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The effect of *Helicobacter pylori* eradication on arterial stiffness and qt dispersion.

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Abstract

The association of *Helicobacter pylori* (HP) with cardiovascular disease remain inconclusive. Studies regarding arterial-stiffness (AS) in patients with HP infection are limited. We aimed to evaluate AS and QTc dispersion in patients with HP infection and the effect of eradication treatment on these outcomes. We enrolled patients with HP infection and healthy subjects. We measured AS and QTc dispersion in the baseline visit and after eradication treatment. We compared baseline measurements between the patients and controls. We compared baseline and follow-up variables to observe the effect of eradication treatment on AS and QTc dispersion. Baseline characteristics were similar between the groups. There was no significant difference in AS measures between the groups. QTc dispersion was significantly higher in the HP group compared with controls. After eradication, QTc dispersion tended to normalize. There was also a statistically significant improvement in augmentation index and a tendency towards improvement in pulse wave velocity. The findings of this study indicate possible influence of HP infection on ventricular repolarization and a potential benefit of eradication on ventricular repolarization and measures of arterial stiffness.

Keywords: Atherosclerosis, Electrocardiography, *Helicobacter Pylori*, Vascular stiffness.

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Introduction

Recent studies indicate that *Helicobacter pylori* (HP) may be associated with increased risk of atherosclerosis and cardiovascular diseases (CVD) [1-3]. However, other studies found no association between HP infection and coronary heart disease (CHD) [4,5]. Furthermore, some studies suggest that eradication of HP may reduce the rates of acute myocardial infarction [6,7]. Measurement of arterial stiffness (AS) is simple and non-invasive and may give important information about the CVD risk in the future. The QT interval represents depolarization and repolarization of the ventricles, while corrected QT dispersion (QTcd), the maximum variation in the QT interval in 12-lead ECG, reflects inhomogeneity of ventricular repolarization [8]. Increased QTcd has been shown to be associated with propensity for arrhythmias in patients with CHD and chronic heart failure [9]. Recent studies indicate an association between arterial stiffness and HP infection. However, the effect of eradication of HP infection on arterial stiffness and QTcd is not known. We aimed to compare arterial stiffness and QTcd in HP positive and HP negative patients with dyspepsia and observe the effect of HP eradication on these variables.

Methods

Subjects

This study took place in the outpatient internal medicine clinics of Haseki Training and Research Hospital and Istanbul University, Istanbul Faculty of Medicine between April 2013 and May 2014. We screened subjects presenting with dyspepsia that had histologic evidence or stool antigen test result for HP positivity or negativity and enrolled those who gave written informed consent. The exclusion criteria were CVD (atrial fibrillation, CHD, chronic heart failure, heart valve diseases, peripheral arterial disease, and cerebrovascular disease), diabetes mellitus, cirrhosis, a glomerular filtration rate of <60 ml/ min/1.73 m^2, unstable angina, familial hyperlipidaemia, pregnancy, disorders of the aorta, connective tissue diseases, congenital long QT syndromes, and evidence of ischemic changes in ECG examination. We also excluded subjects with a history of proton pump inhibitor (PPI) use within the last 2 weeks or HP eradication treatment within the last month, and HP positive subjects with a history of penicillin allergy. We divided the subjects into two groups (HP positive and HP negative groups).

The ethics committee of Istanbul University, Istanbul Faculty of Medicine approved the study (protocol number: 2013/1752). We conducted the study in accordance with the declaration of Helsinki and its later amendments.

Measurements

We recorded demographic data, smoking, medication history, and presence of gastrointestinal symptoms. We measured subjects' heights, weights, and waist circumferences. We used overnight fasting blood and urine samples for complete blood count, creatinine, uric acid, urea, HDL and LDL cholesterol, triglycerides, C reactive protein, albumin, and spot urine albumin/creatinine ratio (UACR). We estimated glomerular filtration rate (GFR) using Cockcroft-Gault formula. We performed standard 12-lead ECG examination. We defined QTcd as the difference between the maximum and minimum corrected QT intervals. We assessed arterial stiffness using an oscillometric device (TensioMed, Budapest, Hungary) as reported previously [10]. We recorded augmentation index (AiX), pulse wave velocity (PWV), pulse rate, and blood pressure (BP) measurements. The eradication treatment consisted of amoxicillin 1 g bid, clarithromycin 500 mg bid, bismuth 300 mg qid, and lansoprazole 30 mg bid for 2 weeks, followed by bismuth 300 mg qid for 2 more weeks and lansoprazole 30 mg/day for 4 more weeks. We controlled arterial stiffness, ECG, and HP eradication (by stool antigen test) which took place at least 2 weeks after completion of eradication treatment.

