

# Significant association of *cagA* positive *Helicobacter pylori* strains with risk of premature myocardial infarction

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## Abstract

**Objective**—To investigate whether genetic diversity of *Helicobacter pylori* influences its association with coronary heart disease, and specifically whether the risk is confined to infection with the more virulent strains bearing the cytotoxin associated gene-A (*cagA*) antigen.

**Design and setting**—Case-control study in hospital admitting unselected patients with myocardial infarction.

**Methods and subjects**—Serological status for *cagA* and *H pylori* were determined in 342 cases of acute myocardial infarction and 214 population based control subjects free of clinical coronary heart disease.

**Results**—38.0% of cases and 30.8% of controls were *cagA* seropositive (odds ratio 1.38, 95% confidence interval (CI) 0.94 to 2.01,  $p = 0.08$ ). In subjects < 65 years old (153 cases, 153 controls), *cagA* seropositivity was associated with a 1.80-fold increase (95% CI 1.07 to 3.03,  $p = 0.02$ ) in myocardial infarction risk, which increased further to 2.25-fold (95% CI 1.12 to 4.53,  $p = 0.01$ ) in subjects < 55 years. There was no significant association of *cagA* status with classical coronary heart disease risk factors. *H pylori* seropositivity was present in 60.2% of cases and 53.7% of controls (odds ratio 1.12, 95% CI 0.83 to 1.51,  $p = 0.43$ ). *H pylori* seropositivity was not increased in young cases and did not show any interaction with age.

**Conclusions**—The association of chronic *H pylori* infection with risk of myocardial infarction appears to be restricted to *cagA* bearing strains. The association is age dependent and stronger in younger subjects. Genetic heterogeneity of *H pylori* may explain some of the discordant findings with regard to the association of *H pylori* with coronary heart disease.

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*Helicobacter pylori* is a microaerophilic spiral shaped Gram negative bacterium that colonises the gastric lumen of humans and other primates. Infection is commonly acquired in childhood and is usually chronic.<sup>1</sup> Raised concentrations of IgG antibodies to *H pylori* are a fairly reliable indicator of the presence of infection. The bacterium is now recognised to be of major aetiological importance in peptic ulcer disease<sup>2</sup> and in gastric cancer.<sup>3</sup> More recently, in conjunction with a variety of other chronic infections, interest in the possible association between *H pylori* infection and coronary heart disease has developed.<sup>4</sup> Mendall and colleagues were the first group to report a higher prevalence of *H pylori* seropositivity in patients with coronary heart disease compared with healthy volunteers.<sup>5</sup> However, subsequent studies have produced conflicting findings<sup>6-12</sup> and the significance of the association remains uncertain.<sup>4</sup> Confounding by the strong relation of *H pylori* infection to other coronary heart disease risk factors such as age and social class may, at least partly, explain the contradictory results. However, recent studies have shown that there is also genetic diversity within *H pylori* which affects its virulence. Specifically, strains bearing the cytotoxin associated gene-A (*cagA*) provoke a heightened inflammatory response in vivo<sup>13</sup> and show a stronger relation with peptic ulcer disease<sup>14</sup> and gastric cancer.<sup>15</sup> There is increasing evidence, from both clinical

and experimental observations, that inflammation plays an important role in coronary heart disease.<sup>16-18</sup> Thus it is possible that any impact of *H pylori* infection on coronary heart disease is crucially dependent on the type of infecting strain.

In a previous study<sup>9</sup> comparing subjects with acute myocardial infarction with population based controls, we observed no overall association between *H pylori* seropositivity and myocardial infarction risk despite adjustment for covariates. To investigate whether the type of *H pylori* strain causing the infection is of relevance, we have analysed blood samples from our cohorts for anti-*cagA* antibodies as an indicator of infection with more virulent *H pylori* strains. We report a significant and age dependent association of infection with *cagA* positive *H pylori* strains and risk of myocardial infarction. Our findings suggest that genetic heterogeneity of *H pylori* may explain some of the discordant findings with regard to the association of *H pylori* with coronary heart disease.

