Cardiac Involvement in Patients with Gastroesophageal Reflux Disease (GERD)

Ahlam Talaat Zarea Hassan, Hanan Mahmoud Ahmed and Lobna Abdel-Wahid Ahmed

Department of Internal Medicine, Faculty of Medicine, Assiut University, Assiut, Egypt

Corresponding Author
Ahlam T. Zarea.

Mobile:
+201021377015

E mail:
ahlam_pg0919390@m ed.aun.edu.eg

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Background and study aims: Acid regurgitation and/or heartburn are symptoms of Gastrointestinal Reflux Disease (GERD), which is the most frequent gastrointestinal diagnosis. Non-cardiac chest pain is well documented to be linked to gastroesophageal reflux illness. We aimed to assess the link between GERD and cardiac arrhythmia.

Patients and Methods: A total of 50 GERD patients were chosen from the Gastroenterology Unit of the Internal Medicine Department at Assiut university hospitals for this cross-sectional study. Patients had their medical histories taken, physical examinations performed, biochemical tests performed, and a full heart examination performed.

Results: The SDDN (R-R interval) was determined to be 100.1±18.8 on average. Patients with S-T depression made up half of the sample, with an average S-T depression score of 0.92±0.20. Furthermore, around two-thirds of the individuals developed arrhythmia. There was a favorable connection between the occurrence of GERD and cardiac arrhythmia when all correlates were adjusted. The intercept (constant) in the final model after controlling for all correlates was 15.81, and four correlates, positive diabetes history, smokers, and patients with S-T segment depression/arrhythmia, were found as independent predictors of reflux episode number.

Conclusion: The presence of GERD enhanced the likelihood of cardiac arrhythmia, according to this study. There was a link between having GERD and having cardiac arrhythmia .

INTRODUCTION

Metabolic-associated fatty liver Gastroesophageal reflux disease (GERD) can cause bothersome symptoms (such as heartburn and nausea/vomiting) that degrade a person's quality of life. It is a condition in which stomach acid rushes up into the oesophagus, oropharynx, and/or respiratory tract on a regular basis. This results in injury and, as a result, problems (reflux-induced symptoms, erosive esophagitis, and long-term complications) [1], It could have a significant negative impact on everyday activities, work productivity, sleep, and overall quality of life. GERD is described as moderate to severe bothersome symptoms that occur one or more days per week, according to the Montreal Consensus [1]. This gave a reasonable explanation for acid suppression medication without examination, prompting patients to seek symptomatic treatment for their primary problem. The Montreal definition was revised because the complexity of symptoms and causes necessitates re-evaluating the concept of GERD as a composite, symptom-based entity in order to obtain more precise patient management [2].

Non-erosive reflux disease (NERD), which manifests as GERD symptoms without erosions on endoscopic inspection, and erosive esophagitis (EE), which manifests as GERD symptoms with erosions, are two distinct entities. It is important to note that EE can occur even when there are no symptoms [3]. The presence of characteristic GERD symptoms without esophageal mucosal erosion during upper

endoscopy and the absence of recent acid-suppressive medication were used to diagnose NERD [4]. "Evidence in support of this diagnosis includes, but is not limited to, responsiveness to acid suppression, positive 24-hour pH monitoring, or identification of particular unique endoscopic, morphological, or physiological findings," the criteria was changed based on pathobiology and diagnosis. NERD is the most common type of GERD around the world [5]. Even though GERD symptoms are evident, only one-third of GERD patients have endoscopically positive findings, while others have no visible mucosal breaks [6].

Cardiac ischemia can be asymptomatic or induce angina pectoris (chest discomfort that mimics GERD heartburn). It happens when the heart muscle doesn't get enough blood. Atherosclerosis, or the long-term deposition of cholesterol-rich plaques in the coronary arteries, is the most common cause of angina. In most Western countries, ischemic heart disease is the leading cause of death and a major cause of hospital admissions [7].

Electrocardiography (ECG), followed by echocardiographic coronary angiography and/or scintigraphy, is frequently used to diagnose angina. Many people who go to the emergency room with chest pain don't have coronary artery disease (CAD). According to earlier research, 81 percent to 86 percent of patients with acute chest pain assessed in an emergency hospital did not exhibit coronary ischemia [8, 9].

