**SCIENTIFIC LETTER**

**Helicobacter pylori and atrial fibrillation: a possible pathogenic link**

A S Montenero, N Mollichelli, F Zumbo, A Antonelli, A Dolci, M Barberis, C Sirolla, T Staine, L Fiocca, N Bruno, S O’Connor

Recent advances have raised the hope of effective pharmacological or non-pharmacological treatments of atrial fibrillation (AF), and of better understanding of the pathophysiological mechanisms involved in the initiation and persistence of the arrhythmia. Inflammatory changes in the atrial structure have been observed after cardiac surgery and persistence of the arrhythmia. Inflammatory changes in the pathophysiological mechanisms involved in the initiation of AF may be involved in the chronic atrial inflammation resulting in AF.

This study aimed: (1) to confirm the data previously reported that showed higher concentrations of CRP in patients with AF; and (2) to assess the possible association between *H pylori* infection and AF in patients without demonstrable structural cardiac disease, by comparing them with a group of normal healthy volunteers.

**METHODS**

For this case–control study we enrolled 59 consecutive patients with a paroxysmal or persistent form of AF who were admitted to our cardiology department for cardioversion and electrophysiological study. This group included patients without structural heart disease even though some patients were prescribed medication for hypertension.

We also investigated a control group of 45 healthy volunteers who were assessed from their medical history and a clinical examination to have no history of atrial arrhythmias or concomitant acute or chronic disease. Exclusion criteria were myocardial infarction, prior cardiothoracic surgery, ischaemic heart disease, valvar disease, thyroid dysfunction, congenital heart disease, diabetes, and acute or chronic infections. All patients underwent a physical examination, ECG, echocardiography, electrophysiological study, routine laboratory tests, thyroid function tests, a serological test for *H pylori* infection, and CRP determination (not high sensitivity).

All chemical tests and CRP were measured on a Roche Modular system. For CRP determination, we used a homogeneous immunoturbidimetric assay with calibration material referring to CRM470 IFCC International Reference Standard with a 0–6 mg/l reference range. IgG antibodies to *H pylori* were assayed by the enzyme linked immunosorbent assay (ELISA) *H pylori* IgG kit (Adaltis Italia, Casalecchio di Reno, Bologna, Italy) on a semiautomatic ELISA processor (Labotech, Adaltis Italia) with an analytical range of 5–100 IU/ml and a cut off established at 15 IU/ml.

Results are presented as mean (SD) for continuous normally distributed variables, as median (interquartile range) for non-normally distributed data, and as percentages for categorical data. Groups were compared by unpaired *t* test or one way analysis of variance for normally distributed variables, and by the Kolmogorov-Smirnov test or Mann-Whitney test where data were not normally distributed. To account for covariate effects between groups, the analysis of variance was adjusted for covariates after natural log transformation of skewed distribution. Data were analysed with SPSS (SPSS Inc, Chicago, Illinois, USA).

**RESULTS**

Table 1 shows the mean (SD) age of the AF and the control groups enrolled between March 2002 and January 2003, together with other demographic and clinical characteristics. There were no significant differences in the mean ages of the two groups. There was a difference in the number of patients being treated for hypertension, which was larger in the AF group than in the control group. There were no significant differences between the groups regarding the presence of traditional risk factors, cholesterol, low density lipoprotein cholesterol, and triglycerides.

Table 2 shows the mean (SD) age and demographic and clinical characteristics of the group with chronic AF subdivided into persistent (n = 29) and paroxysmal (n = 30) AF. Patients with persistent AF were older than patients with paroxysmal AF and they had a higher prevalence of treated hypertension. There were no significant differences between the groups regarding the presence of traditional risk factors.

In the AF group *H pylori* seropositivity (97.2 (50.5–100.0) IU/ml) and CRP (8 (6–10) mg/l) were significantly higher (p < 0.001) than in the control group (5.3 (5.0–33.9) IU/ml and 1 (0–2) mg/l, respectively).

**Abbreviations:** AF, atrial fibrillation; CRP, C reactive protein; ELISA, enzyme linked immunosorbent assay
The groups with persistent and paroxysmal AF as described with paroxysmal AF after adjustment for differences in age in respectively) in patients with persistent AF than in those with AF, which leads us to hypothesise that AF. In addition, we report high concentrations of CRP, which correlation between AF and believe to be the first that shows a highly significant therefore established the study reported here, which we festing in AF. Chung and colleagues 3 were the first to realise AF and H pylori infection were associated. We soon realised that AF and H pylori infection were associated. We therefore established the study reported here, which we believe to be the first that shows a highly significant correlation between AF and H pylori. The association between AF and H pylori was very strong in patients with persistent AF. In addition, we report high concentrations of CRP, which confirm the presence of systemic inflammation in patients with AF, which leads us to hypothesise that H pylori infection may be the substrate of this systemic inflammation manifesting in AF. Chung and colleagues 3 were the first to document an inflammatory state in patients with AF.

