Association of *Helicobacter pylori* with Coronary Artery Disease and Myocardial Infarction Assessed by Myocardial Perfusion Imaging

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ABSTRACT: **Background:** The relationship between *Helicobacter pylori* infection and coronary artery disease (CAD) has as yet not been fully examined. The myocardial perfusion imaging (MPI) stress test has proven its efficacy as an integral part of diagnosing CAD.

Objectives: To investigate the association between CAD and *H. pylori* infection using MPI.

Methods: This prospective study evaluated CAD positivity among consecutive patients referred to a tertiary medical center for a stress/rest MPI. All patients were tested for serum anti-*H. pylori* and CagA protein immunoglobulin G antibodies. The CAD positivity group included patients with ischemia and/or myocardial infarction (MA) on a stress MPI, coronary artery bypass graft surgery (CABG), or percutaneous coronary interventions (PCI). CAD-negative subjects were defined as participants with a normal MPI, no pathological Q waves in resting ECG tracing, and no history of CAD. Both groups were compared for *H. pylori* and CagA seropositivity. Patients' demographic data, risk factors for CAD, and childhood socioeconomic status were recorded.

Results: The study group consisted of 300 consecutive patients, 170 men and 130 women; 64% (110/173) CAD-positive patients and 47% (60/127) CAD-negative participants were found seropositive for *H. pylori* infection ($P = 0.005$). In the adjusted analysis, *H. pylori* infection was found to be associated with CAD positivity (odds ratio 1.83, 95% confidence interval 1.06–3.17, $P = 0.031$), and MI (fixed perfusion defects on MPI) (OR 3.36, 95%CI 1.44–7.84, $P = 0.005$). No association was noted with CagA positivity.

Conclusions: In patients undergoing a stress MPI, serum anti-*H. pylori* antibodies positivity was found to be associated with CAD, independent of traditional cardiovascular risk factors.

IMAJ 2014; 16: 341–346

KEY WORDS: *Helicobacter pylori*, CagA, coronary artery disease (CAD), myocardial perfusion scan, myocardial infarction (MI)

Chronic inflammation plays a pivotal role in the initiation, progression and complications of coronary atherosclerosis together with major risk factors for coronary artery disease [1]. A number of seroepidemiologic studies have suggested an association between coronary atherosclerosis and chronic infections [2]. *Helicobacter pylori* infection is the most common chronic bacterial infection worldwide [3]. The infection colonizes gastric mucosa and can elicit life-long inflammatory and immune responses concurrently with the release of various bacterial and host-dependent cytotoxic substances [4]. Several studies have found an association of *H. pylori* infection with the development of CAD [4-6]; others dispute this finding [7,8]. Today, this issue is still controversial. Another disagreement among researchers is whether an infection with virulent cytotoxic strains of *H. pylori* bearing the cytotoxin-associated gene A (CagA-positive strains) is associated with CAD [9,10].

A myocardial perfusion imaging stress test is widely regarded as a clinically useful non-invasive imaging modality for diagnosing patients with suspected CAD [11]. Although coronary angiography is a valuable diagnostic test for detecting coronary artery stenosis, it does not provide perfusion or contractility data when the heart is physiologically stressed. Non-invasive stress MPI can detect myocardial ischemia, as reflected by reversible perfusion defects, important components in diagnosing atherosclerotic obstructive CAD [11], and a strong predictor of adverse outcomes such as future myocardial infarctions. MI on an MPI study is diagnosed as a non-reversible fixed defect with no significant changes in activity between post-stress and rest images [12]. MPI is an established method for non-invasively assessing the functional significance of coronary stenosis and can reveal valuable information of risk stratification. Patients with stable angina and normal MPI results have a low mortality risk and, therefore, no intervention is required [13].

CAD = coronary artery disease
MPI = myocardial perfusion imaging
MI = myocardial infarction

We conducted a prospective study of consecutive patients referred for a stress MPI to assess the association between *H. pylori* seropositivity CagA status and CAD and to evaluate the coronary distribution of fixed or reversible perfusion defects on a stress MPI.