It is common knowledge that non-cardiac chest pain is linked to GERD [10]. Because the distal oesophagus and the heart share a shared afferent vagal supply, it's difficult to tell the difference between esophageal and cardiac ischemia chest pain, and GERD can induce non-cardiac chest pain that mimics ischemic cardiac discomfort. In clinical contexts, this leads to the misdiagnosis of GERD chest discomfort as angina pectoris and vice versa [11]. Furthermore, coexistence of GERD and myocardial ischemia may predispose to myocardial ischemia by shifting the sympathovagal balance towards its parasympathetic component. This mechanism could trigger an esophagogastric-cardiac reflex, resulting in decreased myocardial perfusion [12]. The goal of this study was to look into the cardiac symptoms of GERD patients and to look into the independent correlates of reflux numbers in those patients.

PATIENTS AND METHODS

Between February 2019 and January 2020, 50 GERD patients were randomly recruited from the Gastroenterology Unit of the Internal Medicine Department at Assiut university hospitals for this cross-sectional study. Using the G*Power 3 software, the sample size was estimated [13]. The minimum required sample size for a 30 percent effect size in rate of cardiac involvement was 50 patients, with a power of 80 percent and a type I error of 5%.

Patients in the current trial had to be at least 18 years old, have GERD symptoms, and be free of cardiac symptoms and/or structural heart problems. Patients with ischemic heart disease (IHD), cancer patients, and those with a high risk of cardiac affection were also excluded (i.e., grand obesity).

Clinical and laboratory assessment:

The diagnosis of GERD was made based on the patient's medical history. All patients underwent a physical examination, as well as biochemical tests such as a complete blood count (CBC), serum electrolytes (sodium, potassium, magnesium, and calcium), kidney function tests (blood urea and serum creatinine), and ambulatory 24-hour oesophageal pH monitoring. Cardiac examination included: 12 leads ECG and 24 hours ECG monitoring (Holter).

Statistical analysis:

Data were verified, coded by the researcher, and analysed using IBM-SPSS 21.0 (IBM-SPSS Inc., Chicago, IL, USA) [14]. Means, standard deviations, medians, ranges, and percentages were determined as descriptive statistics. Test of significance: To compare the means of dichotomous data, an independent t-test analysis was used. The link between variables was tested using correlation analysis (Spearman's Rank correlation). The multivariable linear regression models included the clinical and demographic covariates that had statistical significance in the univariate analyses. When the p value is less than 0.05, it is deemed significant.

RESULTS:

A total of 50 patients were enrolled in this study. Of them 25 were males and 25 were females. The patient's age ranged between 26 and 58 years with a mean of 32.4 years. About half

(44%) of the sample were smokers. As regard co-morbidity, 22 of patients were diabetic (44%) while 28 patients were non-diabetic (56%). Also, 19 patients were hypertensive (38%) and 31 of patients were non-hypertensive (62%) **(Fig. 1)**.

For the ECG findings, it was found that the mean SDDN (R-R interval) was 100.1 ± 18.8. Patients with S-T depression represented 50% of the sample with mean S-T depression of 0.92 ± 0.01. Moreover, the findings of this study revealed that presence of GERD was associated with increase in risk of cardiac arrhythmia in 36 (72%) of patients while those without arrhythmia were 14 (28%) **(Fig. 2)**. Referring to the types of arrhythmia; the current work showed that 14 patients had premature atrial contractions (PACs) (28%) while 13 patients had premature ventricular contractions (26%). As well; 12% of the sample were found to have atrial tachycardia (n=6) while only two patients had ventricular tachycardia (4%) and only one patient had pause (2%). It was also found that the mean number of reflux episodes was 6.8 ± 0.7 **(Table 1)**.

Table. 2 showed the unadjusted multivariate linear regression analysis of the factors affecting reflux episode numbers. The intercept (reflux numbers) was 5.84 (95% CI: 1.3 – 26.9) after adjusting for all correlates (p=0.041). Moreover, with one-year increase in age there was 0.09 degree increase in reflux episodes and it was statistically non-significant (p=0.392). Males had insignificant 0.65 degree decrease in reflux episodes compared with female. For diabetic patient there was non-significant increase in reflux episodes by 3.23 degrees compared with non-diabetics. Also, hypertensive patients had 0.80 increase in reflux episodes compared with those with normal blood pressure and this was statistically insignificant (p=0.706).

