Relation of Cag-A-Positive *Helicobacter Pylori* Strain and Some Inflammatory Markers in Patients with Ischemic Heart Diseases

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Recently, a potential link between infectious agents and athero-sclerosis has been suggested. *H. pylori* strains bearing the cytotoxin associated gene A (Cag–A) provoked a heightened inflammatory response in vivo and showed stronger relation to gastric complication of this infection. The association between Cag-A positive strain and vascular diseases producing conflicting results. So, the present study aimed to estimate the seroprevalence of *H. pylori* Cag-A positive strains as a risk factor among different groups of ischemic heart disease and to study its interaction with high sensitivity CRP (hs-CRP) and IL6 as inflammatory host responses. The present study was conducted on anti *H. pylori* IgG positive 60 ischemic heart disease (IHD) patients and 20 apparently healthy individuals as a control group. IHD patients were classified into 3 groups: (group I) with acute myocardial infarction, unstable angina pectoris patients (group II), chronic stable angina pectoris patients (group III). For all patients and control groups serum anti Cag-A IgG, IL6, hs-CRP, CK, CKMB, LDH, AST and Lipid profile were estimated. IL6 and hs-CRP levels were increased in groups I, II and III as compared with group IV (P<0.001) with positive correlation between IL6 and hs-CRP in groups I, II and III (P<0.05). The percentage of anti Cag-A positive cases was similar among the patient groups, but significantly higher than in the control group. Thus, infection with Cag-A positive *H. pylori* strain may play a role as a risk factor in development of ischemic heart diseases through provocation of high inflammatory response or through other mechanism. Therefore eradication of this infection is important as it is much less expensive than long term treatment of the other risk factors.

Ischemic heart disease (IHD) is the most common cause of mortality worldwide (Freed *et al.*, 2005). The course is changeable, with acute symptoms and remission periods. Acute coronary syndromes include unstable angina and acute myocardial infarction with or without Q wave (Rodriguez *et al.*, 2003).

Ischemic injury of cardiomyocytes caused by spasm or thrombosis of coronary artery plays the main role in the pathogenesis of acute coronary syndrome. Thrombosis may be caused by an increase in inflammatory reaction in atheromatous plaque at the cellular and humoral levels (Rodriguez *et al.*, 2003).

Interleukin 6 (IL6) is a multifunctional cytokine with both endocrine and paracrine effects, which mediates several functions in the host's defense and promotes atherogenesis, dyslipidaemia, hypertension and insulin resistance by mediating the effect of activated macrophages and lymphocytes (Bennet *et al.*, 2003).

C- reactive protein (CRP) is an acute phase protein and an indicator of inflammatory activity present in the body (Fenu *et al.*, 2004). Moreover, it has been suggested that CRP may not only be a marker of generalized inflammation but directly and actively participates in both atherogenesis and atheromatous plaque disruption (Ramon *et al.*, 2004).

Infectious diseases may play a role in IHD cases or they may intensify the effect of other risk factors. The association of Coronary artery disease (CAD) and *Chlamydia*
pneumoniae (C. pneumoniae) is firmly established while the link with other infectious agents such as Cytomegalovirus, Herpes simplex virus and Helicobacter pylori (H. pylori) is more controversial (Fong, 2000).

H. pylori is a microaerophilic spiral shaped Gram negative bacterium that colonize the gastric lumen of humans and other primates. Infection is usually chronic (Graham et al., 1991), with proven association with gastric ulcer and adenocarcinoma. It has also been associated with atherosclerosis in a substantial number of studies, although other studies show an absence of this association (Pakodi et al., 2000).

There is now a clear evidence that Cag A positive strains play a major role in the pathogenesis of gastric complications of this infection (Huang et al., 2003). However, studies on the Cag A status and vascular disease producing mixed results (Pasceri et al., 2006). Establishing a causal link between this infection and CAD would be of a major public health importance, since the eradication of the bacterium is easy and much less expensive than long term treatment of the other risk factors (Pellicano et al., 2003).

So the aim of the present study was to estimate the seroprevalence of H. pylori Cag A positive strains as a risk factor among different groups of ischemic heart disease and to correlate this seropositivity with IL6 and CRP as inflammatory markers.

