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Original article

Hypertension is frequently present in patients with reflux esophagitis or Barrett's esophagus but not in those with non-ulcer dyspepsia

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Abstract

Background: Elevated mortality due to cardiovascular disease has been reported for patients with Barrett's esophagus (BE). We compared the prevalence of risk factors for cardiovascular disease in patients with BE, reflux esophagitis (RE), and non-ulcer dyspepsia (NUD) with that of the general population. **Methods:** Patients with upper gastrointestinal complaints and BE, RE, or NUD were compared with a matched cohort from the general population using a questionnaire and blood pressure and cholesterol measurements. **Results:** Hypertension occurred more frequently in patients with BE (odds ratio 5.1, $P<0.0001$) and RE (odds ratio 3.8, $P<0.001$), but not in those with NUD. Serum total cholesterol was higher in BE ($P=0.02$) and borderline in RE ($P=0.06$) but not in NUD. Mean HDL cholesterol levels, body mass index, and smoking did not differ. **Conclusions:** This study suggests that BE and RE found at diagnostic endoscopy are associated with an increased prevalence of hypertension and a higher total cholesterol level than in the general population. If so, this would explain the increased mortality during the follow-up of BE patients, and it should be taken into account when designing or evaluating follow-up studies of BE.

Keywords: Barrett's esophagus; Reflux esophagitis; Non-ulcer dyspepsia; Esophageal cancer; Coronary heart disease; Hypertension

1. Introduction

The prevalence of endoscopically confirmed esophagitis in the community is thought to be as much as 2% [1]. Esophagitis can progress to complications such as deep ulceration, stricture formation, and the development of Barrett's esophagus (BE) [2]. Because BE has a pre-malignant potential [3] and because of the dramatically rising incidence of adenocarcinoma in the esophagus in the past decade [4], several groups have proposed endoscopic biopsy surveillance for BE patients to detect malignancy at an early and curable stage [5,6]. However, earlier studies have cast doubt on the effectiveness of endoscopic biopsy surveillance since few patients diagnosed as having BE actually die from adenocarcinoma of the esophagus [7–10].

In a follow-up study of 166 patients in whom the diagnosis BE had been established between 1973 and 1986, we found an elevated mortality (50%) compared to what was expected in an age and sex-matched control population [10]. During a mean follow-up of 9.3 years (amounting to 1440 patient years), eight patients developed esophageal cancer at random intervals, giving one case in 180 patient years. Seventy-nine patients died, one-third due to cardiovascular disease (CVD), and in only two cases was esophageal cancer the cause of death [10]. These results raised the hypothesis that patients with gastroesophageal reflux disease (GERD), or at least a sub-

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group with BE, have an increased risk of CVD with an increased prevalence of one or more CVD risk factors. This study was undertaken to investigate the prevalence of the main risk factors for CVD (blood pressure, cholesterol, smoking) in patients with BE, in patients with reflux esophagitis (RE), and in patients without endoscopic abnormalities and to compare these with the normal population. The study was part of an epidemiological investigation into the prevalence of *Helicobacter pylori* in RE, BE, and non-ulcer dyspepsia (NUD) patients.

2. Materials and methods

The patients we studied were 20–59.9 years of age and had RE, BE, or NUD. Two sources of data were used: One allowed us to review computerized endoscopic and medical data of all patients with BE found at routine endoscopy in the University Hospital Rotterdam in the years 1992–1996. Information regarding the length of BE and the histological criterion of a biopsy sample from the BE was noted. Patients were included if the BE met the criterion of columnar mucosa of at least 3 cm in the tubular esophagus found at endoscopy or histological proof of intestinal metaplasia (IM) when the columnar mucosa was less than 3 cm [11]. The patients studied were offered repeat esophagogastroduodenoscopy (EGD) with a biopsy to confirm the diagnosis of BE. If the patient refused EGD, we used the older data about the length of the Barrett's segment and histology. Secondly, all consecutive patients with GERD or with no endoscopic abnormalities who were referred to the University Hospital Rotterdam–Dijkzigt for diagnostic upper gastrointestinal endoscopy during the period January 1999 to July 2000 were asked to participate in the study. GERD was defined as the presence of endoscopic signs of RE, BE, or both. RE was scored according to the Savary–Miller system [12] as follows: grade 0, normal esophageal mucosa with no abnormalities; grade 1, mucosal erythema or diffusely red mucosa, with or without friability; grade 2, linear erosions extending from the gastroesophageal junction upward in relation to the folds; grade 3, confluent erosions extending around the entire circumference; grade 4, frank ulcer, stricture, or BE.