PATIENTS AND METHODS

This prospective study was approved by the Rabin Medical Center Institutional Review Board. All participants were assigned a study number and data were transferred to forms to insure confidentiality. Between 1 November 2005 and 28 February 2006 all consecutive patients aged 18 years or older who presented for a stress MPI were asked to participate in the study. Indications for MPI were angina symptoms, chest pain, suspected CAD, cardiac related symptoms or risk stratifications in patients with known CAD. Those who agreed to participate gave informed consent and were subsequently included in the study. Serology for *H. pylori* status was obtained at the time of the MPI. Demographic, clinical and procedural data and risk factors for atherosclerosis were collected prospectively following a review of the clinical record. Height and weight were measured by an experienced nurse. Patients were excluded if they had been treated for an *H. pylori* infection.

Body mass index was calculated as weight in kilograms divided by the square of the height in meters. We assessed the association between *H. pylori* seropositivity status and presence of CAD. CAD positivity was defined if one or more of the following was present: reversible and/or fixed perfusion defects on a stress MPI, coronary artery bypass graft surgery, or percutaneous coronary interventions. CAD-negative subjects were defined as participants with a normal MPI, no pathological Q waves in resting electrocardiograph tracing, and no history of CAD. The association between anti-CagA seropositivity status and CAD positivity was evaluated.

In a secondary analysis, we examined the association between *H. pylori* seropositivity status and distribution of reversible or fixed perfusion defects (interpreted as MI) in CAD-positive patients.

CONFOUNDERS

The following risk factors for atherosclerosis were recorded: age, gender, diabetes mellitus, hypertension, hypercholesterolemia, family history of coronary heart disease, BMI, and history of smoking. Childhood socioeconomic status parameters included father's income classified as below average versus average or above average, and crowding index defined as the number of persons per room during childhood.

Diabetes was defined as a history of hyperglycemia requiring previous or current pharmacological therapy. Hypertension was defined as an elevation in systolic or diastolic blood pressure (> 140/90 mmHg) or the need for ongoing antihypertensive medication. Hypercholesterolemia was defined as a total cholesterol level of > 200 mg/dl. Family history was positive if a first-degree relative had experienced a coronary event prior to age 55 for men and 65 for women. Ever-smoked was defined as a self-report of 10 or more packs/years of cigarette use at some point in the patient's life.

STRESS MPI PROTOCOL

Prior to testing, patients were asked to discontinue antiischemic drugs for at least 24 hours and beta-blockers for 48 hours. All tests were conducted under fasting conditions. After insertion of an intravenous line, each patient underwent stress testing by either exercising on a treadmill (the Bruce protocol) or following the dipyridamole protocol. Heart rate, blood pressure, and ECG tracings were recorded before and at each stage of exercise, when symptoms peaked or at a maximal predicted heart rate.

The Bruce protocol is used to monitor cardiac function in exercising patients. The patient is injected with thallium-201 (3–4 mCi) when exercise peaks while continuing exercising for 30–60 seconds. The dipyridamole protocol involves injecting thallium 4 minutes after termination of a dipyridamole infusion. In our study, SPECT (single-photon emission computed tomography) imaging was performed 10 minutes after the thallium injection and again 3–4 hours later, at rest.

Additional thallium reinjection imaging was performed in patients with fixed defects. SPECT acquisition was performed with a large-field digital gamma camera (SP4-HR, Elscint Ltd., Haifa, Israel) at a 180° angle, starting at the 45° right anterior oblique angle and positioning at 6° intervals for 30 seconds per image. Redistribution images were repeated 3–4 hours after stress using the same parameters. The acquisition and processing protocols have been previously described [14].

MPI SPECT PROCESSING

After reconstruction of the images, two-dimensional polar plot maps were generated to assess the extent of perfusion abnormality in each of the three coronary arteries. The total extent of myocardial ischemia was expressed as a percentage of global perfusion of the left ventricle.

Perfusion defects were visually and semi-quantitatively analyzed. Defects were classified as a 'fixed defect' (a defect present in both resting and on stress MPI images), and a 'reversible defect' (a defect present only on the resting MPI image). Filling defects were diagnosed as ischemia when two contiguous slices showed reversibility or when bull's-eye mapping showed an increase in the intensity of perfusion defects of more than 10% in the redistribution phase. Perfusion defects in the anterior wall

BMI = body mass index

SPECT = single-photon emission computed tomography

and septal region were allocated to the left anterior descending coronary artery, defects in the lateral wall to the left circumflex coronary artery, and inferior defects to the right coronary artery. Two nuclear cardiologists, blinded to the patient's *H. pylori* CagA status, reached a consensus on all MPI readings.

