Clinical Investigations

Is There a Link Between Gastroesophageal Reflux Disease and Atrial Fibrillation?

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ABSTRACT

Background: Previous studies suggest a potential association between gastroesophageal reflux disease (GERD) and atrial fibrillation.

Objective: To explore the potential association between GERD and atrial fibrillation.

Materials and Methods: This was a retrospective study created from a database containing all health care encounters for patients who received ambulatory care in the National Capitol Area military health care system between January 1, 2001 and October 28, 2007. The study population included all subjects at least 18 years of age (n = 163 627). Our primary outcomes of interest were *International Classification of Diseases, Ninth Revision (ICD-9)* diagnoses of atrial fibrillation and GERD.

Results: Among 163 627 patients, 7992 (5%) had atrial fibrillation and 47 845 (29%) had GERD. The presence of GERD increased the relative risk (RR) of a diagnosis of atrial fibrillation (RR: 1.39, 95% confidence interval [CI]: 1.33–1.45). In sensitivity analyses, this relationship persisted after adjustment for cardiovascular disease risk factors (RR: 1.19, 95% CI: 1.13–1.25) and diagnoses known to be strongly associated with atrial fibrillation (RR: 1.08, 95% CI: 1.02–1.13).

Conclusions: The presence of GERD is associated with an increased risk of a diagnosis of atrial fibrillation.

Introduction

Atrial fibrillation is the most common cardiac arrhythmia with 2.2 million people in the United States and 4.5 million people in the European Union suffering from either paroxysmal or persistent atrial fibrillation.[1] Gastroesophageal reflux disease (GERD) is also the most common gastrointestinal diagnosis recorded during visits to outpatient clinics.[2] There have been several case reports suggesting that GERD may initiate paroxysms of atrial fibrillation.[3–6] However, the sheer commonality of these 2 diagnoses make it difficult to assess any significant relationship between them.

Although few studies have shown a potential association between these 2 diagnoses, the results were limited by the small numbers of patients studied. Our study goal was to assess whether there is a relationship between GERD and atrial fibrillation in a large population of patients, after controlling for known risk factors for atrial fibrillation including age, hypertension, coronary artery disease and coronary artery disease risk factors, cardiomyopathy, and valvular heart disease.

Methods

The cohort consisted of all adult (age >18 years) ambulatory encounters in the United States Army National Capitol Area military health care system between January 1, 2001 and October 28, 2007. From this database, *International Classification of Diseases, Ninth Revision (ICD-9)* diagnoses of atrial fibrillation and GERD were abstracted. In addition, demographic information (sex, race, and age) and other potential confounders (ICD-9 diagnoses of hypertension, diabetes mellitus, hyperlipidemia, tobacco abuse, hyperthyroidism, coronary artery disease, cardiomyopathy, valvular heart disease, and patients with a history of coronary artery bypass (CABG) surgery were collected.

The univariate association between atrial fibrillation and our primary and secondary variables were explored using χ^2 or student t tests. In order to further explore the relationship between GERD and atrial fibrillation, a multivariable logistic regression model was created adjusting for age, sex, and race as well as other known risk

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factors for coronary artery disease (hypertension, diabetes, hyperlipidemia, and tobacco use). Finally, we tested the sensitivity of this relationship to models that also adjusted for diagnoses known to be associated with atrial fibrillation including alcohol abuse, hyperthyroidism, known diagnoses of coronary artery disease, cardiomyopathy, valvular heart disease, a history of an atrial septal defect, and a history of CABG surgery. Model fit was tested using the Hosmer-Lemeshow test.[7] The assumption of linearity of continuous variables across the logistic function was tested using the Box-Tidwell test.[8] All analyses were done using STATA (v 9.2, College Station, TX). This study was approved by the Walter Reed Army Medical Center institutional review board.

Results

Of our 163 627 subjects, 5% of patients had atrial fibrillation (n = 7992) and 29% (n = 47 845) had GERD (Table 1). The cohort was 55% male (n = 90 136) with an average age of 51.8 years (range, 18–109). A total of 59% were white (n = 96 175) and 21% were African American (34 254). Demographic correlates with atrial fibrillation included older age (relative risk [RR]: 1.07, 95% confidence interval [CI]: 2.14–2.37), being male (RR: 1.54, 95% CI: 1.47–1.61), and being white (RR: 2.25, 95% CI: 2.14–2.37). Univariate associations with atrial fibrillation included having a diagnosis of hypertension, diabetes, hyperlipidemia, hyperthyroidism, alcoholism, or tobacco abuse (Table 2). In addition, there was a strong relationship between the presence of ischemic heart disease and atrial fibrillation (RR: 7.87, 95% CI: 7.54–8.21) as well as with the presence of cardiomyopathy, atrial septal defect, or being status post CABG surgery (Table 2).

On univariable analysis, the presence of GERD was associated with an increased incidence of atrial fibrillation (RR: 1.39, 95% CI: 1.33–1.45; Table 2). After adjusting for age, sex, race, and known atherosclerotic risk factors (hypertension, diabetes, hyperlipidemia, and tobacco use) GERD was still associated with increased risk of atrial fibrillation (RR: 1.19, 95% CI: 1.13–1.25; Table 3). Finally, even after further adjustment for strong correlates of atrial fibrillation, including ischemic heart disease, cardiomyopathy, atrial septal defect, and being status post CABG, the presence of GERD was still associated with atrial fibrillation (RR: 1.08, 95% CI: 1.02–1.13; Table 4).

Discussion

The results of this study revealed the presence of GERD increased the risk of atrial fibrillation by 40% in the largest

Table 1. Baseline Characteristics of Study Population

Variable	Percent (n)
Male	55% (n = 90 136)
Female	45% (n = 73 491)
White	59% (n = 96 175)
African American	21% (n = 34 254)
Atrial fibrillation	5% (n = 7992)
GERD	29% (n = 47 845)
Hypertension	49% (n = 79 330)
Diabetes	14% (n = 23 134)
Hyperlipidemia	48% (n = 78 152)
Tobacco use	19% (n = 31 061)
Ischemic heart disease	15% (n = 24 659)
Cardiomyopathy	3% (n = 5045)
Atrial septal defect	0.5% (n = 859)
Status post CABG	2% (n = 3632)
Hyperthyroidism	2% (n = 3772)
Alcoholism	5% (n = 7523)

Abbreviations: CABG, coronary artery bypass graft; GERD, gastroesophageal reflux disease.