If the patient had no malignancies or active peptic ulcer disease, he or she was asked to fill in a standard questionnaire about the presence of risk factors of CVD, current medication, and smoking behavior. One patient with BE was excluded because he was unable to travel.

With a simple checklist we ascertained the following demographic characteristics of all three study cohorts: age, sex, weight, height, smoking (current, past, never), date of first diagnosis of BE, and date of last endoscopy.

A blood sample for laboratory testing was taken at the outpatient clinic for most of the BE patients and on the day of endoscopy for the other participants. The study populations (RE, BE, and NUD) answered the following questions used for comparison in the present study: (1) Do you currently use medication for hypertension? (2) Have you ever smoked? If yes → (3) Do you still smoke? Answering categories: yes (→ current smokers); If no (→ ex-smokers) (4) Have you ever smoked? Answering categories: no, never (→ never smokers). Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$. Blood pressure was measured once at rest at the end of the outpatient visit with a mercury sphygmomanometer. Systolic pressure was recorded at the first Korotkoff phase and diastolic pressure at the fifth Korotkoff phase.

The Medical Ethics Committee of the University Hospital Rotterdam approved the study. Informed consent was obtained from all participating patients before the endoscopy was performed.

A reference population was derived from the Monitoring Project on Risk Factors for Chronic Diseases (MORGEN project). This project was carried out in the Netherlands from 1993 to 1997. The general purpose was to determine both the prevalence of risk factors for chronic disease (e.g. plasma cholesterol, blood pressure, smoking habits) and the prevalence of some specific, chronic conditions in a random sample of the general population [13]. Information on current health status, medical history, current medication use, smoking behavior, and family history was obtained using a self-administered questionnaire at home. We asked the following questions for comparison with the study groups: (1) Do you currently use medication for hypertension? (2) Do you smoke? Answering categories: Yes (→ current smokers), No, not anymore (→ ex-smokers), No, and have never smoked (→ never smokers). Height and weight were measured with participants wearing indoor clothes, without shoes, and with empty pockets. Body mass index was calculated as weight (kg)/height $(m)^2$. At the research center, the systolic and diastolic blood pressures were measured twice on the right arm in all subjects in a sitting position with a mercury manometer (random zero sphygmomanometer). Systolic pressure was recorded at the first Korotkoff phase and diastolic pressure at the fifth Korotkoff phase.The average of the two measurements was used in the original analysis, but in present study we used the first measurement for reasons of comparison.

In both studies the participants were asked to write down all medication used and blood was taken for determination of serum total and high-density lipoprotein (HDL) cholesterol concentrations with an automated enzymatic procedure.

In both studies all cholesterol determinations were performed at the Clinical Chemistry Laboratory of the University Hospital in Rotterdam, which is the coordinator of the Dutch National Cholesterol Standardization Program. All respondents sat down for 5 min before the blood pressure measurement was taken. The criterion for hypertension used in all groups (both studies) was at least one of the following factors: systolic blood pressure $\geq$160

mmHg, diastolic blood pressure ≥95 mmHg, or use of antihypertensive medication. According to the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) and the World Health Organization, which defines and classifies hypertension in adults, this blood pressure range represents mild to moderate hypertension [14,15]. In the present study, a systolic blood pressure of 160 mmHg or more and a diastolic blood pressure of 95 mmHg or more was chosen since we only have single measurements in these cohorts and since these values have previously been used as cut-off points for the definition of hypertension in a population study [16]. The current systolic blood pressure threshold for hypertension treatment is 140 mmHg for all adults. The WHO and the International Society of Hypertension have proposed that normal pressure be lower than 130 mmHg, with an optimum pressure of less than 120 mmHg [14,15]. The cut-off limit of our study could exclude individuals with mild hypertension, but is unlikely to misclassify normotensive persons.

2.1. Statistical analysis

For the continuous, potential risk factors (BMI, SBP, DBP, total and HDL cholesterol), the study group was compared with the reference population as follows. The reference population was stratified by sex and 5-year age categories. The mean was computed per stratum. From the observed value of each patient in the study group, the mean of the corresponding stratum of the reference group was subtracted, and the average difference was determined. A 95% confidence interval was computed and the null hypothesis of no mean difference was tested with Student's one-sample test. Since the stratum sizes of the reference group were large (>1000), there was no need to account for the uncertainty in the stratum-specific means. To investigate whether the difference between the study and reference population was related to age and/or sex, multiple linear regression analysis was used with (continuous) age and sex as independent variables. For the categorical potential risk factors (smoking behavior and hypertension), both the study and the reference groups were stratified by sex and 5-year age categories, followed by computation of the Mantel–Haenszel odds ratio, the 95% confidence interval, and the Mantel–Haenszel test. A homogeneity test was performed to investigate whether the odds ratio differed between strata.

