (\(P = 0.03\)) within the SR group, which was not found in the AF group.

### Table 2 Demographic data for HUT study cohort

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AF ((n = 9))</th>
<th>SR ((n = 9))</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63 ± 2</td>
<td>55 ± 3</td>
<td>0.06</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>32 ± 2</td>
<td>28 ± 3</td>
<td>0.28</td>
</tr>
<tr>
<td>LA diameter (mm)</td>
<td>55 ± 2</td>
<td>50 ± 3</td>
<td>0.26</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>1/9</td>
<td>2/9</td>
<td>1.0</td>
</tr>
<tr>
<td>Digoxin</td>
<td>5/9</td>
<td>6/9</td>
<td>1.0</td>
</tr>
<tr>
<td>ACE-I</td>
<td>8/9</td>
<td>8/9</td>
<td>1.0</td>
</tr>
<tr>
<td>Diuretics</td>
<td>9/9</td>
<td>9/9</td>
<td>1.0</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>9/9</td>
<td>9/9</td>
<td>1.0</td>
</tr>
</tbody>
</table>

ACE-I, angiotensin-converting enzyme-inhibitor; LA, left atrium.

### Table 2 Haemodynamic response to HUT for SR and AF

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline ((n = 9))</th>
<th>Tilt 20° ((n = 9))</th>
<th>Tilt 30° ((n = 7))</th>
<th>Tilt effect</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (b.p.m.)</td>
<td>69 ± 5</td>
<td>68 ± 6</td>
<td>72 ± 4</td>
<td>0.47</td>
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<tr>
<td>MAP (mmHg)</td>
<td>75 ± 4</td>
<td>74 ± 5</td>
<td>70 ± 7</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>4.0 ± 0.3</td>
<td>4.2 ± 0.4</td>
<td>3.4 ± 0.2</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>18 ± 3</td>
<td>11 ± 4</td>
<td>10 ± 6</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>107 ± 6</td>
<td>106 ± 6</td>
<td>99 ± 7</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>61 ± 5</td>
<td>59 ± 6</td>
<td>58 ± 6</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td>10 ± 2</td>
<td>3 ± 2</td>
<td>0.8 ± 2</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>AF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (b.p.m.)</td>
<td>75 ± 3</td>
<td>77 ± 4</td>
<td>73 ± 7</td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>91 ± 6</td>
<td>87 ± 7</td>
<td>82 ± 8</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>4.9 ± 0.4</td>
<td>4.5 ± 0.5</td>
<td>4.5 ± 0.4</td>
<td>0.31</td>
<td></td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>21 ± 2</td>
<td>15 ± 2</td>
<td>11 ± 1</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>126 ± 10</td>
<td>123 ± 8</td>
<td>114 ± 8</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>73 ± 5</td>
<td>68 ± 5</td>
<td>66 ± 5</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td>8 ± 2</td>
<td>7 ± 3</td>
<td>2 ± 2</td>
<td>0.04</td>
<td></td>
</tr>
</tbody>
</table>

Significance value reflect the significance of tilt on each parameter, as determined by one-way RM ANOVA.

In response to HUT, the whole body sympathetic activity did not differ significantly between the AF and SR groups (Figure 2). During HUT, there was, however, significant within-group increases in arterial NE in both the AF \((P = 0.02)\) and SR groups \((P = 0.002)\) (Figure 2A). In association, there was no significant within-group change in total body NE spillover in response to HUT (Figure 2B) and there was a decrease in NE clearance in both groups, which approached significance in the SR group \((P = 0.05)\) (Figure 2C). In conjunction with our clinical studies, Sirius Red staining of the right atrial appendages demonstrated a significant increase in collagen content in the AF group \((AF 32 ± 3\%\), SR 22 ± 2\%; \(P = 0.025\)) (Figure 3). The demographic and clinical data for the surgical cohort are presented in Table 3. There was a trend to increased left atrial dimensions with the surgical AF group \((P = 0.08)\) in comparison with the SR group. Otherwise, apart from digoxin usage \((P = 0.014)\), there were no significant differences between the surgical AF or SR group.