SEROLOGY FOR ANTI-*H. PYLORI* AND CagA ANTIBODIES

Specimens of venous blood were obtained on the same day as the stress MPI. Samples were stored at -20°C until assayed. Immunoglobulin G antibodies against *H. pylori* infection were tested by the enzyme-linked immunosorbent assay (Orion Diagnostica, Finland). A pilot study of patients who had undergone an endoscopy at our hospital was validated and showed a sensitivity of 94%, specificity of 90%, and positive and negative predictive values of 100% and 90%, respectively. IgG antibodies against CagA protein were tested using an ELISA kit (Genesis Diagnostics Ltd, UK) according to the manufacturer's instructions.

HIGHLY SENSITIVE C-REACTIVE PROTEIN TEST

The stored serums were tested for highly sensitive C-reactive protein test on a Roche Integra 400 analyzer, using a latex particle enhanced immunoturbidimetric kit [15]. The analytical sensitivity (lower detection limit) of the kit was 0.0085 mg/dl (reference range 0–0.5 mg/dl). Within-day precision coefficient of variation was 4.8% at a level of 0.12 mg/dl; between-day CV was 3.0% at a level of 0.4 mg/dl.

STATISTICAL ANALYSIS

Continuous variables were tested for normal distribution using the Kolmogorov-Smirnov test. Normally distributed continuous variables were expressed as mean and standard deviation and non-normally distributed variables as median and interquartile range. Categorical variables were summarized as frequencies and proportions. Continuous variables were compared using the Student *t*-test or ANOVA (comparisons between groups were done using post-hoc analysis, Scheffé's method) for normally distributed variables and the Mann-Whitney test or Kruskal-Wallis test for non-normally distributed variables. Differences in proportions among categorical data were assessed using the chi-square or Fisher exact test.

The independent association between *H. pylori* and CAD was assessed by multivariate analysis. Variables with a *P* value of < 0.3 on univariate analysis were included in the multivariate analysis. Logistic regression was used for this purpose. Odds ratios with a 95% confidence interval were reported. The association between *H. pylori* and the distribution of reversible or fixed coronary perfusion defects in CAD-positive patients was assessed by multivariate analysis. Statistical analysis was performed using the SPSS version 19. *P* value < 0.05 was considered statistically significant.

IgG = immunoglobulin G
ELISA = enzyme-linked immunosorbent assay
CV = coefficient of variation

Table 1. Comparison of *H. pylori* seropositivity and risk factors for CAD between CAD-negative group and CAD positive groups

	CAD-negative (n=127)		CAD-positive (n=173)		*P*
Helicobacter pylori	60	(47.2%)	110	(63.5%)	0.005
Male	46	(36.2%)	124	(71.6%)	< 0.001
Diabetes	34	(26.7%)	58	(33.5%)	0.210
Hypertension	70	(55.1%)	114	(65.8%)	0.058
Hypercholesterolemia	67	(52.7%)	141	(81.5%)	< 0.001
Family history	28	(22.0%)	57	(32.9%)	0.038
Smoker	11	(8.6%)	16	(9.2%)	0.861
Age (yr), mean (SD)	65.4	(11.9)	68.5	(10.1)	0.021
BMI, mean (SD)	27.3	(5.0)	27.1	(3.9)	0.604
HsCRP, median (IRQ)	0.3	(0.1–0.6)	0.3	(0.2–0.6)	0.941
Crowding index, median (IQR)	2.0	(1.3–3.3)	2.0	(1.3–3.0)	0.882

CAD = coronary artery disease, HsCRP = highly sensitive C-reactive protein, IRQ = interquartile range, BMI = body mass index

RESULTS

Of the 300 patients who had undergone a stress MPI, 170 (57%) were men and 130 (43%) women; mean age was 67.2 ± 11 years; 127 patients (42%) were CAD-negative and 173 (58%) were CAD-positive. Table 1 demonstrates stratification of the patient population by absence or presence of CAD. CAD-positive patients were older and included more men than the CAD-negative subjects ($P = 0.021$, $P < 0.001$, accordingly) with a significantly higher prevalence of hypercholesterolemia and family history of CAD ($P < 0.001$, $P = 0.038$, accordingly).