Statistical analysis

We presented categorical data with numbers and percentages, and continuous data with mean ± standard deviations or median (minimum-maximum) where appropriate. We assessed the normality of the distribution of the continuous data using Kruskal Wallis test. We compared categorical variables using chi square test and continuous variables using Mann Whitney U or Student t tests as needed. We compared the baseline and follow up data using paired samples test or Wilcoxon test. We performed the correlation analyses using Pearson or Spearman tests as necessary. We sought variables with independent associations with QTcd, PWV and Aix using linear regression analyses. We considered a two sided p value of <0.05 as statistically significant.

Results

We enrolled a total of 77 subjects (47 in the HP positive group and 30 in the HP negative group) to this study. We confirmed HP infection in the treatment group with histologic assessment in 45, urea breath test in one, and stool HP antigen test in another one. In the control group, we excluded HP infection depending on histologic evidence in 6, urea breath test negativity in 1, and stool HP antigen negativity in the remaining 23 subjects.

Treatment and follow up adherence

Five subjects experienced adverse effects including nausea, vomiting, or dyspepsia related to eradication treatment. Only one of these subjects stopped the treatment after 7th day, all of the others completed the eradication treatment regimen. Ten of the subjects were lost to follow up. Two of the subjects did not undergo follow-up stool antigen testing. Unsuccessful eradication occurred only in one of the subjects.

Comparison of the study groups

Comparison of the HP positive and HP negative groups is shown in Table 1. Heartburn and epigastric pain were more common in the HP positive group. The HP positive group had higher QTcd. Other study variables were similar among the groups.

Correlations between arterial stiffness, QTcd and other variables

There were positive correlations between QTcd and AiX (r=0.2, p=0.06), systolic (r=0.2, p=0.08) and diastolic BP (r=0.2, p=0.07). There were negative correlations between QTcd and albumin (r= -0.24, p=0.057). Among these factors only HP positivity tended to be independently associated with a higher QTcd (r2 of the model 0.21, OR=13.4 ([-0.61]-[27], p=0.06).

There were positive correlations between AiX and age (r=0.6, p<0.001), male gender (r=0.27, p=0.02), waist circumference (r=0.32, p=0.004), BMI (r=0.4, p<0.001), glucose (r=0.24, p=0.04), CRP (r=0.33, p=0.005), and systolic BP (r=0.53, p<0.001) and diastolic BP (r=0.52, p<0.001). There were negative correlations between AiX and albumin (r=-0.32, p=0.008). Among these factors (r^2 of the model 0.4) only

systolic BP had an independent correlation with AiX (OR=0.64 (0.16-1.12, p=0.01).

Table 1. Comparison of HP positive and HP negative groups.

	HP positive (n=47)	HP negative (n=30)	p
Sex (male/female)	23/24	18/12	0.3
Age (years)	37.2 ± 10.6	36.3 ± 9.7	0.7
Body mass index (kg/m^2)	25.9 ± 5.5	27.5 ± 4.8	0.2
Waist circumference (cm)	94 ± 13.6	97.2 ± 11.1	0.3
Smoking (%)	31.9	23.3	0.4
Previous PPI use (%)	55.3	36.7	0.1
Nausea/vomiting (%)	17	6.7	0.3
Epigastric pain (%)	61.7	16.7	<0.001
Bloating (%)	29.8	20	0.3
Heartburn (%)	74.5	46.7	0.013
Systolic BP (mmHg)	127.4 ± 15.5	124.2 ± 15.6	0.4
Diastolic BP (mmHg)	77 ± 10.4	71.7 ± 8.7	0.13
GFR (ml/min)	132.5 ± 30	144.7 ± 33.3	0.11
CRP (mg/dl)	0.2 (0.01-2.2)	0.3 (0.02-2.3)	0.3
Aix (%)	-40 ([-77]-[73])	-40.6 ([-77]-[27])	0.7
PWV (m/s)	6.9 (5.1-19.9)	7.4 (5.2-10.8)	0.6
QTcd (msn)	50.5 ± 28.4	33.9 ± 15.8	0.003

HP: *Helicobacter pylori*; PPI: Proton Pump Inhibitor; BP: Blood Pressure; GFR: Glomerular Filtration Rate; CRP: C Reactive Protein; RDW: Red Cell Distribution Width; Aix: Augmentation Index; PWV: Pulse Wave Velocity; QTcd: Corrected QT Dispersion

There were positive correlations between PWV and age (r=0.4, p=0.001), waist circumference (r=0.45, p<0.001), BMI (r=0.4, p=0.001), glucose (r=0.4, p<0.001), CRP (r=0.34, p=0.003), and systolic BP (r=0.43, p<0.001) and diastolic BP (r=0.54, p<0.001). There was a negative correlation between PWV and HDL cholesterol (r= -0.3, p=0.008). Among these factors (r^2 of the model 0.24) only glucose level tended to have an independent association with PWV (OR=0.66 ([-0.11]-[0.14], p=0.09).