Subjects and Methods

The present study was conducted on 60 cases positive for anti H. pylori IgG selected from 96 patients with ischemic heart disease as proved by clinical and laboratory evaluation from Cardiology Department of Specialized Medical hospital, Mansoura University (28 males and 32 females) with ages ranged from 39 to 60 years (52.25 ± 5.88). A total of 20 subjects (positive for anti H. pylori IgG) selected from 50 apparently healthy individuals with no clinical evidence of CAD and none of them had any traditional risk factors (Diabetes, smoking and hypertension) for atherosclerosis (14 males and 6 females) with ages ranged from 38 to 58 years (48.95 ± 3.94) served as a control group. Cases and controls were classified according to their clinical data and investigations into the following groups:

Group I: patients with acute myocardial infarction (12 Patients).
Group II: Patients with unstable angina pectoris (23 Patients).
Group III: Patients with chronic stable angina pectoris (25 Patients).
Group IV: Control group (20 Persons).

Informed consents were obtained from all individuals included in the study.

For all patients, history taking, clinical examination, Electrocardio–graphy and Echocardiography were carried out. Plasma samples were collected from patients after 2–3 hours of admission for assessment of IL6 and sera for cardiac enzymes Creatine Kinase (CK) and Creatine Kinase muscle brain type (CKMB). While 12 hours fasting serum samples were collected for estimation of lipid profile using enzymatic colorimetric method (Diasys ; Holzheim, Germany), cardiac enzymes Lactate dehydrogenase (LDH) and Aspartate aminotransferase (AST) using kinetic enzymatic method (Roch diagnostics, GMBH, Mannheim, Germany) and specific laboratory investigations including hs-CRP level, anti H. pylori IgG and anti Cag-A IgG.

Serum IL6 levels were estimated using an enzyme-linked immunosorbent assay (ELISA) technique (Cytimmune science Inc.; Rochville, Europe): The microtiter plate provided in the kit has been pre-coated with a monoclonal antibody specific to IL-6. Standards or samples were then added to the appropriate microtiter plate wells with a biotin-conjugated polyclonal antibody preparation specific for IL-6 and incubated. IL-6 if present, will bind and become immobilized by the antibody pre-coated on the wells and then be “sandwiched” by biotin conjugate. After a washing cycle, avidin conjugated to Horseradish Peroxidase (HRP) was added to each microplate well and incubated. After another cycle of washing, substrate was added and color developed. The test was performed according to manufacturer instructions.

Serum hs-CRP levels were determined using an enzymatically amplified "two step" sandwich type immunoassay, in which standards, controls and unknown samples are incubated in microtiter wells which have been coated with anti- hs-CRP antibody
Anti Cag IgG antibodies detection was based upon an ELISA, (DRG international Inc., USA) here horseradish peroxidase is used as enzyme tracer. During the first incubation, the sample anti-Cag-A IgG antibodies, if any, are bound to the Cag-A antigen coated wells. A wash cycle eliminates all unbound materials. In the incubation that follows, a second antibody (anti-human IgG conjugated with peroxidase) will bind to the Cag-A antigen–antibody complex. After a further wash cycle, a colorless chromogen solution (tetramethylbenzidine, TMB) in a substrate–buffer is added to the wells, where it yields a colored compound, by reacting with the peroxidase enzyme. Adding H$_2$SO$_4$ will stop color development. The color intensity, measured in a spectrophotometer at 450 nm, will thus be directly proportional to the anti-Cag-A IgG antibody concentration in standards and samples.

A standard curve on linear graph paper was drawn by plotting the absorbances obtained for each standard (Y axis) against its concentration in Relative Units (RU/ml; X axis). While samples with values less than 10 RU/ml were judged non reactive for anti Cag-A IgG, samples with values within 10 and 15 RU/ml were considered weakly positive, and samples with values higher than 15 RU/ml reactive for anti Cag-A IgG.