H. pylori infection was significantly higher in CAD-positive patients than in CAD-negative subjects (odds ratio 1.95, 95% confidence interval 1.2–23.11, $P = 0.005$). Diabetes mellitus, hypertension, smoking history, crowding index, HsCRP level and BMI showed no significant difference between CAD-positive and negative participants. In crude analyses, CagA seropositivity in the CAD-positive group was not statistically different from the CAD-negative group (40% vs. 48.3%, $P = 0.294$); patients with fixed defects were associated with positive *H. pylori* status (OR 2.93, 95%CI 1.50–5.75, $P = 0.002$), and CAD-positive patients with no fixed defects tended to be associated with positive *H. pylori* status (OR 1.62, 95%CI 0.97–2.69, $P = 0.065$). CagA seropositivity was not statistically different between CAD-FD (38.2%), CAD-NFD patients (42.9%) and

HsCRP = highly sensitive C-reactive protein
OR = odds ratio
CAD-FD = CAD-positive patients with fixed defects
CAD-NFD = CAD-positive patients with no fixed defects

Table 2. Comparison of *H. pylori* seropositivity and risk factors for CAD between CAD-negative subjects and CAD-positive patients with no fixed defects and patients with fixed defects

	CAD-negative (n=127)		CAD-positive without MI (CAD-NFD) (n=115)		CAD-positive with MI (CAD-FD) (n=58)		*P*
Helicobacter pylori	60	(47.2%)	68	(59.1%)	42	(72.4%)	0.005
Male	46	(36.2%)	78	(67.8%)	46	(79.3%)	< 0.001
Diabetes	34	(26.7%)	35	(30.4%)	23	(39.6%)	0.211
Hypertension	70	(55.1%)	80	(69.5%)	34	(58.6%)	0.063
Hypercholesterolemia	67	(52.7%)	87	(75.6%)	54	(93.1%)	< 0.001
Family history	28	(22.0%)	38	(33.0%)	19	(32.7%)	0.117
Smoker	11	(8.6%)	8	(6.9%)	8	(13.7%)	0.328
Age (yr), mean (SD)	65.4	(11.9)	68.7	(10.0)	68.0	(10.7)	0.057
BMI, mean (SD)	27.3	(5.0)	27.3	(3.9)	26.7	(3.9)	0.597
HsCRP, median (IRQ)	0.3	(0.1–0.6)	0.3	(0.2–0.6)	0.2	(0.1–0.4)	0.445
Crowding index, median (IQR)	2.0	(1.3–3.3)	2.0	(1.3–3.0)	2.0	(1.3–3.6)	0.467

CAD = coronary artery disease, CAD-NFD = CAD-positive patients with no fixed defects, CAD-FD = CAD-positive patients with fixed defects, HsCRP = highly sensitive C-reactive protein, IRQ = interquartile range

CAD-negative subjects (48.3%, $P = 0.515$). The prevalence of men and hypercholesterolemia was significantly higher in CAD-FD and CAD-NFD patients than in controls ($P < 0.001$, $P < 0.001$, respectively) [Table 2].

In the multivariate analysis, controlled for gender, age, diabetes, hypertension, hypercholesterolemia, and family history of CAD [Table 3], *H. pylori* seropositivity was independently associated with fixed defects versus non-CAD [Table 3]. The odds ratio for fixed defects (MI) was higher (3.36, 95%CI 1.44–7.84) than for CAD-positive patients without fixed defects (1.55, 95%CI 0.86–2.77), and CAD-positivity (1.83, 95%CI 1.06–20.2) versus CAD-negative subjects. Both men and hypercholesterolemia were independently associated with CAD-positivity, CAD without fixed defects and CAD with fixed defects [Table 3].