Table 2
Endoscopic features

	Reflux esophagitis	Barrett's esophagitis
Grade I	5	
Grade II	11	
Grade III	–	
Grade IV	15	
Length BE (cm) mean (range)		4.7 (0.8–8.5)
Intestinal metaplasia (%)		30 (88)[a]
Dysplasia (%)		6 (17.6)[a]

Number of subjects per grade according to the Savary–Miller endoscopic scoring system.
[a] Information was not available for two subjects.

3. Results

Eighty-six patients aged 20–59.9 years with upper gastrointestinal complaints in whom BE ($n=34$), RE ($n=31$), or NUD ($n=21$) was diagnosed at routine endoscopy took part in the study and were evaluated. We found 212 patients (137 men and 75 women) diagnosed with BE who were alive and without adenocarcinoma in the age range 18–80 years. One hundred and nine responded to the invitation to participate. Of these, 88 were found to have BE at repeat endoscopy, 34 of whom were in the age category 20–59.9 years. The other participating individuals were all consecutive patients with GERD or no endoscopic abnormalities who were referred to the University Hospital Rotterdam–Dijkzigt for diagnostic upper gastrointestinal endoscopy during the period January 1999 to July 2000. Demographic characteristics are given in Table 1 and endoscopic features in Table 2. Twenty-seven patients (79%) in the BE group were using proton pump inhibitors (mostly omeprazole). This was less frequent in the RE group (17 patients, 55%) and in the NUD group (only four patients,19%; $P<0.0001$).

The prevalence of risk factors for CVD are shown in Tables 3 and 4. Body mass index was not significantly different between groups. Mean systolic blood pressure was significantly higher in the BE and RE groups than in controls, as can be seen in Table 3, which shows the mean blood pressures of all patients within a group, whether or

Table 1
Demographic characteristics of the patients in the three subgroups

	Reflux esophagitis	Barrett's esophagus	Non-ulcer dyspepsia
Age	44±10	48±8.4	44±11
Number of subjects	31	34	21
Male	21	26	11
Weight (kg)[a]	81±18	77±15	76±11
Height (cm)[a]	175±10	175±10	175±10

[a] Means±S.D.

Table 3
Mean level of cardiovascular risk factors

Variable	Mean (S.D.)		*P* value	95% CI
	Study group	Controls		
Body-mass index				
Barrett's esophagitis group	25.5 (3.6)	26.0 (0.9)	0.5	−1.7–0.8
Reflux esophagitis group	26.1 (6)[a]	25.5 (0.6)	0.6	−1.7–2.9
Non-ulcer dyspepsia group	24.6 (4.4)	25.5 (0.3)	0.3	−2.8–1
Systolic blood pressure, mmHg (S.D.)				
Barrett's esophagus group	136 (17)	127 (5)	0.004	3.4–16
Reflux esophagitis group	134 (16)	124 (6)	0.002	4.2–16.5
Non-ulcer dyspepsia group	129 (14)	124 (6)	0.07	−0.5–11
Diastolic blood pressure, mmHg (S.D.)				
Barrett's esophagus group	82 (11)	80 (3)	0.4	−2.4–5.3
Reflux esophagitis group	83 (14)	79 (3)	0.05	5.8–10
Non-ulcer dyspepsia group	80 (9)	78 (3)	0.2	−1.6–5.7
Serum total cholesterol, mmol/l (S.D.)				
Barrett's esophagus group	6.0 (1.2)	5.5 (0.3)	0.02	6.8–0.9
Reflux esophagitis group	5.7 (1.0)	5.4 (0.4)	0.06	−1.5–0.7
Non-ulcer dyspepsia group	5.8 (1.5)	5.4 (0.5)	0.3	−0.3–1
Serum HDL cholesterol (S.D.)				
Barrett's esophagus group	1.38 (0.4)	1.26 (0.4)	0.08	−2.3–0.3
Reflux esophagitis group	1.27 (0.5)	1.29 (0.1)	0.3	−0.2–0.2
Non-ulcer dyspepsia group	1.35 (0.3)	1.34 (0.2)	0.9	−0.2–0.2

95% CI=95% confidence interval.
Body-mass index was calculated as the weight in kilograms divided by the square of the height in meters.
P values were calculated using the one-sample Student's *t*-test.
[a] One subject was not available for analysis.