Moreover, numbers of reflux episodes were insignificantly higher (1.20) in smokers than non-smokers. For heart rate, with one beat/minute increase, there was insignificant increase by (0.09) in reflux episodes. Additionally, with one unit increase in SDDN (Standard Deviation of Normal-to-Normal R-R Interval), there was non-significant increase in reflux episodes by 0.01.

On the other hand, patients with S-T depression had 4.36 degrees increase in the reflux episode numbers compared with those with normal ECG and it was statistically significant (p=0.038). Likewise, occurrence of arrhythmia was associated with statistically significant (p=0.031) increase in the reflux number by 4.97 degrees.

Table 3 showed the adjusted multivariate linear regression analysis of the significant factors affecting reflux number. After adjusting of all correlates there was still relationship between the presence of GERD and cardiac arrhythmia. In other words, in the final model and after adjusting for all correlates, the intercept (constant) was 15.81 (95% CI: 2.4 – 29.2, p =0.022). Moreover, with one-year insignificant increase in age there was increase in reflux episodes by 0.03 degree. For sex, males had non-significant lower reflux number (1.09) compared with fem.

Contrarily, there were significant correlation between the number of reflux episodes and presence of DM i.e., diabetic patient had significant higher reflux episode number (2.15) compared with non-diabetic and this was statistically significant (p=0.021). Likewise, for smoking, there was increase in reflux episode number by (2.90) compared with non-smoking with statistically significant results (p=0.032). Also, there were significant correlation between the number of reflux episodes and presence of ECG abnormalities i.e., patients with S-T depression/arrhythmia had increase in reflux episodes by (5.92 and 5.81, respectively) compared with those with normal ECG findings and this was statistically significant (p<0.001).
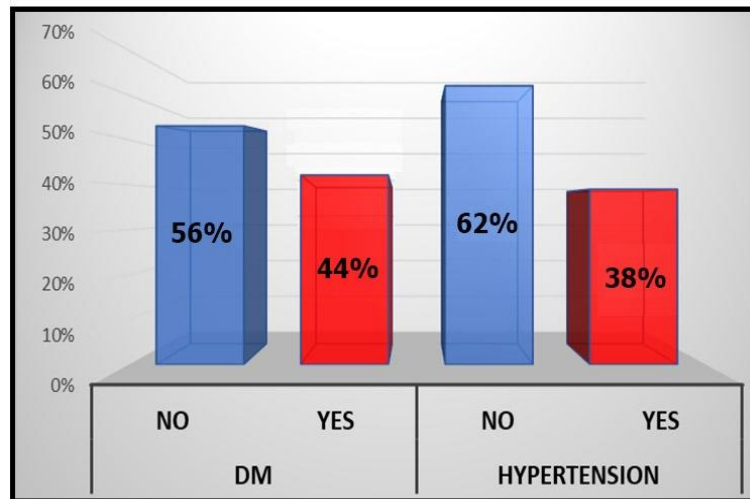
Fig. 1: Distribution of the sample according to Disease Frequency.
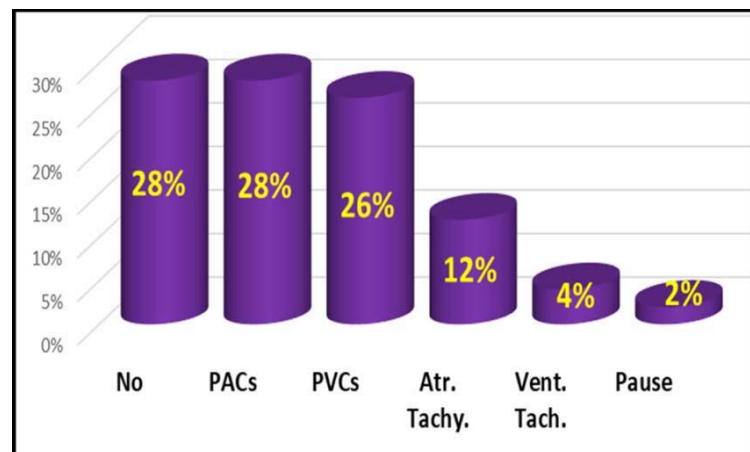
Fig. 2: Sample Distribution according to Types of Arrythmia.

Table (1): ECG Findings of the studied sample and reflux number .