### Discussion

In this study, we have found for the first time a significant difference in cardiac sympathetic drive response in CHF patients to HUT, when comparing AF patients with those in SR. This data can only be derived invasively by the measurement of transcardiac NE gradients or spillover, rather than HR spectral analysis that is invalidated by the presence of AF. Our study was predicated by data from our group and
that have shown that modulation of filling pressures can alter cardiac sympathetic activation. This relationship has been hypothesized to be due to the presence of cardiopulmonary baroreceptors (possibly located in the left atrium) providing input into centres controlling efferent cardiac sympathetic nerve activity.\textsuperscript{3,23}

The cardiac sympathetic and total body sympathetic response to HUT has not been previously characterized in CHF, although a previous study demonstrated an attenuated peripheral venous NE response in CHF patients in comparison with normal subjects.\textsuperscript{11} In conjunction, HR responses to postural change in CHF are known to be blunted,\textsuperscript{11,24,25} consistent with numerous studies demonstrating attenuated arterial baroreceptor function in CHF.\textsuperscript{26,27} Although the specific pathogenic mechanism responsible for baroreceptor dysfunction in CHF is uncertain, the process does appear to be reversible and may improve with treatment.\textsuperscript{28} In relation to the control of cardiac sympathetic tone in CHF, two previous studies\textsuperscript{7,8} found that cardiac sympathetic tone decreased with decreasing filling pressures, whereas one study found a non-significant rise.\textsuperscript{9} In the latter study, it was demonstrated that the influence of sodium nitroprusside on cardiac sympathetic activity in the CHF group was significantly less than that in the control group, leading the authors to conclude that the baroreflex control of cardiac sympathetic tone was blunted in CHF. Our current study extends these findings by demonstrating that the baroreflex control of cardiac sympathetic tone is further impaired in the setting of AF. Although our studies and others, as described earlier, have principally focused on the potential role of intra-cardiac filling pressures as a driving force for cardiac adrenergic activity, we cannot exclude the possibility that volume receptors play an important role.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AF (11 patients)</th>
<th>SR (12 patients)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>70 ± 3</td>
<td>64 ± 3</td>
<td>0.21</td>
</tr>
<tr>
<td>LA diameter (mm)</td>
<td>5 ± 0.1</td>
<td>4.5 ± 0.3</td>
<td>0.08</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>2/12 (17%)</td>
<td>4/12 (34%)</td>
<td>0.68</td>
</tr>
<tr>
<td>ACE-I</td>
<td>6/12 (50%)</td>
<td>5/12 (42%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Digoxin</td>
<td>6/12 (50%)</td>
<td>0/12 (0%)</td>
<td>0.014</td>
</tr>
<tr>
<td>Male</td>
<td>6/12 (50%)</td>
<td>6/12(50%)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

LA, left atrium; ACE-I, angiotensin-converting enzyme-inhibitor.

Figure 2  Line graphs demonstrate the effect of tilt on whole body NE kinetics. (A) Arterial plasma NE concentration. (B) Total body NE spillover rate. (C) Total body NE clearance rate. *P < 0.05 for the within-group response to tilt as determined by one-way RM ANOVA. See Supplementary material online for a colour version of this figure.

Figure 3  Sirius Red staining human right atrial appendages AF (A) vs. SR (B) ×10 magnification. See online supplementary material for a colour version of this figure.
In a previous study, we showed that the resting cardiac NE spillover rate was a predictor of survival in HF patients, and accordingly, it could be proposed that the blunted cardiac sympathetic response in AF patients would actually be accompanied by lower mortality. However, of equal consideration, in a previous study, we showed that HF patients with low cardiac NE stores were at higher risk of death from progressive HF. Although speculative, it is therefore possible that the blunted cardiac adrenergic response to haemodynamic stress in AF patients could also reflect the presence of reduced tissue stores and therefore contribute to HF progression by virtue of an inability to mount a cardiac adrenergic response to acute haemodynamic perturbation.