Table 4. Multivariate analysis of risk factors for fixed perfusion defects (MI) in the right coronary artery territory

	Fixed defects in the territory of RCA vs. fixed defects in territories of other coronary arteries (n=58)		
	OR	(95%CI)	*P*
H. pylori	21.64	(2.08–224.86)	0.010
Male	3.68	(0.57–.61)	0.169
Age (yr)	0.99	(0.93–1.06)	0.769
Diabetes	2.34	(0.56–9.83)	0.245
Hypertension	1.79	(0.44–7.36)	0.417
Hyperlipidemia	0.25	(0.01–5.39)	0.374
Family history	1.74	(0.37–8.13)	0.482

RCA = right coronary artery

Fixed defects in the distribution of RCA (19/20) vs. fixed defects in the distribution of other coronary arteries in 58 patients (with MI) were significantly associated with positive *H. pylori* status on both crude (OR 12.39, 95%CI 1.50–102.56, $P = 0.020$) and multivariate analysis (OR 21.64, 95%CI 2.08–224.86, $P = 0.010$). Fixed defects in the distribution of other coronary arteries were not associated with positive *H. pylori* status [Table 4]. The presence of reversible defects (ischemia) in the distribution of coronary arteries on stress MPI was not associated with positive *H. pylori* status on crude analysis.

DISCUSSION

Our findings revealed a significantly higher rate of *H. pylori* seropositivity in CAD-positive patients compared to the CAD-negative patients. To the best of our knowledge, this is the first study designed to assess the association between *H. pylori* infection and CAD in a prospective study of patients who had undergone a stress MPI. MPI is an established method for non-

RCA = right coronary artery

Table 3. Odds ratio and 95% confidence interval for coronary artery disease and CAD with and with no fixed defects from a multivariable logistic regression

	CAD-positive*			CAD-NFD*			CAD-FD*		
	OR	(95%CI)	*P*	OR	(95%CI)	*P*	OR	(95%CI)	*P*
Helicobacter pylori	1.83	(1.06 – 3.17)	0.031	1.55	(0.86–2.77)	0.143	3.36	(1.44–7.84)	0.005
Male	6.84	(3.79–12.36)	< 0.001	5.52	(2.97–10.27)	< 0.001	10.62	(4.27–26.40)	< 0.001
Age (yr)	1.06	(1.03–1.09)	< 0.001	1.05	(1.02–1.08)	0.001	1.04	(1.00–1.09)	0.064
Diabetes	1.17	(0.65–2.11)	0.607	0.93	(0.49–1.80)	0.839	1.61	(0.70–3.67)	0.262
Hypertension	1.22	(0.69–2.14)	0.501	1.56	(0.84–2.89)	0.156	0.61	(0.26–1.41)	0.248
Hyperlipidemia	3.36	(1.83–6.17)	< 0.001	2.46	(1.30–4.66)	0.006	9.85	(2.93–33.06)	< 0.001
Family history	1.90	(1.00–3.61)	0.051	2.06	(1.04–4.07)	0.038	1.67	(0.67–4.20)	0.275

*vs. normal perfusion scan

invasively assessing the functional significance of coronary stenosis by minimizing any misclassification of CAD patients. The test determines the presence or absence of effort-induced ischemia (reversible defects) or MI (fixed defects), or both, in the two groups, thus providing additional and important diagnostic criteria for detecting patients with silent and undiagnosed CAD. Detection of ischemia and/or MI on a stress MPI indicated the presence of CAD even in the absence of other findings.

Aiming to minimize misclassification of the presence or absence of CAD, we selected a CAD-negative group without known CAD or any ischemic findings or MI on a stress MPI. In order to adjust for confounders, we included major and well-established risk factors.

Our results indicated that *H. pylori* seropositivity is independently associated with CAD (OR 1.83, 95%CI 1.06–3.17) and MI (OR 3.36, 95%CI 1.44–7.84). No significant difference was found in anti-CagA seropositivity among the CAD-positive and CAD-negative groups. Our findings support a recent study by Jafarzadeh et al. [16] who reported significantly higher anti-*H. pylori* antibodies in the serum of 120 patients with ischemic heart disease compared to non-CAD controls. The seroprevalence and mean titer of anti-CagA IgG did not significantly differ between patient and control groups. A similar observation was reported by Pellicano and co-authors [17] who studied 223 consecutive patients with confirmed acute MI and compared them with matched controls. Anti-CagA antibodies were detected in 33.8% of infected patients with acute MI versus 26.8% in the control subjects ($P = 0.17$, OR 1.40, 95% CI 0.84–2.33), indicating no relationship between *H. pylori* infection with CagA-positive strains and ischemic heart disease.