Table 2. Univariable Analysis of Atrial Fibrillation Risk

Variable	Relative Risk	95% CI
GERD	1.39	1.33–1.45
Age	1.07	1.07–1.08
Male sex	1.54	1.47–1.61
White	2.25	2.14–2.37
Hypertension	5.68	5.35–6.03
Diabetes	2.53	2.42–2.65
Hyperlipidemia	2.33	2.23–2.44
Tobacco use	1.06	1.00–1.12
Ischemic heart disease	7.87	7.54–8.21
Cardiomyopathy	5.86	5.56–6.18
Atrial septal defect	2.79	2.35–3.31
Status post CABG	7.84	7.45–8.26
Hyperthyroidism	1.76	1.58–1.96
Alcoholism	0.89	0.80–0.99

Abbreviations: CABG, coronary artery bypass graft; CI, confidence interval; GERD, gastroesophageal reflux disease.

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Table 3. Relationship Between GERD and Atrial Fibrillation, Adjusted for Coronary Disease Risk Factors

Variable	Relative Risk	95% CI
GERD	1.19	1.13–1.25
Age	1.08	1.07–1.08
Male sex	1.69	1.60–1.77
White	1.65	1.56–1.75
Hypertension	1.75	1.64–1.88
Diabetes	1.21	1.15–1.28
Hyperlipidemia	1.15	1.09–1.23
Tobacco use	1.47	1.38–1.56

Abbreviations: CI, confidence interval; GERD, gastroesophageal reflux disease.

Table 4. Relationship Between GERD and Atrial Fibrillation, Adjusted for Coronary Disease Risk Factors and Diagnoses Strongly Associated With Atrial Fibrillation

Variable	Relative Risk	95% CI
GERD	1.08	1.02–1.13
Age	1.07	1.06–1.07
Male sex	1.40	1.33–1.48
White	1.62	1.53–1.71
Hypertension	1.53	1.43–1.65
Diabetes	1.04	0.98–1.10
Hyperlipidemia	0.89	0.84–0.95
Tobacco use	1.19	1.11–1.27
Ischemic heart disease	2.66	2.51–2.82
Cardiomyopathy	3.48	3.20–3.78
Atrial septal defect	4.36	3.42–5.55
Status post CABG	1.60	1.47–1.75
Hyperthyroidism	1.91	1.67–2.19
Alcoholism	1.38	1.21–1.58

Abbreviations: CABG, coronary artery bypass graft; CI, confidence interval; GERD, gastroesophageal reflux disease.

population of patients studied to date. This relationship persisted, though was weaker, after eliminating patients with conditions strongly associated with atrial fibrillation and adjusting for common cardiovascular risk factors. Even when adjusted for strong correlates with atrial fibrillation, such as ischemic heart disease and cardiomyopathy, there was still a relationship between the presence of GERD and atrial fibrillation. These findings mirror numerous case reports suggesting an association between GERD and atrial fibrillation that have been published over the past decade.[3–6]

A number of hypotheses regarding how GERD may be associated with atrial fibrillation have been proposed over the years. Multiple studies have demonstrated a link between vagal nerve stimulation and the induction of atrial fibrillation.[9] This relationship has been shown to be particularly strong among younger patients with lone atrial fibrillation who have been found to have increased vagal tone.[10] Esophageal stimulation with acid has also been shown to increase vagal afferent traffic and may play a role in the initiation of paroxysms of atrial fibrillation.[11,12]

In addition to increased vagal tone, atrial inflammation may also play a role in the genesis of atrial fibrillation. The presence of atrial inflammation among patients with known paroxysmal lone atrial fibrillation was demonstrated by Frustaci et al with the identification of myocarditis in 66% of right atrial septal biopsies taken from 12 patients with lone atrial fibrillation.[13] The decrease in paroxysms of atrial fibrillation that have been observed with statin use supports this mechanism.[14,15] Moreover, prior reports of atria-esophageal fistulas secondary to percutaneous transcatheter ablation illustrate the very close proximity between these 2 structures and the potential to transmit inflammation.[16] The inflammatory response associated with chronic GERD may theoretically provide a mechanism of initiating paroxysms of atrial fibrillation via the close juxtaposition of the esophagus and atria.

A number of limited studies have been conducted over the past decade to investigate the role of GERD in atrial fibrillation. Weigl et al[17] performed an observational study of 18 patients with symptomatic lone paroxysmal atrial fibrillation (PAF) who were on proton pump inhibitor (PPI) therapy for at least 2 months after being endoscopically diagnosed with reflux esophagitis. A decrease or complete disappearance of at least 1 PAF related-symptom occurred in 78% of patients. In addition, antiarrhythmic drugs were discontinued in 5 patients and no patients required an increased dose or a new prescription of an antiarrhythmic medication.[17]

The association between intraesophageal decreases in pH and the onset of atrial fibrillation has also been described. Gerson et al[18] studied 3 patients with symptoms of both palpitations and reflux who underwent simultaneous Holter and 24-hour pH monitoring while off of acid suppressive therapy. All patients reported a reduction in arrhythmia symptoms on acid suppressive therapy with a significant association between a decrease in intraesophageal pH and the onset of atrial fibrillation on Holter monitoring observed in 2 of the 3 patients studied.[18]

Not all studies in this area have been as promising. Bunch et al[19] conducted a retrospective study looking at

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a database of 5288 randomly selected patients. Among patient's surveyed, 14% developed atrial fibrillation over a follow-up period of approximately 11 years. The presence of any GERD was not associated with risk for atrial fibrillation (hazard ratio: 0.81, 95% CI: 1.53–2.14, $P < .001$) after adjustment for other risk factors. Sub-analysis revealed that patients with more frequent GERD had a slightly higher atrial fibrillation risk and patients with esophagitis were more likely to develop atrial fibrillation.[19]

Limitations to this study include the dependence on ICD-9 code accuracy. In addition, due to the cross-sectional nature of our data, we did not follow patients over time to evaluate a causative mechanism and thus our data is, at best, correlative.