The development of AF is increasingly recognized as a marker of atrial remodelling, including fibrosis, with a significant impact on the probability of further or sustained AF. In our study of patients, undergoing non-valvular heart disease-related cardiac surgery, we confirmed the presence of significantly greater levels of atrial fibrosis in AF patients. Although these samples were not obtained from the patients undergoing the catheterization studies, it may be postulated that the presence of atrial fibrosis, in the context of AF, could contribute to HF pathophysiology by altering the cardiac sympathetic responses to haemodynamic stressors, such as those associated with normal changes in posture. In this context, it has been observed that in a canine model of CHF, changes in atrial compliance may reduce the sensitivity of left atrial B nerve receptor endings in conjunction with loss of their end-arteriorizations. We did not, however, perform detailed histologic studies on the pattern of innervation in our tissue samples because these tissues were obtained from the right atrial appendage only. Our clinical study cohort did not have significantly different left atrial dimensions \( P = 0.26 \) consistent with the hypothesis that the difference in baroreceptor-mediated changes in cardiac sympathetic tone could be secondary to alterations in atrial compliance due to remodelling and fibrosis. Of interest, in a study of non-HF subjects with paroxysmal AF, Grassi et al. found evidence of sympathoinhibition during AF, in the context of a modest rise in central venous pressure.

In the current study, the SR and AF patient groups were generally well matched except for baseline differences in MAP and DBP, this difference had, however, abated with HUT. As discussed previously, our group has shown PCWP to be the main haemodynamic determinant of cardiac sympathetic tone in CHF. Otherwise, the two groups had a borderline age difference \( P = 0.06 \); however, the actual difference in age mean was only 8 years. Regional increases in sympathetic activity have been demonstrated at extremes of age only. A difference in autonomic response with ageing has also been demonstrated to HUT, although only in comparison of young to old subjects.

**Limitations**

In the present study, we compared the cardiac sympathetic response to baroreceptor unloading in two cohorts of patients, those in SR and those in AF. Although it may have been of interest to examine sympathetic function before and after cardioversion in the AF patients, we considered this impractical given the need for a repeat invasive study and the potential for failure of cardioversion or AF recurrence. We measured a corrected transcardiac NE gradient, given that CS thermodilution catheters are not currently available. This measurement was based on the NE veno-arterial gradient across the heart with correction for neural re-uptake across the heart. It does not incorporate CS blood flow, which is a potential source of bias. However, it has been previously shown in three studies that CS flow does not significantly change in CHF patients with a decrease in filling pressures, thereby reducing the likelihood of marked variations in CS blood flow as a confounding factor. Moreover, in a retrospective analysis of a previous study from our group, we found that changes in CS blood flow in response to unloading did not differ between SR and AF patients (unpublished results).

In the current study, the SR and AF patient groups were generally well matched except for baseline differences in MAP and DBP, this difference had, however, abated with HUT. As discussed previously, our group has shown PCWP to be the main haemodynamic determinant of cardiac sympathetic tone in CHF. Otherwise, the two groups had a borderline age difference \( P = 0.06 \); however, the actual difference in age mean was only 8 years. Regional increases in sympathetic activity have been demonstrated at extremes of age only. A difference in autonomic response with ageing has also been demonstrated to HUT, although only in comparison of young to old subjects.

**Conclusion**

In conclusion, the present study demonstrates for the first time, the influence of AF on the cardiac sympathetic response to a haemodynamic challenge in CHF patients. Further studies are now required to define precisely the relationship between these observations to changes in atrial architecture and function. These studies are pivotal to the further understanding of the mechanisms that contribute to the accelerated progression of CHF in the setting of AF.

**Supplementary material**

Supplementary material is available at European Heart Journal online.

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**Conflict of interest:** none declared.

**References**

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