Statistical Analysis

Data entry and analyses were performed using statistical package for social Scientists software (SPSS) for windows version 11 (SPSS, Inc., Chicago, IL, USA). The quantitative data were presented as a range, mean and standard deviation. Student t-test was conducted to compare the mean of continuous variable for two different groups of individuals. The qualitative data were presented as numbers and percentages. The Chi-square ($\chi^2$) was used to find the association between variables of qualitative data. Odds ratios with 95% confidence intervals were calculated to find the potential risk. The P value of < 0.05 indicates a significant result. Linear correlation coefficient (r) was calculated to test the association between two quantitative variables by using Pearson's product moment correlation (r).

Results

Statistical analysis of clinical data and laboratory results of patients and controls are shown in table (1), total cholesterol, triglycerides, and LDL levels were significantly higher and HDL levels were significantly lower in groups I, II and III as compared to the control group IV.

CK and CK MB mean levels were significantly increased in groups I and II in comparison to group IV ($P<0.001$) and showed no statistical difference between group III and control group IV ($P= 0.54$ and 0.11, respectively).

LDH mean levels in groups I, II and III were significantly higher than in group IV ($P= 0.006$, 0.02 and 0.002, respectively). AST mean levels were significantly increased in group I ($P<0.001$) and in group III ($P= 0.01$), but not in group II ($P= 0.06$) in comparison to group IV.

The mean IL6 & hs-CRP levels were significantly increased in groups I, II and III as compared to group IV ($P< 0.001$), with significant positive correlation between IL6 and hs-CRP levels in groups I, II and III (Table 2 & 3).

Table 4 shows no difference of the percentage of anti Cag-A positive cases between groups I, II and III with significant difference between each group and the control group. The risk of atherosclerosis is increased by 4 folds in group III, 6 folds in group II and 7 folds in group I (OR 4.1, 6.6 & 7.0, respectively) in comparison to the control group.

The mean serum levels of IL6 and hs-CRP did not differ between anti Cag-A positive and negative cases in each group; however their levels were significantly higher in total anti Cag-A positive cases versus negatively studied individuals. There was no difference between anti Cag-A positive and negative cases with regard to total leucocytic count (TLC) and platelets count while total cholesterol level was significantly higher in total anti Cag-A positive versus negative cases but not within the same group (Table 5).
Anti Cag-A levels were positively correlated to IL6 and hs-CRP levels ($P=0.001$ & 0.007, respectively; data not shown in the table).

Table 1. Clinical Data and Laboratory Results of Studied Groups

| No Group | Group I | Group II | Group III | Group IV | *P<  
|---------|---------|----------|-----------|----------|------- 
| Age     | 12      | 23       | 25        | 20       |       
| mean±SD | 54.3±2.4| 52.5±4.1 | 51.9±6.4  | 52.9±3.9 | NS    
| Range   | 51-60   | 45-59    | 39-60     | 42-58    |       
| Sex No (%) |        |          |           |          |       
| Male    | 8 (66.7%)| 9 (39%)  | 11 (44.5%)| 14 (70%) | NS    
| Female  | 4 (33.3%)| 14 (60.9%)| 14 (56%)  | 6 (30%)  |       
| Hypertensive | 7 (58.3%)| 12 (52.2%)| 5 (20%)   | 0 (0%)   | 0.001 
| Smokers | 6 (50%)  | 10 (43.5%)| 12 (48%)  | 0 (0%)   | 0.001 
| Diabetics | 9 (75%)  | 14 (60.9%)| 19 (76%)  | 0 (0%)   | 0.001 
| Total cholesterol mg/dl (mean±SD) | 235.5±6.7 | 216.8±28.6 | 216.7±17.1 | 156±25.1 | 0.001 
| Triglyceride mg/dl (mean±SD) | 188.3±7.7 | 147.7±14.1 | 148.2±12.3 | 103.5±35.3 | 0.001 
| HDL mg/dl (mean±SD) | 39.9±4.4 | 35.4±8.8 | 37.1±9.9 | 59.3±6.6 | 0.001 
| LDL mg/dl (mean±SD) | 162.8±5.4 | 151.8±34.5 | 149.4±23.4 | 76.0±21.2 | 0.001 
| CK U/L (mean±SD) | 1143.3±384.4 | 191.3±41.9 | 110.7±28.13 | 104.16±34.43 | 0.001 
| CKMB U/L (mean±SD) | 229.3±98.5 | 27.5±8.8 | 17.2±6.3 | 14.29±5.9 | 0.001 
| LDH U/L (mean±SD) | 496.3±197.7 | 463.6±209.7 | 490±180.8 | 343±99.3 | 0.001 
| AST U/L (mean±SD) | 59.76±2.86 | 25.39±5.7 | 27.9±8.15 | 22.16±4.89 | 0.001 

*P ≤ 0.05 is significant. NS= not significant.