Conclusion

This study suggests an association between the diagnoses of GERD and atrial fibrillation in the largest population of patients studied to date. Acid suppressive therapy with PPIs may provide a potential, nontoxic means of controlling symptomatic paroxysms of atrial fibrillation, particularly if accompanied by symptoms of reflux esophagitis. However, further prospective study is needed to determine if a true causal mechanism exists between the 2 diagnoses and to assess whether the mechanism, if present, is dependent on a specific sub-type of atrial fibrillation (ie, lone atrial fibrillation, vagally mediated atrial fibrillation, etc). In addition, the response of atrial fibrillation-related symptoms to PPI therapy and the potential for PPI therapy to reduce the development of atrial fibrillation merits further investigation.

Disclaimer

The views expressed in this paper are those of the author and do not reflect the official policy of the Department of Army, Department of Defense, or the U.S. Government.

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Long-Term Risk of Atrial Fibrillation With Symptomatic Gastroesophageal Reflux Disease and Esophagitis

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The mechanisms underlying the triggers and maintenance of atrial fibrillation (AF) are not fully understood. One potential unproved mechanism is that gastroesophageal reflux disease (GERD), in which acid reflux induces local and systemic inflammation, may increase triggered activity in the myocardium and pulmonary veins and increase AF risk. A self-report questionnaire was mailed to a random sample of 5,288 residents of Olmsted County, Minnesota, aged 25 to 74 years to assess the presence and frequency of GERD from 1988 to 1994. The long-term risk for AF over a period of 11.4 ± 5.0 years was determined through review of clinical evaluations and the electrocardiographic database in those without previous AF. The average age was 53 ± 17 years, and 2,571 subjects (49%) were man. Of these patients, 741 developed AF (cumulative probability of AF at 18 years 20%, 95% confidence interval [CI] 17% to 22%). Age (hazard ratio [HR] 1.09, 95% CI 1.08 to 1.10, p <0.001), male gender (HR 1.81, 95% CI 1.53 to 2.14, p <0.001), hypertension (HR 1.36, 95% CI 1.14 to 1.61, p = 0.0006), and heart failure (HR 1.74, 95% CI 1.16 to 2.60, p = 0.007) were independently associated with the risk of AF. The presence of any GERD was not associated with risk for AF (HR 0.81, 95% CI 0.68 to 0.96, p = 0.014) after adjustment for other risk factors. The frequency of GERD did not significantly affect the risk for AF, although patients with more frequent GERD had a slightly higher AF risk. Esophagitis increased the risk for AF (HR 1.94, 95% CI 1.35 to 2.78, p <0.001), but the association did not persist when accounting for other risk factors (p = 0.72). In conclusion, in this large population-based study of patients surveyed for GERD, no association was found with the presence or frequency of symptoms and AF. Patients with esophagitis were more likely to develop AF, although this association requires further study. **(Am J Cardiol 2008;102:1207–1211)**

New risk factors or risk "markers" for atrial fibrillation (AF) continue to be reported. Broadly, these risk factors include systemic inflammation,[1] obesity and sleep apnea,[2] alcohol use,[3,4] and specific genetic mutations.[5–7] Environmental factors also play a key role in certain situations. In 1 study of patients who developed lone AF, the environmental triggers were variable but distinct and included sleeping (44%), exercise (36%), alcohol use (36%), and eating (34%).[8] Although the roles of sleeping[2] and alcohol intake[3,4] have been previously established, less is known about the mechanisms underlying the association of AF and the gastrointestinal tract. One potential explanation is that gastroesophageal reflux disease (GERD) underlies the association of eating and AF. A study of 3 patients showed that AF onset was associated with a pH decrease during 24-hour intraesophageal pH monitoring.[9] It is reasonable to surmise that this association exists because of the proximity of the esophagus, left atrium, and pulmonary veins. Focal inflammation of the esophagus may involve the myocardial and pulmonary vein tissues and increase the risk for triggered atrial activity. Also, it is conceivable that systemic effects from cytokine release and impaired esophageal contractility associated with GERD could potentially increase the risk for AF.[10] Therefore, to examine this potential association, we undertook a large population-based study that surveyed the presence and frequency of GERD and long-term risk for AF.

Methods

According to the United States census, Olmsted County, Minnesota, had a population of nearly 120,000 in 2005. Nearly 80% of the county's residents live within 5 miles of the city of Rochester. Health care is provided predominantly by 2 groups: the Mayo Medical Center and the Olmsted Medical Center. Within these 2 health systems, medical diagnoses and surgical procedures are indexed when made as outpatients, emergency room visits, nursing home care, hospital admissions, and death certificates.[11] This database allows investigation of the impacts of diseases on a population over time. Using this database, a random sample of the population was obtained, aged 25 to 74 years from 1988 to 1994. Patients were excluded from the estimation of AF risk if they had preexisting diagnoses of AF. This database was used to abstract the general patient demographics

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Table 1
Baseline demographics of Olmsted County, Minnesota, patients on the basis of the presence of any gastroesophageal reflux disease symptoms

Variable	GERD Symptoms		p Value
	Yes (n = 2,577)	No (n = 2,706)	
Age (yrs)	51 ± 17	55 ± 18	0.0001
Men	1,316 (51%)	1,253 (46%)	0.0006
Hypertension	592 (23%)	649 (24%)	0.399
Diabetes mellitus	200 (8%)	238 (9%)	0.178
Dyslipidemia	478 (19%)	454 (17%)	0.097
Coronary artery disease	217 (8%)	239 (9%)	0.596
Previous myocardial infarction	133 (5%)	155 (6%)	0.396
Congestive heart failure	49 (2%)	84 (3%)	0.006
Previous atrial fibrillation	69 (3%)	113 (4%)	0.003

(Table 1). The diagnoses were determined by attending physicians and not based on strict criteria.