not they were on antihypertensive treatment. The mean systolic blood pressure in the NUD group was higher than in the reference population, although the difference was not statistically significant. The mean diastolic blood pressure was significantly higher in the RE group, but it did not differ in the BE and NUD groups. The frequencies of hypertension in study groups and controls are given in Table 4. Hypertension occurred significantly more frequently among the BE ($P<0.0001$; odds ratio 5.1) and RE ($P<0.001$; odds ratio 3.8) patients than among controls, but not among patients in the NUD group ($P=0.34$; odds ratio 1.7). Beta blockers were the most frequently given treatment for hypertension in the three study groups: in ten (29%) BE patients, two (6%) RE patients, and two (9.5%) NUD patients, followed by ACE inhibitors: in four (12%), one (3.3%), and one (5%), respectively. In the third and fourth places came calcium antagonists: two (6%), two (6.4%), and one (5%), and hydrochloorthiazide: two (6%), two (6.4%), and three (14%), respectively. Combination treatment with beta blockers and calcium antagonists was being used by two BE patients, one RE patient, and one NUD patient. Two BE patients were being given the combination of an ACE inhibitor and a beta blocker, as was one RE patient. Five of the patients with GERD and one with NUD, diagnosed as having hypertension, had a history of myocardial infarction. An additional three normotensive patients had a history of myocardial infarction. Five patients were known to have diabetes mellitus;

Table 4
Prevalence of hypertension

	Hypertension (%) (total group)	*P* value	Odds ratio	95% CI
Barrett's esophagus	47	<0.0001	5.61	2.5–10.0
	32			
	19			
	8			
Reflux esophagus		<0.001	3.76	1.7–8.3
Non-ulcer dyspepsia		0.34	1.7	0.5–5.0
Reference group		–	–	–

Values for hypertension are shown as percent of hypertension in the three study and in the reference population.
P values were calculated using the Mantel–Haenszel test stratified on age and sex. 95% CI=95% confidence interval.

no new cases were identified by blood sugar measurements. Two of the diabetics were also hypertensive.

Two known hypertensives had a serum creatinine slightly above the normal limit, as did one normotensive patient. One normotensive patient had a serum creatinine of 310 μmol/l. Serum creatinine values were normal in all other cases.

Serum total cholesterol levels (Table 3) were significantly higher in the BE group ($P=0.02$), with a trend in the RE group ($P=0.06$), but not in the NUD group. HDL cholesterol levels and the prevalence of smoking habits did not differ between the study groups and controls. The prevalence of both current smoking and no smoking tended to be highest in the youngest age categories (almost 50% in both categories) but decreased with age to the lowest levels of 30 and 20%, respectively, in the 55–59.9 years category. Past smoking was lowest in the youngest age category—around 10%—and highest in the 55–59.9 category—almost 50%. Mean blood glucose level was lower in the RE and NUD groups.

4. Discussion

This is the first study to consider the issue of the prevalence of risk factors for CVD in patients with all grades of GERD. It was undertaken in patients with endoscopically confirmed and clearly defined subgroups of GERD and in patients without endoscopic abnormalities, classified as NUD. We observed a higher blood pressure in the RE and BE groups than in the reference population, but not in the NUD group. Whether hypertension occurred before or after the start of gastrointestinal complaints could not be assessed in this study (the questions asked did not specify the chronology of complaints). We also observed a significantly higher serum total cholesterol in the BE group, with a trend in the RE patients, but not in the NUD group. The mean HDL cholesterol level was borderline significantly higher in the BE group. However, this did not differ between the two other study groups and the reference group. Although BMI was higher in BE patients than in controls, the difference did not reach statistical significance.

To appreciate the findings of this study, certain methodological aspects should be considered. The diagnoses in the study groups were originally made with diagnostic endoscopy in patients with upper gastrointestinal complaints. All patients meeting our criteria for RE, BE, or NUD and diagnosed in the abovementioned periods were asked to participate in a study to look for the prevalence of *Helicobacter pylori* infection. They were not asked to participate in a study to detect risk factors for CVD. A notice was included in the invitation that we would like to know a few things about their general health status. Therefore, it is not likely that the responses of the three study groups were influenced by the presence of CVD risk factors. The individuals participating in the MORGEN study were considered a valid control group because participants were derived from the general population living in the same area and examined in the same time period. Comparability of the two sets of data was achieved by using the same items from the standard questionnaire of the reference group and the three study populations with regard to the presence of CVD risk factors. Therefore, we could not use questions about known family history of CVD for comparison because of differences in the phrasing of the questions used.