## Methods

### SUBJECTS

The recruitment of patients and controls has been previously described.<sup>9</sup> Briefly, patients who satisfied the World Health Organisation criteria for myocardial infarction<sup>19</sup> were recruited from admissions to the coronary care

Table 1 Characteristics of cases and controls

	Cases (n=342)	Controls (n=214)
Age (years)*	65.1 (11.7)	54.8 (12.6)
Male	66.9%	58.8%
White	88.0%	92.9%
History of hypertension*	33.1%	16.8%
Diabetes*	12.1%	3.7%
Current smoker*	32.5%	18.2%
Angina	28.3	–
Previous myocardial infarct	19.3%	–
Positive family history*	38.2%	25.1%
BMI (kg/m <sup>2</sup> )	25.7 (4.2)	25.4 (3.7)
Total cholesterol (mmol/l)	5.6 (1.2)	5.6 (1.0)
HDL cholesterol (mmol/l)	1.2 (0.3)	1.2 (0.3)

Values are mean (SD) or per cent of group.

\*p < 0.001, cases v controls.

BMI, body mass index; HDL, high density lipoprotein.

unit (CCU) at Leicester Royal Infirmary. The CCU, serving a population of around 300 000, accounts for more than 65% of admissions of cases with myocardial infarction in Leicester. The period of recruitment was between July 1993 and April 1994, and more than 97% of eligible subjects were recruited. Control subjects were recruited randomly from adult visitors to patients with non-cardiovascular illnesses on general medical and surgical wards at the Leicester Royal Infirmary, to provide subjects likely to be representative of the source population from which the cases came. Those reporting a history of myocardial infarction or angina were excluded from the analysis.

Cases and controls filled in a standard questionnaire about their personal histories, had height and weights measured, and provided blood samples for laboratory analysis. The study was approved by the local research ethics committee.

#### BIOCHEMICAL MEASUREMENTS

Serum total and high density lipoprotein (HDL) cholesterol were measured using a Kodak Ektachem E700 CXR automatic analyser in a quality controlled hospital biochemistry laboratory. For cases, the first blood sample taken after admission was used for the analysis.

#### DETERMINATION OF *H pylori* AND *cagA* SEROLOGICAL STATUS

*H pylori* status was determined serologically, as described previously,<sup>9</sup> using an established IgG enzyme linked immunosorbent assay (ELISA) based on an ultracentrifuged sonicate antigen. IgG antibodies to the *cagA* protein were quantified on whole blood samples using a commercial ELISA kit (*Helicobacter p120* (CAGA) ELISA, Viva Diagnostics, Hurth, Germany). The ELISA was validated by concurrent western blot

analysis of 207 of the samples, randomly chosen, to confirm the presence or absence of anti-*cagA* antibodies using a reference strain (NCTC 11637, National Collection of Type Cultures, London, UK) as antigen. Optimal sensitivity and specificity values were calculated for the assay from these data. Using an ELISA unit value of 5.2, 17 of 207 ELISA samples were false positive (that is, they had a unit value  $\geq 5.2$ , but no detectable anti-*cagA* antibody on immunoblot) and 16 of 207 ELISA samples were false negative (that is, a unit value of  $< 5.2$ , but detectable anti-*cagA* antibody on immunoblot). Therefore, optimal sensitivity and specificity values were 86.7% and 85%, respectively, for use of the ELISA on this study population.

#### STATISTICAL ANALYSIS

Distribution of *cagA* seropositivity and qualitative risk factors between cases and controls or qualitative risk factors between *cagA* positive and *cagA* negative cases or controls were compared using the  $\chi^2$  test. Quantitative sample means were compared by analysis of variance. Logistic regression was used to analyse the effects of *cagA* seropositivity on myocardial infarction status and its interaction with linear age effect adjusted for sex. Adjustment was then made for other covariates by including them in the regression. The effects of these adjustments were tested by comparing the odds ratios associated with *cagA* and the corresponding age interaction term, when estimated with and without adjustment.<sup>20</sup> In these analyses, age was adjusted for by pooling estimates made at different ages to obtain Mantel-Haenszel estimates and separately, by including a linear age term but no interaction, in a logistic regression. The changes in the odds ratio associated with *cagA* seropositivity adjusted for age were then plotted against the appropriate age cut off.

#### Results

In all, 556 subjects (342 cases, 214 controls) were analysed. Table 1 summarises their characteristics. Cases were significantly older than controls, and classical risk factors (hypertension, diabetes, smoking, and positive family history) were more prevalent in cases. Body mass index and total and HDL cholesterol concentrations were similar.

Three hundred and twenty one subjects were *H pylori* seropositive (206 of 342 cases (60.2%) and 115 of 214 controls (53.7%), odds ratio (OR) 1.12, 95% confidence interval (CI) 0.83 to 1.51, p = 0.43); 196 subjects were *cagA* seropositive. The distribution of *cagA* seropositivity in cases and controls is shown in table 2.