To assess the frequency of heartburn in the community, patients were sent a study questionnaire, as previously reported.[12] The gastroesophageal reflux questionnaire was designed as a self-report instrument. The following definitions were used to define GERD, as previously reported[12]: (1) heartburn, a burning pain or discomfort behind the breastbone in the chest; (2) acid regurgitation, a bitter- or sour-tasting fluid coming into the throat or mouth; (3) chest pain, any pain or discomfort felt inside the chest but not including heartburn or any pain that is primarily in the abdomen; (4) dysphagia (trouble swallowing), a feeling that food sticks in the throat or chest; (5) globus, a feeling as if there is a lump in the throat when not swallowing; (6) dyspepsia, an ache or pain occurring mainly in the upper abdomen and not including heartburn, chest pain, or pain with menstrual periods; (7) hoarseness, a rough and harsh voice; and (8) bronchitis, coughing as often as 4 to 6 times a day on ≥4 days a week. Questions were also asked to determine if a patient had asthma, heart disease, or pneumonia. Symptom frequency was then measured using the following scale: 1 = none in past year, 2 = less than once a month, 3 = about once a month, 4 = about once a week, 5 = several times a week, and 6 = daily. For the purposes of this study, we used a simplified version of this scale: none, some (less than once a month or monthly), weekly, and daily. This study questionnaire was sent to 5,288 random residents of Olmsted County from 1988 to 1994. They received reminder letters at 2, 4, and 7 weeks. Those who indicated at any point that they did not want to participate were not contacted further. Nonresponders were contacted by telephone to request their participation. The spectrum of response has been previously reported.[12]

In 2007, we analyzed the records of the surveyed patients. AF was diagnosed from their medical records from inpatient and outpatient evaluations, the electrocardiographic database, and International Classification of Diseases, Ninth Revision, codes.

Statistical analysis: Continuous variables are reported as mean ± SD, and categorical variables are summarized as percentages. Survival free of the end point of AF was estimated using the Kaplan-Meier method. These estimates were made using the presence and frequency of GERD. Univariate associations of clinical variables with AF were assessed in a Cox proportional-hazards model. Multivariate models were constructed using the stepwise selection technique with these Cox models.

Results

The subjects' average age was 53 ± 17 years, and 2,571 (49%) were men. Of these patients, 2,577 (49%) reported GERD on the survey. One hundred eighty-two patients (3%) had histories of AF. These patients were excluded from the subsequent analysis that looked at the impact of GERD on risk for AF.

Among the 2,577 subjects who reported GERD symptoms, the average age was 52 ± 17 years, and 1,316 (51%) were men. A comparison of the baseline variables on the basis of the report of GERD is listed in Table 1. Patients who reported GERD were younger and more often men. They were less likely to have previous AF or congestive heart failure. In Table 2, demographics are listed on the basis of the frequency of GERD. Patients with daily GERD symptoms were older and more likely to have coronary artery disease and previous myocardial infarctions.

Of the 5,288 patients initially surveyed, 741 (14%) developed AF over a follow-up period of 11.4 ± 5.0 years. Of the baseline variables listed in Table 1, age, gender, hypertension, congestive heart failure, and esophagitis were associated with the risk for AF (Figure 1). There was a slight but significant inverse association with reported GERD symptoms and risk for AF.

Figure 2 displays the Kaplan-Meier analysis examining the association of any reported GERD symptoms and AF. In this general analysis, there was an inverse association of GERD symptoms and risk for AF ($p < 0.001$). Figure 3 displays the association of the frequency of GERD symptoms and AF. Although those with daily symptoms had a higher risk for AF, it was of borderline significance in comparison with the other GERD symptom groups (hazard ratio 1.54, 95% confidence interval 0.96 to 2.46, $p = 0.07$), with no significance found when adjusting for other confounding variables ($p = 0.260$). Finally, Figure 4 shows subgroup analysis on the basis of age. We did not find a clear association of risk with GERD symptoms in 3 age-based groups (<50, 50 to 65, and >65 years). However, as expected, the risk for AF in general was much greater in the older groups compared with the younger group (Figure 4).

Finally, 173 patients had known esophagitis on the basis of International Classification of Diseases, Ninth Revision, codes when they were surveyed. We do not know if all of these patients underwent endoscopy. The general demographics of those patients with and without esophagitis are listed in Table 3. Patients with esophagitis were older and more likely to have coronary artery disease, previous myocardial infarctions, and AF. Of these patients, 45 (26%) developed AF, as opposed to 696 (14%) in the group without esophagitis. There was an increased hazard for AF over time on the basis of the diagnosis of esophagitis (hazard ratio 1.94, 95% confidence interval 1.35 to 2.78, $p < 0.001$). However, the hazard did not remain significant when accounting for age, gender, hypertension, and heart failure ($p = 0.72$).

Table 2
Baseline demographics of Olmsted County, Minnesota, patients on the basis of the frequency of gastroesophageal reflux disease symptoms

Variable	GERD Symptoms				p Value
	Daily (n = 115)	Weekly (n = 653)	Some (n = 1,809)	None (n = 2,706)	
Age (yrs)	57 ± 16	53 ± 16	51 ± 17	54 ± 18	0.0001
Men	61 (53%)	331 (51%)	924 (51%)	1,253 (46%)	0.007
Hypertension	30 (26%)	171 (26%)	391 (22%)	649 (24%)	0.072
Diabetes mellitus	9 (8%)	51 (8%)	140 (8%)	238 (9%)	0.601
Dyslipidemia	27 (23%)	136 (21%)	315 (17%)	454 (17%)	0.033
Coronary artery disease	22 (19%)	55 (8%)	140 (8%)	239 (9%)	0.0004
Previous myocardial infarction	12 (10%)	33 (5%)	88 (5%)	155 (6%)	0.062
Congestive heart failure	1 (1%)	10 (2%)	38 (2%)	84 (3%)	0.030
Previous atrial fibrillation	3 (3%)	14 (2%)	52 (3%)	113 (4%)	0.021
Esophagitis	20 (17%)	70 (11%)	53 (3%)	30 (1%)	0.0001

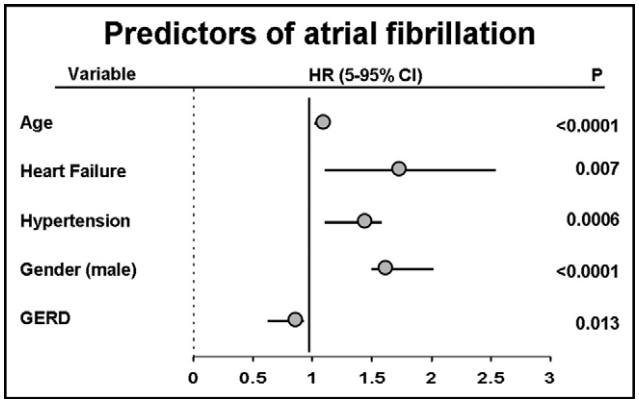

Figure 1. Hazard ratios (HRs) are displayed for each demographic factor associated with AF. The presence of any GERD symptoms was added to the model and slightly decreased the risk for AF (HR 0.81, 95% confidence interval [CI] 0.68 to 0.96, p = 0.013).