Table 2. Comparison of IL6 and hs-CRP among the Studied Groups.

<table>
<thead>
<tr>
<th>IL6 (ng/ml)</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>Group IV</th>
<th>*P (each gr. Versus gr. IV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean±SD</td>
<td>7.78±0.97</td>
<td>6.5±1.32</td>
<td>6.28±1.1</td>
<td>2.66±1.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(range)</td>
<td>6.3-9.9</td>
<td>4.1-9.1</td>
<td>2.77-9.8</td>
<td>1.1-4.8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hs-CRP (ng/ml)</th>
<th>Mean±SD</th>
<th>Mean±SD</th>
<th>Mean±SD</th>
<th>Mean±SD</th>
<th>*P ≤ 0.05 is significant.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(range)</td>
<td>12205±5582</td>
<td>12647±6672</td>
<td>8222±3985</td>
<td>2168±1527</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>7840-28970</td>
<td>4530-32100</td>
<td>4010-16970</td>
<td>1110-6500</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Table 3. Correlation between IL6 and hs-CRP Levels in the Diseased Groups.

<table>
<thead>
<tr>
<th>Hs-CRP</th>
<th>r</th>
<th>P</th>
<th>r</th>
<th>P</th>
<th>r</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.9</td>
<td>&lt;0.001</td>
<td>0.71</td>
<td>&lt;0.001</td>
<td>0.84</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*P ≤ 0.05 is significant.

Table 4. Percentages of anti Cag-A Positive Cases among Studied Groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>+ve cases</th>
<th>-ve cases</th>
<th>*P&lt;</th>
<th>Odds ratio*</th>
<th>95% confidence interval*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>9</td>
<td>75</td>
<td>3</td>
<td>25</td>
<td>0.0269</td>
</tr>
<tr>
<td>II</td>
<td>17</td>
<td>73.9</td>
<td>6</td>
<td>26.1</td>
<td>0.0060</td>
</tr>
<tr>
<td>III</td>
<td>16</td>
<td>64</td>
<td>9</td>
<td>36</td>
<td>0.0361</td>
</tr>
<tr>
<td>IV</td>
<td>6</td>
<td>30</td>
<td>14</td>
<td>70</td>
<td></td>
</tr>
</tbody>
</table>

* P ≤ 0.05 is significant. NS= not significant.

Each group versus group IV.
Group I versus group III  P= 0.7110 (NS)
Group II versus group III  P= 0.5419(NS)
Group I versus group II  P= 1.00 (NS)

Table 5: Relation of CagA Seropositivity to TLC, Platelet Count, Total Cholesterol and Inflammatory Markers Levels.