In the whole cohorts, 38.0% of cases and 30.8% of controls were *cagA* seropositive (odds ratio 1.38, 95% CI 0.94 to 2.01, p = 0.08). Because of the significant difference in age distribution of cases and controls we examined the potential impact of this on the association of *cagA* seropositivity with risk of myocardial infarction. In subjects under 65 years of age (n = 153 cases, 153 controls) there was 1.80-fold (p = 0.02) increase in myocardial infarction risk associated with *cagA* seropositivity

Table 2 Distribution of *cagA* seropositivity in cases and controls

	Whole cohorts		< 65 Years		< 55 Years	
	<i>cagA</i> <sup>+</sup>	<i>cagA</i> <sup>-</sup>	<i>cagA</i> <sup>+</sup>	<i>cagA</i> <sup>-</sup>	<i>cagA</i> <sup>+</sup>	<i>cagA</i> <sup>-</sup>
Cases	130	212	57	96	27	39
Controls	66	148	38	115	28	91
Unadjusted	OR 1.38 (0.94 to 2.01) p = 0.08		OR 1.80 (1.07 to 3.03) p = 0.02		OR 2.25 (1.12 to 4.53) p = 0.01	
Adjusted*	OR 1.20 (0.81 to 1.79) p = 0.35		OR 1.78 (1.04 to 3.03) p = 0.03		OR 2.20 (1.09 to 4.41) p = 0.03	

\*Adjusted for age and sex.

*cagA*<sup>+</sup>/*cagA*<sup>-</sup>, *cagA* seropositive/seronegative; OR, odds ratios with 95% confidence intervals.

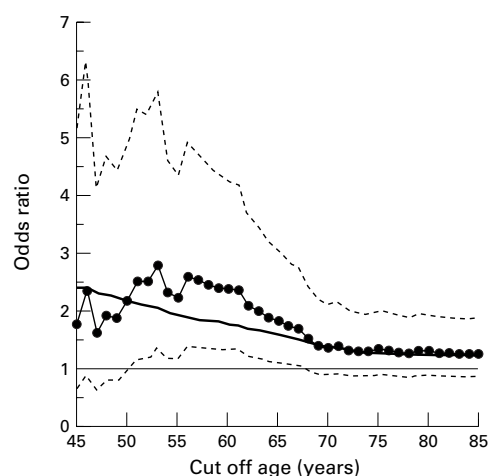


Figure 1 Age dependency of the association of *cagA* positive strains of *H pylori* with risk of myocardial infarction. The odds ratio estimates for risk of myocardial infarction associated with *cagA* seropositivity for different age cut off values from the Mantel-Haenszel analysis adjusted for age and sex are shown in the line with the closed circles (with 95% confidence intervals in dotted lines). The corresponding estimates from the logistic regression are shown by the solid line.

(prevalence: cases 37.2%, controls 24.8%), which increased further to 2.25-fold ( $p = 0.01$ ) in subjects less than 55 years old (prevalence: cases 40.9%, controls 23.8%) (table 2). The association remained significant in the younger age groups when adjusted for age and sex (table 2). In the Mantel-Haenszel analysis, the age and sex adjusted odds ratio remained significant to an age of about 65 years (fig 1). A logistic regression analysis showed a significant interaction ( $p = 0.03$ ) between age and the effect of *cagA* seropositivity on risk of myocardial infarction. The odds ratio associated with *cagA* seropositivity declined on average by 30% (95% CI, 3–49%) per decade (fig 1, solid line). Analysis for *H pylori* seropositivity showed no similar increased risk in younger subjects<sup>9</sup> or interaction with age (data not shown).

The distribution of risk factors in cases stratified by *cagA* status is shown in table 3. There was no significant association of *cagA* status with any of the risk factors, and adjustment of the logistic regression for the covariates had no significant impact on either the overall association ( $p = 0.85$ ) or the interaction with age ( $p = 0.81$ ). There was no significant association of any risk factors with *cagA* status in controls either (data not shown).

