

## 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.<sup>1</sup> Gastroesophageal reflux disease (GERD) is also the most common gastrointestinal diagnosis recorded during visits to outpatient clinics.<sup>2</sup> There have been several case reports suggesting that GERD may initiate paroxysms of atrial fibrillation.<sup>3–6</sup> 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  $\chi^2$  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.<sup>7</sup> The assumption of linearity of continuous variables across the logistic function was tested using the Box-Tidwell test.<sup>8</sup> 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.

**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.<sup>3–6</sup>

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.<sup>9</sup> 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.<sup>10</sup> 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.<sup>11,12</sup>

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.<sup>13</sup> The decrease in paroxysms of atrial fibrillation that have been observed with statin use supports this mechanism.<sup>14,15</sup> 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.<sup>16</sup> 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<sup>17</sup> 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.<sup>17</sup>

The association between intraesophageal decreases in pH and the onset of atrial fibrillation has also been described. Gerson et al<sup>18</sup> 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.<sup>18</sup>

Not all studies in this area have been as promising. Bunch et al<sup>19</sup> conducted a retrospective study looking at

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.<sup>19</sup>

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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