<table>
<thead>
<tr>
<th>Group</th>
<th>CagA No</th>
<th>IL6 level</th>
<th>Hs-CRP</th>
<th>TLC</th>
<th>Total Cholesterol</th>
<th>Platelet count</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean±SD *P&lt;</td>
<td>Mean±SD *P&lt;</td>
<td>X±SD P&lt;</td>
<td>X±SD *P&lt;</td>
<td>X±SD P&lt;</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>+ve 9</td>
<td>7.5±0.8</td>
<td>9450±3572</td>
<td>8.3±0.3</td>
<td>234±6</td>
<td>198±5</td>
</tr>
<tr>
<td></td>
<td>-ve 3</td>
<td>7.3±0.5</td>
<td>9843±1120</td>
<td>8.6±0.2</td>
<td>236±9</td>
<td>185±8</td>
</tr>
<tr>
<td>II</td>
<td>+ve 17</td>
<td>4.5±1.1</td>
<td>2005±7565</td>
<td>8.7±1.6</td>
<td>216±25</td>
<td>227±57</td>
</tr>
<tr>
<td></td>
<td>-ve 6</td>
<td>6.2±1.5</td>
<td>9464±4900</td>
<td>8.4±0.9</td>
<td>218±40</td>
<td>209±34</td>
</tr>
<tr>
<td>III</td>
<td>+ve 16</td>
<td>6.2±2.3</td>
<td>7955±3966</td>
<td>8.2±1.9</td>
<td>218±17</td>
<td>179±27</td>
</tr>
<tr>
<td></td>
<td>-ve 9</td>
<td>6±1.8</td>
<td>7473±3432</td>
<td>9.1±2.9</td>
<td>213±17</td>
<td>220±79</td>
</tr>
<tr>
<td>IV</td>
<td>+ve 6</td>
<td>2.2±0.6</td>
<td>1588±507</td>
<td>7.8±1.1</td>
<td>152±19</td>
<td>189±31</td>
</tr>
<tr>
<td></td>
<td>-ve 14</td>
<td>2.8±1.1</td>
<td>2419±1756</td>
<td>7.6±2.1</td>
<td>156±27</td>
<td>205±44</td>
</tr>
<tr>
<td>Total</td>
<td>+ve 48</td>
<td>6±2.2</td>
<td>8970±6107</td>
<td>8.4±1.5</td>
<td>211±29</td>
<td>201±45</td>
</tr>
<tr>
<td></td>
<td>-ve 32</td>
<td>4.8±2.2</td>
<td>4294±4309</td>
<td>8.1±2.2</td>
<td>191±41</td>
<td>208±52</td>
</tr>
</tbody>
</table>

*P ≤ 0.05 is significant. NS= not significant.
Discussion

Under physiological conditions, vascular endothelium has antithrombogenic potential. Activation of endothelial cells by proinflammatory cytokines or infectious agents is associated with a loss of antithrombotic properties (Bonetti et al., 2003). Proinflammatory cytokines derived from monocytes, macrophages and/or adipose tissue trigger CRP in the liver which is acute phase reactant and marker of inflammation (Ridker, 2003), and itself promotes inflammation (Pasceri et al., 2000), and increases concentration and activity of plasminogen activator -1 (Devaraj et al., 2003).

Many seroepidemiological studies suggested a relationship between infection and the pathophysiology of ischemic heart disease (Nieminen et al., 1993; Ericson et al., 2000). The proposed ways in which infectious agents may induce or accelerate atherosclerosis include; direct invasion of vessel wall, local release of endotoxins, molecular mimicking of microbial antigens and vessel wall, systemic increase of cytokines or change in lipid profiles (Fong, 2000).

Possible association of H. pylori infection and coronary artery disease has been suggested (Mendall et. al., 1994); however subsequent studies have produced conflicting findings (Danesh et al., 1999; Wald et al., 1997). H. pylori strains bearing the cytotoxin associated gene A (Cag-A) are more virulent and produce more inflammatory response in vivo (Peek et al., 1995), and so, the aim of the present study was to estimate the seroprevalence of anti Cag-A bearing H. pylori strains as a risk factor among IHD patients versus controls and to verify its relation to proinflammatory cytokine IL6 and hs-CRP as a possible mechanism of atherosclerosis.

Among 96 IHD patients, 60 cases were included in this study in addition to 20 subjects of 50 apparently healthy individuals. The selection was based on that both cases and controls be anti H. pylori IgG sero-reactives.

The percentages of seroreactivity to H. pylori were estimated to be 62.5% in patients and 40% among controls. Similarly Gunn et al. (2000) reported that 60.02% and 53.7 among myocardial infarction patients and control groups respectively were seroreactive to H. pylori.

IL6 and hs-CRP mean levels were significantly increased in patients as compared to the control group with significant positive correlation between IL6 and hs-CRP levels in patients groups.

The percentages of cases serologically reactive to Cag -A bearing H. pylori strains were 75%, 73.9%, 64% and 30% in groups I, II, III and IV, respectively which were significantly higher in patients than in the control group (P<0.05) with increased risk of IDH by 4 folds in group I, 6 folds in group II and 7 folds in group III in comparison to control group (OR: 4, 6.6, 7, respectively). Pasceri & colleagues (2000) showed that 43% of patients with range of coronary syndromes were anti Cag-A positive compared to 17% among controls.