In the present study, the association of *H. pylori* infection with MI was strongest with MI defined on the basis of fixed perfusion defects on MPI. The odds ratio for MI seropositivity was 2.93 (95%CI 1.50–5.75) and was largely unchanged after adjustment (OR 3.36, 95%CI 1.44–7.84), suggesting that exact adjustment for the truly relevant factors would have little effect. In addition, all CAD-negative subjects in this study had normal perfusion on the stress MPI without evidence of MI or ischemia.

Some studies included only patients with MI [5]. The results might partly reflect the relationship between *H. pylori* infection and CAD if the patients who presented with angina, but without MI, were not included. In the current study, however, we separately analyzed CAD-positive patients without MI and patients with MI and found that the association of *H. pylori* infection with MI was statistically significant while the association in CAD-positive patients without MI tended to be significant.

Infection was proposed as a cause of atherosclerosis at the beginning of this century [18]. The modern "response-to-injury" model of atherosclerosis suggests that infection could contribute to the formation of atherosclerosis via damage to vessel endothelium [19]. In addition, it has been suggested that autoimmune reactions against endogenous heat shock protein 60, an endothelial antigen, could trigger atherogenesis [20]. *H. pylori* contains HSP60-like subunits, and the possibility of an association between *H. pylori* infection and an immune response to HSP60 is under investigation.

We examined whether a relationship exists between prevalence of *H. pylori* infection and specific territories of coronary vessels. We examined whether a relationship exists between prevalence of *H. pylori* infection and specific territories of coronary vessels. A significant link was found on the MPI between *H. pylori* seropositivity in patients with fixed defects in the distribution of the RCA. This association remained statistically significant after adjustment for CAD risk factors (OR 21.64, 95%CI 2.08–224.86, $P = 0.010$). Perfusion defects in the distribution of the other coronary arteries showed no correlation with *H. pylori* infection (data not shown). Confidence intervals were wide-ranging, leaving room for the possibility that *H. pylori* could have a moderate effect on MI risk in RCA territory, as this territory is adjacent to the stomach and hypothetically might be associated with the gastric colonization of *H. pylori*. Thus, additional prospective studies with a larger number of patients should be performed to possibly narrow the confidence intervals found in this study.

Many previous studies did not adjust for socioeconomic status, known to affect the risk of CAD and *H. pylori* carrier status. How childhood socioeconomic deprivation can increase the risk of CAD is not fully known. Acquisition of *H. pylori* infection in childhood could be one of the reasons. We included data on three individual markers of childhood low socioeconomic status (father's low income, father's occupation as a manual laborer, and high household density during childhood) for both groups and found no correlation between *H. pylori* seropositivity, crowding at childhood, and CAD. We believe that the relationship between *H. pylori* infection and the risk of CAD cannot be entirely explained by low socioeconomic status, although a limitation of our study is the lack of more detailed information relating to childhood socioeconomic status.

In addition, it is well known that infections are able to modify serum lipids. Alterations of the lipid metabolism due to chronic *H. pylori* infections could represent an atherogenic link. Hyperlipidemia, especially hypercholesterolemia, is an established risk factor of atherosclerosis. In this study, hypercholesterolemia was independently associated with CAD.

LIMITATIONS

A possible limitation of our study is that it was performed on a selected population referred for a stress MPI in order to diagnose ischemia in a suspected unknown CAD patient as well as patients with known CAD, thus our results may not necessarily apply to the general population.

HSP60 = heat shock protein 60

CONCLUSIONS

This prospective study among consecutive patients who had undergone a stress MPI supports the hypothesis that chronic infections may contribute to an accelerated atherosclerotic process in the coronary arteries, suggesting an independent association of seropositivity for *H. pylori* and risk of subsequent CAD and MI.

Acknowledgments

The authors thank Mrs. Phyllis Curchack Kornspan for her editorial assistance.

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