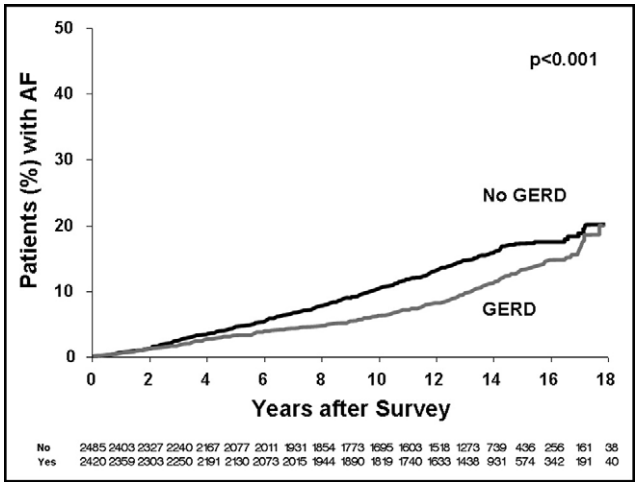

Figure 2. Kaplan-Meier analysis of the presence or absence of GERD symptoms and long-term risk for AF.

Discussion

In this large population-based study of patients followed over a period of >10 years, we found an inverse relation between the presence of GERD and AF. The frequency of AF did affect this relation, with patients who reported daily GERD symptoms having the highest risk for AF, although the risk differences did not reach statistical significance. This latter observation may have been due to confounding variables, because these patients were more likely to be older and have previous coronary artery disease and esophagitis.

In general, the study results were contrary to what we had hypothesized. In fact, GERD symptoms as a whole resulted in AF less often. There are several potential explanations for this finding.

First, patients with GERD who are symptomatic from noncardiac diseases may seek medical treatment more often than those without these symptoms. Repeat medical attention may also result in the identification and treatment of traditional risk factors for AF, such as hypertension, diabetes, and congestive heart failure.[13–16] The observation that there were similar rates of these traditional risk factors in the GERD and no-GERD groups makes this possibility less likely. Similarly, if patients with GERD presented more often to physicians, this action should also increase the likelihood of AF diagnosis, but the opposite was seen.

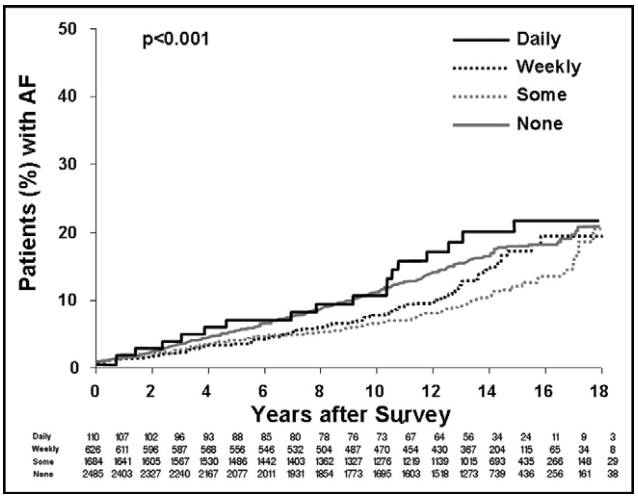

Figure 3. Kaplan-Meier analysis of the presence and frequency of GERD symptoms and long-term risk for AF. Daily GERD symptoms had the highest risk for AF (hazard ratio 1.30, 95% confidence interval 0.98 to 1.57, p = 0.07).