Table 3 Distribution of risk factors in cases according to *cagA* status

	<i>cagA</i> <sup>+</sup>	<i>cagA</i> <sup>-</sup>	<i>p</i> Value
Age (years)	64.8 (11.9)	65.2 (11.7)	0.77
Male	65.4%	67.9%	0.63
White	85.4%	89.6%	0.24
History of hypertension	37.2%	30.7%	0.23
Diabetes	10.7%	12.9%	0.54
Current smoker	30.9%	33.5%	0.56
Angina	28.8%	28.0%	0.85
Previous myocardial infarct	19.7%	19.0%	0.89
Positive family history	37.5%	38.6%	0.88
BMI (kg/m <sup>2</sup> )	25.8 (4.0)	25.6 (4.3)	0.71
Total cholesterol (mmol/l)	5.7 (1.3)	5.6 (1.2)	0.43
HDL cholesterol (mmol/l)	1.25 (0.35)	1.20 (0.34)	0.34

Data are mean (SD) or per cent of group.

BMI, body mass index; *cagA*<sup>+</sup>/*cagA*<sup>-</sup>, *cagA* seropositive/seronegative; HDL, high density lipoprotein.

## Discussion

Our finding in this study of a specific association between *cagA* positive strains of *H pylori* and the risk of premature myocardial infarction adds to the current debate about the possible role of chronic bacterial infections in the pathogenesis of coronary heart disease.<sup>4 18</sup> Studies to date on the role *H pylori* have produced very conflicting results.<sup>5–12</sup> Study size, study design, and the failure to control for potential confounding factors such as socio-economic class have all been proposed as explanations for the contradictory findings.<sup>4 18</sup> In this study we provide evidence that any effect of *H pylori* infection on coronary heart disease risk may also be related to the type of infecting strain. Such risk appeared independent of classical risk factors for coronary heart disease.

The specific association of *cagA* positive *H pylori* strains with myocardial infarction risk is biologically plausible. The *cagA* gene and the associated vacuolating cytotoxin (VacA) define type I *H pylori* strains which produce a more pronounced gastric inflammatory response, including the induction of interleukin 6 and 8 and tumour necrosis factor  $\alpha$ , compared with type II (*cagA* negative) strains,<sup>13 21</sup> and are more strongly associated with peptic ulcer disease<sup>14</sup> and gastric tumours.<sup>15</sup> Recent studies have shown that this enhanced response in type I strains reflects the presence of a 40 kb DNA insertion flanking *cagA* (the *cag* region), which has the typical features of a pathogenicity island (PAI) encoding for several virulent factors which promote the inflammatory response.<sup>22</sup> Increasing evidence suggests that inflammation (both systemically as well as locally) plays an important role in the development of coronary heart disease and particularly the progression to acute coronary syndromes.<sup>16–18</sup> Systemic markers of inflammation such as C reactive protein and acute phase reactants such as fibrinogen and serum amyloid A have been shown to be associated prospectively with myocardial infarction risk,<sup>23–28</sup> and part of the beneficial effects of aspirin on coronary risk may be related to its anti-inflammatory rather than its antiplatelet effect.<sup>28</sup> Thus it is possible that *cagA* positive *H pylori* strains increase the risk of myocardial infarction through the promotion of an enhanced inflammatory response. Indeed, *H pylori* seropositivity has been associated with raised concentrations of fibrinogen and C reactive protein,<sup>29 30</sup> although, as in the case of the association with coronary heart disease, results have been mixed; a recent meta-analysis<sup>31</sup> suggested that the correlations reflected chance or publication bias. However, studies in such populations have not taken into account the genetic heterogeneity of *H pylori*.

The association of *cagA* positive *H pylori* strains with coronary heart disease has also been examined by Pasceri and colleagues.<sup>32</sup> In 88 patients with ischaemic heart disease (mean (SD) age 57 (8) years, 74 men) and in 88 matched controls, they observed a 3.8-fold adjusted increase in risk of ischaemic heart disease in *cagA* positive subjects (prevalence of

cagA seropositivity: cases 43%, controls 17%). Interestingly, they also observed an increase in overall prevalence of *H pylori* seropositivity in cases (62% *v* 40%). Prevalence of cagA negative strains was similar in patients and controls (19% *v* 23%). Pasceri and colleagues studied patients with a range of coronary syndromes including severe unstable angina, acute myocardial infarction, and chronic stable angina, while our larger study was focused on acute myocardial infarction only. Although the prevalence of infection by cagA positive strains was similar in Pasceri's three patient groups, further studies are needed to define the precise relation of infection with cagA bearing strains with different coronary syndromes, especially as a recent study by Koenig and colleagues found no association in 312 patients with stable coronary heart disease compared with 479 control subjects.<sup>33</sup> However, our findings emphasise the point that the ability to detect any overall association of *H pylori* seropositivity with coronary heart disease may depend not only on the population prevalence of *H pylori* infection but also on the relative proportion infected with cagA positive strains. Studies have shown there is wide variation (28–82%) in cagA seroprevalence in different countries.<sup>34</sup>