The criterion for hypertension was based on both blood pressure measurements and treatment for hypertension. Therefore, it could be argued that the difference in prevalence of hypertension was due to selection bias, as the study patients, many being hospital outpatients, might conceivably be a group requiring more frequent medical attention, which would increase the chance of detection and treatment of hypertension. However, the invitation also included those who had only come for diagnostic endoscopy but were not known as outpatients at our hospital. It should, therefore, represent the great majority of patients currently diagnosed with RE, BE, or NUD. The difference is difficult to explain purely in terms of selection bias. In all participants blood pressure was measured once with a sphygmomanometer in a sitting position after 5 min of rest. We cannot exclude the possibility that the higher levels of blood pressure in the RE and BE groups, compared to those in the control group, were due to circumstances surrounding the measurements (the 'white coat effect' of a physician in the study groups but a research assistant in the MORGEN project) [17]. The phenomenon of 'white coat hypertension' refers to hypertension in a health care institute or doctor's office; it involves multiple factors and does not correlate with the pressor response to the doctor [15]. Thus, it should imply that isolated office hypertension, which might also be the earliest manifestation of real hypertension [18], is equally important in both cases and controls. The same remarkable outcome was not seen in the NUD group compared to controls, which makes a white coat effect unlikely as a reason for higher blood pressure measurements in the other groups. A single measurement does not represent a person's average or usual blood pressure [19], leading to overestimation of the prevalence of hypertension in both the cases and controls. We believe that by depending only on the first measurement in both the patient and the reference groups, the comparison we made is reliable.

In the RE, BE, and NUD groups, weight and height were often self-reported, in contrast to the MORGEN study. Self-reporting tends to give 5–7% lower BMIs than measured BMIs, which tend to be more biased in older and overweight groups [20]. However, self-reporting on BMI is more reliable when used on a younger population [21]. Our three study populations were relatively young (mean age 44 years in the RE and NUD groups and 48 years in the

BE group), but due to the broad age range (20–59.9 years) it could mean that BMI may have been underestimated in the present study, although this is less likely in the youngest age group.

While our findings may be true, the underlying mechanisms are not known. Although high cholesterol may contribute to an increased risk of CVD, differences in the prevalence of hypertension in the present study were statistically more striking. Because we matched for age and gender, age does not play a role in the comparison. Since BMI did not differ between groups, obesity as a hypertensive factor in the RE and BE groups seems unlikely. We did not include any additional investigations in this study to determine whether the patients had secondary hypertension or other factors known to increase blood pressure, such as insulin resistance, high alcohol and salt intake; furthermore, sedentary lifestyle, stress, and low potassium and calcium intake were not examined. One could hypothesize that genetic factors play a role. The influence of genes on blood pressure has been suggested by family studies, and mutations in at least ten genes have been shown to raise or lower blood pressure [18]. Recently, on the basis of clustering of GERD in families, it has also been suggested that there may be a GERD gene [22,23]. The same causative factors—genetic or environmental or both—may be operative in GERD diseases and hypertension. However, further studies need to be performed to establish this possibility.

In an earlier follow-up study at our university hospital, we found surprisingly high mortality rates from CVD in a cohort of 166 patients in whom the diagnosis BE had been established between 1973 and 1986 [10]. In retrospect, those patients would not have benefited from endoscopic surveillance because their elevated mortality was due to CVD in one-third of all cases. This is in agreement with a recently published long-term observational study from MacDonald et al. [24] on BE patients at the University Hospital in the United Kingdom. This high mortality from cardiovascular diseases rather than cancer was recently reported as a surprising finding in a long-term follow-up study of GERD patients treated surgically or medically [25]. Recently, in an elderly population with BE, we found a higher prevalence of myocardial infarction with a notably higher prevalence of hypertension in the same group [26]. The present study was performed on a younger category of the whole spectrum of GERD patients and was compared with another age and sex-matched reference population. Again, we noticed a noteworthy high prevalence of hypertension in the GERD population, particularly within the BE group.

Cardiovascular and overall mortality are known to increase continuously with increasing blood pressure [19]. If our findings are true, they could explain part of the observed higher mortality in the BE population in the follow-up study performed in our hospital performed some years ago [10]. Further studies are needed. These should be prospective and include multiple measurements of blood pressure, examination for organ damage, such as retinopathy, and an evaluation of factors that may contribute to elevated blood pressure, such as salt intake.

In conclusion, BE and RE found at diagnostic endoscopy are associated with an increased prevalence of hypertension and possibly a higher total cholesterol level than in the general population. If our results can be confirmed, they will provide an explanation for the increased mortality during the follow-up of BE patients. They should also be taken into account when designing or evaluating follow-up studies or selecting patients with BE for surveillance.

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