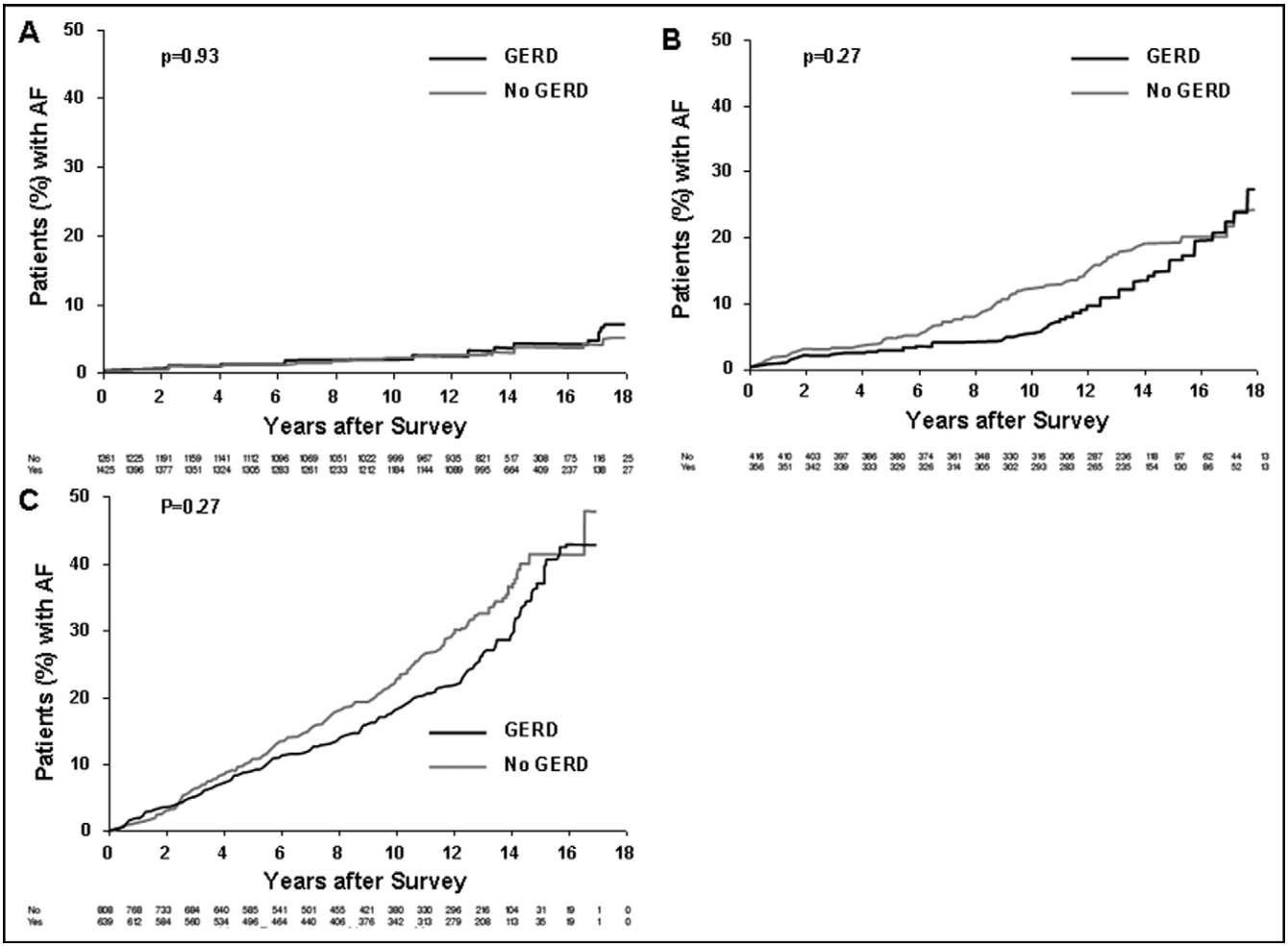

Figure 4. Kaplan-Meier analysis of the presence or absence of GERD symptoms and long-term risk for AF on the basis of age: *(A)* patients aged <50 years, *(B)* patients aged 50 to 65 years, *(C)* patients aged >65 years. In general, the risk for AF increased with advancing age.

Table 3
Baseline demographics of Olmsted County, Minnesota, patients on the basis of the presence of the diagnosis of esophagitis

Variable	Esophagitis		p Value
	Yes (n = 173)	No (n = 5,115)	
Age (yrs)	64 ± 14	53 ± 17	<0.0001
Men	103 (60%)	2,468 (48%)	0.0035
Hypertension	75 (43%)	1,168 (23%)	<0.0001
Diabetes mellitus	26 (15%)	412 (8%)	0.0011
Dyslipidemia	56 (32%)	876 (17%)	<0.0001
Coronary artery disease	42 (24%)	414 (8%)	<0.0001
Previous myocardial infarction	28 (16%)	260 (5%)	<0.0001
Congestive heart failure	7 (4%)	126 (2%)	0.191
Renal failure	3 (2%)	38 (1%)	0.144
Previous atrial fibrillation	14 (8%)	168 (3%)	0.0006

A second possibility is that the management of the disease may have secondary effects that reduce AF. For example, proton pump inhibitors are effective in the management of acid-related disorders. This class of medication reduces esophageal inflammation and extraesophageal manifestations of acid reflux, such as noncardiac chest pain, asthma, and laryngitis.[17–19] In a small study of patients with GERD with endoscopic findings of esophagitis and AF, proton pump inhibitors reduced the frequency and duration of palpitations. The mechanisms underlying the effect of this medication class on the arrhythmia are unknown, but the study suggests that these medications may play a role in the management of AF in select patients with GERD. Although this is a plausible explanation, the data set we presented did not include medication use information, so we could not test it in this population.

Third, in addition to traditional complications of GERD, injury to the distal esophagus may impair vagal nerve response, in particular nerve sensitization in the afferent pathways.[20] This is important, because vagal nerve–mediated parasympathetic stimulation of the heart results in slowing of the sinus and ventricular rates and can increase AF inducibility.[21,22] Subtle effects on vagal nerve function with GERD are a feasible possibility to explain the observed data on a population-based scale. Nonetheless, this hypothesis requires further study to confirm or refute its validity.

Fourth, a diagnosis of GERD is given to patients with symptoms suggestive of acid reflux. However, the amount of reflux and manifestations of reflux can be variable over time.[23]

For example, reflux of barium during x-ray evaluation is positive in only 25% to 75% of symptomatic patients and is falsely positive in up to 20% of normal controls.[23–25] Also, most patients with GERD will have normal endoscopic results,[26] a finding also suggested in our data by the low prevalence of esophagitis. For this reason, esophagitis confirms the diagnosis of GERD, but a lack of endoscopic findings does not exclude it.[23] The discrepancy between symptoms and physical manifestations of injury in the distal esophagus may account for why there is no apparent risk for AF with GERD.

However, the specific finding of esophagitis rather than the general symptoms of GERD seen associated with AF supports our hypothesis that local inflammation may increase the risk for AF. Patients with daily GERD symptoms were more likely to have esophagitis, which may account for some of the increased risk for AF in this group of patients. Unfortunately, those with esophagitis had many other risk factors for AF, and when taking these into account, the increased hazard did not persist. Nonetheless, it is within this population that further study is needed.

One area that requires further study is the possible association of a hiatus hernia, GERD, and AF. A hiatus hernia has the potential to mechanically irritate the left atrium, resulting in arrhythmia. Furthermore, the hernia may also increase reflux and result in severe symptoms and esophagitis.

This study's strengths include a large random community sample, which minimized selection bias. The survey used was a subjective tool to assess for GERD rather than a more objective tool, such as endoscopic diagnosis. However, the questionnaire has been previously validated, and the prevalence rates reported are similar to those of other populations.[12,27] AF diagnosis was based on codes International Classification of Diseases, Ninth Revision, codes from hospital dismissal summaries, the electrocardiographic database, and review of the inpatient and outpatient medical records. Although this is a common means to look for AF in a population-based study, subclinical or asymptomatic AF can be undetected. We do not have information on AF subtype. AF subtype risk may vary with GERD symptoms. Unfortunately, we do not have data on the use of medications to treat GERD. A study looking at the use of these GERD medications, the duration of therapy, and compliance with therapy may provide insight into whether these therapies affect AF. Finally, not all patients underwent endoscopy, and we do not have information on the relative number of patients who did.

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Case report

Swallow syncope associated with paroxysmal atrial fibrillation

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Abstract

Swallow or deglutition syncope is a very unusual potentially lethal but treatable disorder. We report the case of a 26-year-old woman, who presented with a history of recurrent, multiple fainting episodes precipitated by swallowing. Twenty-four-hour manometry and pH recording together with continuous 24-h ECG monitoring revealed multiple episodes of symptomatic and asymptomatic paroxysmal atrial fibrillation, and significant gastro-oesophageal reflux associated with swallowing. Oesophageal function tests and continuous electrocardiographic evaluation is important in the diagnosis of this rare condition. © 2002 Published by Elsevier Science B.V.