The finding that the association of risk of myocardial infarction with cagA positive *H pylori* strains was age dependent is not entirely unexpected as the associations of most vascular risk factors with coronary heart disease tend to be stronger in younger than in older individuals. Although this is the most likely explanation, it needs also to be noted that several studies have shown that the accuracy of serological testing for *H pylori*, and in particular the specificity, declines with age.<sup>35–36</sup> The reasons for this are unclear but cross reactivity between antibodies owing to increased antigenic exposure with age may be a factor. However, although this could explain why an association was not observed in older subjects in our study, it is important to emphasise that it does not affect the significance of the association seen in subjects under 65 years.

#### LIMITATIONS

Our study has several limitations common to cross sectional studies. In particular we cannot exclude the possibility that unrecognised population stratification for relevant factors influenced the findings. Specifically, socioeconomic status is known to affect both the prevalence of *H pylori* infection and the risk of coronary heart disease.<sup>4–18</sup> Although our controls were recruited from hospital visitors, specifically to provide healthy subjects likely to be representative of the source population from which the cases came, details of socioeconomic status were not obtained, and we were not able to adjust for this. However, the specific association with cagA seropositivity in the absence of an overall increase in *H pylori* prevalence in cases argues against this being the explanation for the finding. Another limitation is that, although the effect of infection with cagA strains appeared independent of classical coronary heart disease risk factors, the study does

not provide direct mechanistic information. Therefore, the association of cagA positive strains of *H pylori* on risk of coronary heart disease needs to be confirmed in further—ideally prospective—studies, and whether the effect is mediated through an enhanced inflammatory response needs to be determined. Such studies are worthwhile not only because they may provide important insights on the pathophysiological basis of coronary syndromes, but also because of the considerable potential, if the association is proven, of new forms of therapeutic and preventative treatments directed towards infection eradication.

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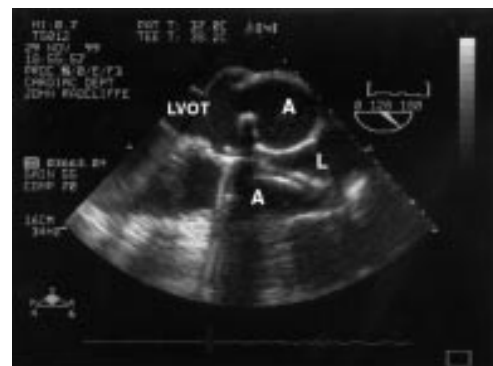
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## IMAGES IN CARDIOLOGY

### Mycotic aneurysm formation with dehiscence of a valved aortic conduit resulting in dynamic aortic obstruction

A 67 year old man presented with acute breathlessness, sharp chest pain radiating to the back on swallowing, and a two month history of “flu like” symptoms. One year previously he had undergone elective implantation of a 25 mm Carboseal valved aortic conduit for severe aortic regurgitation caused by annulo-aortic ectasia. Blood pressure was 85/60 mm Hg, temperature was 38°C, and there was a harsh ejection systolic murmur and a quiet aortic diastolic murmur. Transthoracic echocardiography revealed an 8 cm mycotic false aneurysm around the aortic conduit and cranial systolic displacement of the valve by up to 1 cm. Transoesophageal echocardiography confirmed proximal dehiscence of the valved conduit with vegetations but no valvar regurgitation and a large mycotic abscess. During systole, false aneurysm pressure exceeded aortic pressure, leading to collapse of the aortic conduit and generation of a dynamic pressure gradient of 100 mm Hg (top) (LVOT, left ventricular outflow tract; A, false aneurysm; L, conduit lumen). In diastole, falling pressure in the false aneurysm restored the normal lumen of the conduit (bottom). There was a small amount of retrograde diastolic flow into the aneurysm at the distal suture line in the mid ascending aorta.

At emergency surgery, the valved prosthesis was almost completely dehissed from the annulus, with extensive vegetations. The outer wall of the false aneurysm was formed from fibrous tissue and laminated thrombus, and there was a small defect in the distal aortic suture line. An aortic homograft was inserted



successfully. Multiple blood cultures grew *Propionibacterium* species sensitive to penicillin, and the patient was discharged after six weeks of antibiotic treatment.

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