H pylori is a very strong bacterium, with features that allow it to cross gastric mucus and to attach to epithelial cells, thereby evading the immune response. H pylori infection is responsible for determining an important systemic and mucosal humoral response, but these antibodies do not eradicate the infection and may contribute to tissue damage. 5 Different H pylori strains can determine the specific systemic antibody response in infected patients. Some patients with H pylori have autoantibodies to the H/K -ATPase of gastric parietal cells that can determine corpus atrophy. 6 Considering that there is a similarity between H/K -ATPase, the proton pump of gastric cells, and Na+/K+-ATPase, the pump of cardiac cells, which are inhibited by cardiac glycoside such as digoxin, an interesting hypothesis is that these autoantibodies to H/K -ATPase may also be antibodies to Na+/K+-ATPase, thus determining atrial damage. In fact, cardiac Na+ / K+-ATPase and H/K -ATPase have a similar 35 kDa glycoprotein necessary for their catalytic activity. The role of these pumps is to maintain ionic homeostasis by hydrolysing ATP and therefore loss of this balance may trigger AF by determining abnormal automaticity or triggered activity that causes delay after depolarisation inducing very rapid premature atrial contractions. Several issues remain unresolved.

We have shown the highly significant link between AF and H pylori in our relatively small sample and confirmed that CRP is a good marker for the inflammatory process. More data will be necessary from controlled studies to further identify how H pylori can influence the pathogenesis of AF.

### DISCUSSION
This pilot study was proposed after prolonged clinical observations that a high percentage of patients with AF admitted to our cardiology department had gastric problems. Following these observations, we introduced as standard practice the determination of antibodies to H pylori. Some patients with autoantibodies to the H pylori +/K-ATPase of gastric parietal cells that can determine corpus atrophy. 7 Considering that there is a similarity between H/K -ATPase, the proton pump of gastric cells, and Na+/K+-ATPase, the pump of cardiac cells, which are inhibited by cardiac glycoside such as digoxin, an interesting hypothesis is that these autoantibodies to H/K -ATPase may also be antibodies to Na+/K+-ATPase, thus determining atrial damage. In fact, cardiac Na+/ K+-ATPase and H/K -ATPase have a similar 35 kDa glycoprotein necessary for their catalytic activity. The role of these pumps is to maintain ionic homeostasis by hydrolysing ATP and therefore loss of this balance may trigger AF by determining abnormal automaticity or triggered activity that causes delay after depolarisation inducing very rapid premature atrial contractions. Several issues remain unresolved.

We have shown the highly significant link between AF and H pylori in our relatively small sample and confirmed that CRP is a good marker for the inflammatory process. More data will be necessary from controlled studies to further identify how H pylori can influence the pathogenesis of AF.

### Table 2
Demographic and clinical data for patients with persistent AF and paroxysmal AF

<table>
<thead>
<tr>
<th></th>
<th>Persistent AF</th>
<th>Paroxysmal AF</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68.17 (11.68)</td>
<td>60.60 (12.91)</td>
<td>0.022</td>
</tr>
<tr>
<td>Hypertension</td>
<td>22 (75.9%)</td>
<td>11 (36.7%)</td>
<td>0.009</td>
</tr>
<tr>
<td>Biochemical analyses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>5.034 (0.89)</td>
<td>4.82 (0.95)</td>
<td>0.950</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.65 (0.91)</td>
<td>1.44 (0.95)</td>
<td>0.828</td>
</tr>
<tr>
<td>LDL (mmol/l)</td>
<td>2.93 (0.74)</td>
<td>2.78 (2.17)</td>
<td>0.736</td>
</tr>
</tbody>
</table>

Data are mean (SD) of number (%).

H pylori seropositivity and CRP were both significantly higher (100 (72.6–100.0) IU/ml v 60.2 (35.9–100.0) IU/ml, p = 0.027, and 9 (7–11) mg/l v 7 (6–10) mg/l, p = 0.041, respectively) in patients with persistent AF than in those with paroxysmal AF after adjustment for differences in age in the groups with persistent and paroxysmal AF as described above.

### REFERENCES


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