Keywords: Swallow syncope; Syncopal syndromes; Paroxysmal atrial fibrillation; Esophageal function tests; Gastroesophageal reflux

1. Introduction

Swallow or deglutition syncope is a very unusual potentially lethal but treatable disorder. Apart from a possible case reported by Spans in 1793, the earliest report of oesophageal syncope was by McKenzie in 1906. Most reported cases of swallow syncope are due to bradyarrhythmia [1,2]. The diagnosis and successful management of this condition can pose a clinical dilemma. We discuss the management of a 26-year-old woman with a clinical rarity of swallow syncope associated with paroxysmal atrial fibrillation.

2. Case report

A 26-year-old woman presented with multiple episodes of fainting, central chest discomfort, heartburn and excessive salivation induced by swallowing. She smoked 20 cigarettes, and drank 6 units of alcohol and 3 mugs of caffeinated drinks daily. She was not taking any medication and had no significant past medical history. She was referred for evaluation and management.

On admission, she was in sinus rhythm at a rate of 72 beats/min with a systemic blood pressure of 110/80 mmHg. Physical examination revealed no abnormality. Barium studies and oesophago-gastroscopy confirmed a small hiatus hernia without oesophagitis. Multiple episodes of symptomatic and asymptomatic paroxysmal atrial fibrillation and ventricular ectopic beats were recorded repeatedly during meals or while drinking water on elecrocardiographic monitoring, as shown in Fig. 1. Oesophageal manometry revealed a hypotensive lower oesophageal sphincter with a mean mid-expiratory pressure of 13 mmHg. The sphincter appeared to relax completely. The ambulatory pH study showed upright gastro-esophageal reflux. The fraction of time when the pH was less than 4 in the upright position was 7%, supine 1.4% and total 4.9% (Fig. 2). She complained of distressing symptoms during the test, which coincided with the episodes of significant gastro-oesophageal reflux and arrhythmia. She was successfully treated conservatively with dietary control and a proton pump inhibitor.

3. Discussion

The neurally mediated syncopal syndromes encompass a number of apparently related disturbances of reflex cardiovascular control. Some of these syndromes, such as carotid sinus syndrome and post-micturition syncope, are encountered occasionally in clinical practice, whereas others like swallow syncope are quite rare. Syncope due to atrioventricular heart block induced by swallowing or pneumatic dilatation of the oesophagus has been reported [3,4]. Tachyarrhythmia associated with swallowing has been observed very rarely and not usually associated with syncope [5,6].

The mechanism of swallow syncope is probably related to the innervation of the oesophagus. Both motor and sensory

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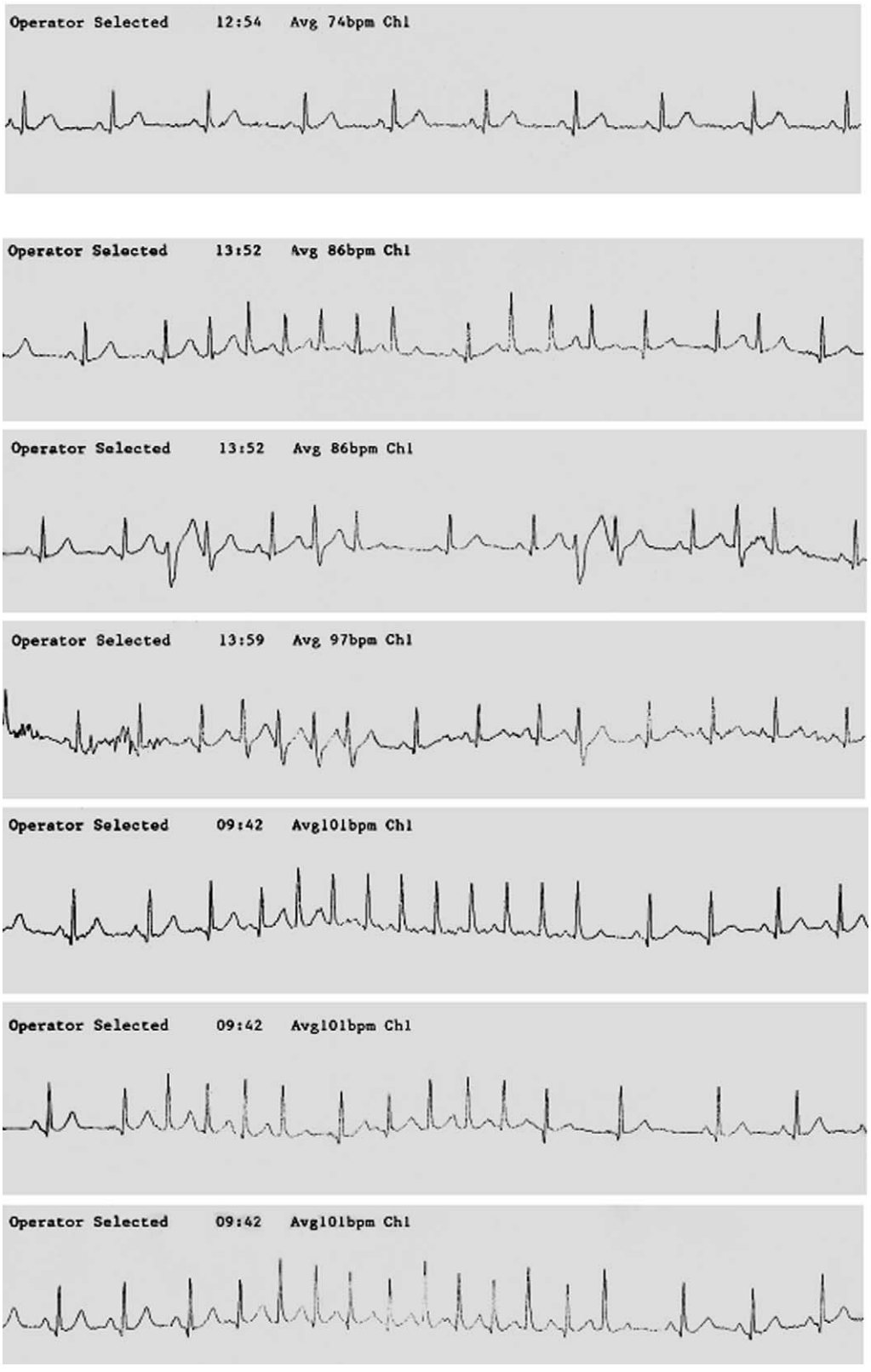