Assessment of the effects of eradication on study variables

After treatment there was a statistically significant but clinically insignificant improvement in AiX and a tendency towards statistically significant improvement in PWV (Table 2). There was also a tendency towards reduction in QTcd after eradication. There was no significant change in BP measurements. After eradication, QTcd of the HP positive group became similar with that of the HP negative group (41.5 ± 22.3 vs. 33.9 ± 15.8, p=0.15).

Table 2. *Comparison of arterial stiffness and QTcd before and after eradication (n=37).*

	Before eradication	After eradication	p
Systolic BP (mmHg)	126.7 ± 15.6	127.2 ± 15.1	0.8
Diastolic BP (mmHg)	77.7 ± 9.7	77.4 ± 9.2	0.8
Aix (%)	-41.8 ([-77] – [73])	-43.1 ([-73] – [32])	0.045
PWV (m/s)	7.8 (5.1-19.9)	7.5 (5-12.2)	0.16
QTcd (msn)	49.5 ± 27.9	41.5 ± 22.3	0.2

BP: Blood Pressure; Aix: Augmentation Index; PWV: Pulse Wave Velocity; QTcd: Corrected QT Dispersion

Discussion

In this study we observed a significantly higher QTcd compared with controls in the HP positive group which tended to decline after eradication. After eradication, QTcd of HP positive subjects became similar with HP negative subjects. Baseline QTcd tended to have an independent association with HP positivity. We did not observe a significant difference between the HP positive and negative groups regarding arterial stiffness measures. While AiX had an independent association with systolic BP, PWV only tended to have an independent association with glucose levels. However, there was a

statistically significant but clinically insignificant improvement in AiX and a tendency towards improvement in PWV after eradication of HP.

Helicobacter pylori infection increases systemic and vascular inflammation, and may precipitate development of atherosclerosis [11]. However, a meta-analysis of five prospective studies failed to show an association between HP seropositivity and CHD [12]. Among elderly persons, HP seropositivity was not associated with cardiovascular disease in a mean follow-up period of 10 years [13]. The association between cytotoxin-associated protein A (CagA) bearing HP strains and CHD is also controversial [14,15]. Among possible mechanisms regarding the association of HP with CVD are HP-induced atherogenic-modified lipid profile, systemic inflammation, HP-induced platelet aggregation, and hypercoagulation [16].

Recent studies suggest an association between HP infection and arterial stiffness [17-19]. These studies indicate a propensity for such an association especially in younger subjects [18]. However, the median PWV values in our study were substantially lower than mean PWV values in the previous studies. In the study of Saijo et al. [18], the mean PWV was 14 m/s in HP positive and 13.4 m/s in HP negative subjects. Similarly in the study of Yoshikawa et al. [17] mean PWV were around 14.6 m/s in HP positive and 13.8 in HP negative subjects. A possible explanation for this difference is the substantially younger mean age in our study. The mean age was 37.2 and 36.3 in HP positive and negative subjects in our study while it was around 50 in the two aforementioned studies [17,18]. However, to our knowledge, Aix has not been studied specifically in patients with HP infection. Insulin resistance is also suggested to be an important factor underlying the association between HP infection and arterial stiffness [17].

A relationship between the prolongation of QTcd and myocardial ischemia has been reported by Roukema et al. [20] who observed increased QTcd in patients with exercise-induced myocardial ischemia. In both experimental and clinical studies, it has been shown that the QT interval shortens in acutely hypoperfused areas, whereas in infarcted myocardium there is a prolonged repolarization time associated with QT prolongation [21]. One study showed that QTcd assessed immediately after bicycle exercise test was significantly higher in patients with coronary stenoses of >50% as compared with subjects without CHD [22]. Despite the presence of several studies regarding the association of HP infection and CVD, prolongation of QT interval or QTcd was not investigated in subjects with HP infection previously. We observed a significantly increased QTcd in HP positive subjects compared with those without HP infection. Interestingly, after eradication of HP, QT dispersion tended to decrease.

Limitations of our study include the non-randomized design, absence of the assessment of CagA expression, confirmation of HP infection mainly using stool antigen test for the control group, and absence of follow-up assessment of the control group.

In conclusion, significantly higher QTcd in the HP positive group and tendency towards decrease in QTcd after eradication support the association between HP infection and CVD. However, HP infection was not associated with increased arterial stiffness and eradication resulted in a slight improvement in measures of arterial stiffness. Further interventional studies are needed to come to a conclusion regarding the effect between HP infection and its eradication on ventricular repolarization and arterial stiffness.

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