On the contrary to our results, Gunn et al. (2000) reported percentage of 38% among patients with acute myocardial infarction and 30.8% among controls with insignificant difference between them. However, when they redistributed patients and controls with regard to age, significant increased risk of myocardial infarction was revealed (1.8 folds and 2.2 folds in age groups less than 65 years and less than 55 years, respectively). They explained these findings as that the
association of myocardial infarction and Cag-A positive H. pylori strains is age dependent as the accuracy of serological testing declined with age (Schembri et al., 1993 & Stevens et al., 1997) which may be attributed to cross reactivity between antibodies owing to increased exposures with age. The mean age of patients and control subjects in our study was between 51 and 54 years and so this limitation was overcome.

In the present study, the mean IL6 and hs-CRP levels were comparable between anti Cag-A positive and negative patients in each group ($P > 0.05$) but were significantly higher in total anti Cag-A positive individuals versus non reactors ($P=0.01$). Therefore, elevation of IL6 and hs-CRP levels is difficult to be judged as a possible mechanism of atherosclerosis as when normal individuals (control group) were included the results were changed. These results are in agreement with those of a previous study in which Cag-A seropositivity was not linked to an increased systemic inflammatory response (Koenig et al., 1999).

We also tried to evaluate total leucocytic count (TLC), platelets count and total cholesterol level as a possible mechanism of atherogenesis in anti Cag-A positive versus negative cases. There was no difference between them apart from mean level of total cholesterol that was higher in total anti Cag-A positives versus negative cases ($P=0.008$) but not within the same group. Therefore, this difference can also be attributed to IHD pathophysiology rather than to the anti Cag-A seropositivity.

Similar to our findings, Farsak et al. (2000) found no relation between total cholesterol level and H. pylori seropositivity, while, Adiloglu et al. (2005) found that the presence of H. pylori correlated with modification of serum lipid profile in a way that may increase the risk of atherosclerosis.

Our findings regarding total leucocytes are not in concordance with the previous proposed mechanism of increased TLC by H. pylori infection (Patel et al., 1995), but this can occur during the acute phase of the infection rather than during its chronic stage.

In the present study, anti Cag-A antibodies levels showed positive correlation with IL6 level ($P=0.001$) and hs-CRP levels ($P=0.007$). Thus, the level of anti Cag-A antibodies may be more important rather than simple positivity. Mayr et al. (2003) suggested that high Cag-A antibody concentration emerged as a nearly significant risk predictor of prevalent atherosclerosis.

Failure to estimate significant difference in IL6, hs-CRP, TLC, total cholesterol and platelet counts as risk factors of atherosclerosis in anti-Cag-A positive versus negative cases is not conclusive. Cag-A negative cases may still be infected with the virulent H. pylori expressing vacuolating cytotoxin (VacA toxin) in culture (Mayr et al., 2003), which was not studied in the present work and we depend on the seropositivity to Cag-A as a surrogate of infection.

It is important to bear in mind that different possible mechanisms of atherosclerosis are to be studied and may explain the possible association of Cag-A seropositivity and IHD. At first, the VacA toxin produce vaculation of gastric epithelial cells (Covacci et al., 1993), similar mechanisms may occur in vascular endothelium. A second mode is autoimmune reaction owing to cross reactivity of anti Cag-A antibodies with vascular wall antigens (Franceschi et al., 2002). Finally, the presence of H. pylori DNA in the atheromatous plaque (Farsak et al., 2000) suggests that this microorganism may play a role in the pathogenesis of atherogenesis.

In conclusion Anti Cag-A bearing H. pylori strains are prevalent in patients with IHD more than healthy controls. The
pathophysiology needs further investigations before it can be judged.

Reference


23. Patel, P; Mendall, M A; Carrington, D; Strachan, D P; Leatham, E; Molineaux, N; Levy, J; Blakeston, C; Seymour, C A; Camm, A J; Northfield, T C. (1995). Association of Helicobacter pylori and Chlamydia pneumoniae infections with coronary heart disease and cardiovascular risk factors. BMJ. 311:711–714.