Fig. 1. The relevant part of a 24-h electrocardiograph showing normal sinus rhythm between meals and periods of paroxysmal atrial fibrillation with ventricular ectopics recorded during meal times.

innervation of the oesophagus is by the vagus. The neurones subserving sensory function from the esophagus and motor function to the heart are in close relationship to each other in the dorsal nucleus of the vagus. Therefore, it seems most likely that swallow syncope is mediated by a central reflex involving an unusual, if not abnormal, connection in this

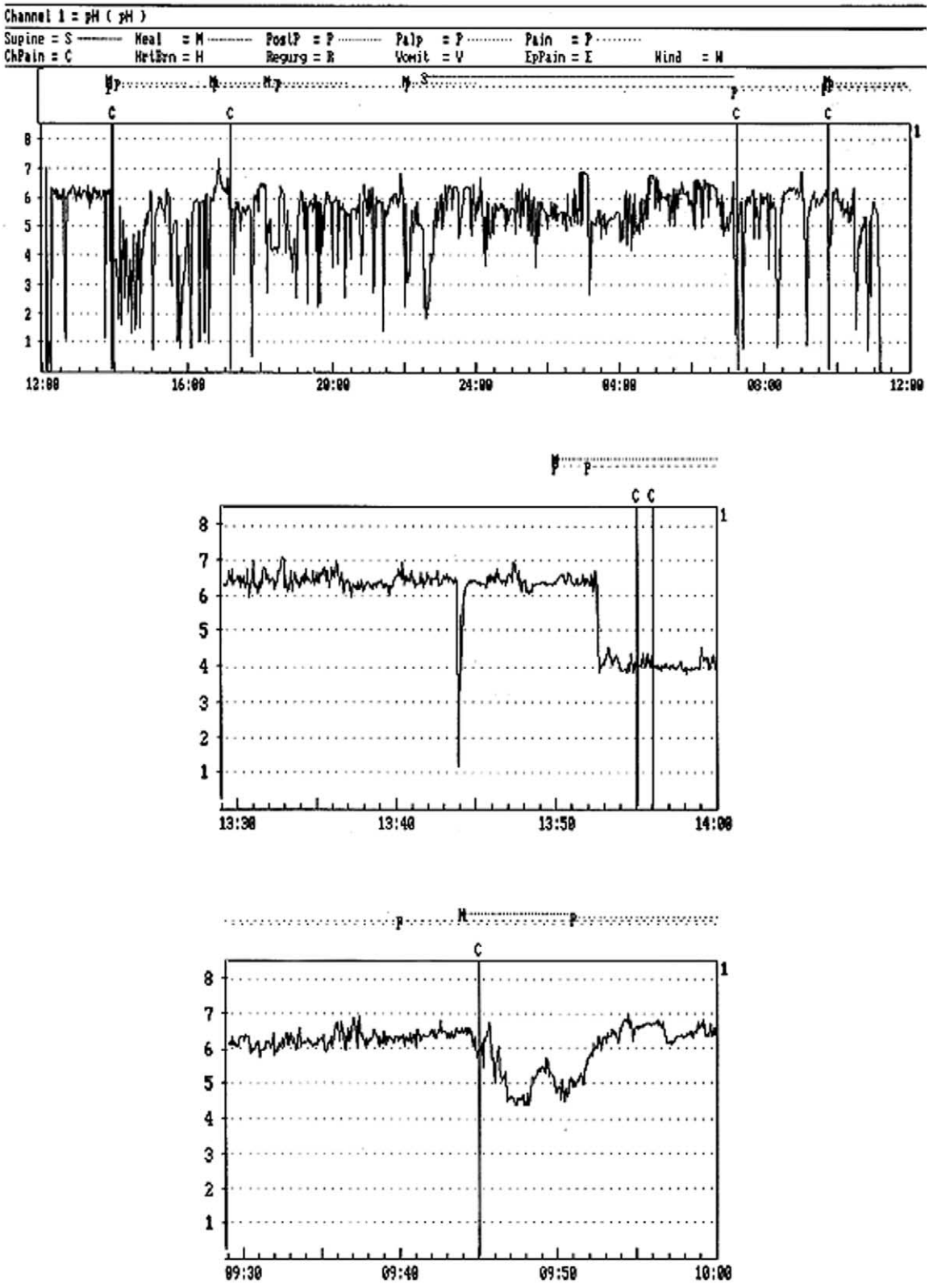

Fig. 2. A portion of the recording obtained from an ambulatory pH monitoring study showing upright gastro-oesophageal reflux.

nucleus. Furthermore, acid stimulation of the lower oesophagus leads to a significant reduction in coronary blood flow in patients with coronary artery disease, but not in patients with heart transplant when the heart is denervated, suggesting a cardio-oesophageal reflex [7]. The physiological inter-relationship between the upper gastrointestinal tract and heart is well known [8]. Dysrhythmias are common during any procedure that involves manipulation of the upper gastrointestinal tract, such as endoscopy of the oesophagus or stomach. Oesophageal syncope represents an extreme form of this phenomenon [1].

The diagnosis of the rare condition should depend on a demonstration of the direct relationship between swallowing and syncope, as in this patient (Fig. 1). Some primary oesophageal diseases that have been associated with this condition include hiatal hernia, carcinoma, achalasia and diffuse spasm [1,9,10]. This case also highlights the importance of investigating patients with swallow syncope for underlying pathological conditions and instituting the appropriate treatment. The discontinuation or reduction of aggravating medications such as digoxin, β-blockers or calcium channel antagonists may be necessary. Several drugs including atropine, adrenaline, ephedrine and isoprenaline have been tried with inconsistent results. Bilateral splanchnic nerve block and bilateral vagal block with various local anaesthetics have been unreliable in controlling symptoms. When syncope is not associated with an oesophageal abnormality that requires correction, the treatment of choice is the insertion of a cardiac demand pacemaker.

Swallow syncope is a rare clinical condition that can be difficult to diagnose and treat successfully. Patients with suggestive symptoms should be have a full oesophageal physiological work-up with a 24-h electrocardiographic monitoring to document the relationship between swallowing and adverse cardiac events, and also to identify underlying oesophageal pathologies. A successful treatment of this condition can be achieved by treating the associated oesophageal disease.

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