Variable	Category	n = 50
SDDN (Standard Deviation of Normal-to-Normal R-R Interval)	• Mean ± SD	100.06 ± 18.8
	• Median (Range)	98 (65 - 145)
S-T Depression	• No	25 (50%)
	• Yes	25 (50%)
S-T Depression No.	• Mean ± SD	0.92 ± 0.2
	• Median (Range)	0.5 (0 - 5)
Arrythmia	• No	14 (28%)
	• Yes	36 (72%)
Type of Arrythmia	• PACs	14 (28%)
	• PVCs	13 (26%)
	• Atrial Tachycardia	6 (12%)
	• Ventricular Tachycardia	2 (4%)
	• Pause	1 (2%)
Reflux No.	• Mean ± SD	6.82 ± 0.7
	• Median (Range)	6.5 (1 - 18)

Table (2): Reflux Number dependent Predictors: Multiple Linear Regression Analyses .

		Estimate*	SE*	t-stat	P-value
Constant		5.835 (-15.31: 26.89)	10.42	0.560	= 0.041
•	Age	0.093 (-0.13: 0.31)	0.11	0.867	= 0.392
•	Sex (Male)	-0.654 (-4.22: 2.91)	1.76	-3.724	= 0.712
•	DM	3.225 (-0.67: 7.12)	1.92	1.679	= 0.102
•	Hypertension	0.800 (-2.33: 3.93)	1.54	0.519	= 0.706
•	Smoking	1.198 (-4.89: 2.50)	1.82	0.675	= 0.515
•	HR	0.091 (-0.04: 0.22)	0.06	1.428	= 0.162
•	SDDN	0.014 (-0.06: 0.09)	0.09	0.370	= 0.713
•	S-T Depression	4.362 (0.25: 8.48)	2.03	2.149	= 0.038
•	Arrythmia	4.971 (0.49: 9.46)	2.21	2.248	= 0.031

*CI= Confidence Interval   *SE= Standard Error

Table (3): Reflux Number Independent Predictors: Multiple Linear Regression Analyses .

		Estimate*	SE*	t-stat	P-value
Constant		15.814 (2.42: 29.21)	6.66	2.376	= 0.022
•	Age	0.028 (-0.14: 0.19)	0.09	0.324	= 0.747
•	Sex (Male)	-1.089 (-3.35: 1.18)	1.12	-0.969	= 0.338
•	DM	2.152 (1.08: 5.65)	0.89	1.985	= 0.021
•	Smoking	2.901 (0.96: 8.56)	0.81	2.459	= 0.032
•	S-T Depression	5.920 (3.68: 8.16)	1.11	5.323	< 0.001
•	Arrythmia	5.804 (3.24: 8.37)	1.82	4.551	< 0.001

*CI= Confidence Interval   *SE= Standard Error

DISCUSSION

The most prevalent gastrointestinal diagnosis is GERD, which is characterised by acid regurgitation and/or heartburn. Over the years, several explanations have been offered about how GERD may be linked to cardiac arrhythmia. Multiple investigations have found a relationship between vagal nerve stimulation and cardiac arrhythmia induction [1-3]. The link was observed to be especially strong in younger patients with greater vagal tone [16]. A probable link between GERD and the development of AF has been hypothesized due to the near proximity of the oesophagus and the atria [17-19]. The goal of this study was to see if there was a link between GERD and the occurrence of cardiac arrhythmias.

GERD and atrial fibrillation (AF) are two disorders that are frequently seen in clinical practice, and their link is being researched since they share several common variables like sleep apnea, obesity, and diabetes. Ludwig Roemheld was the first to identify the link between gastrointestinal symptoms and arrhythmias, coining the term "Roemheld gastro cardiac syndrome" to describe how an esophagogastric

stimulation could cause arrhythmia-related symptoms [20].

The link between GERD and AF, on the other hand, has not been proven consistently (16). In a small-scale population, the presence of GERD was found to raise the incidence of AF by 39 percent (relative risk, 1.39; 95 percent CI, 1.33–1.45), implying a close relationship between AF and GERD. However, Bunch et al. [21] found an inverse relationship between the presence of GERD and AF in a random sample of residents of Olmsted County, Minnesota.

Patients with GERD had a considerably higher incidence of cardiac arrhythmia than those without GERD, according to this study. Furthermore, GERD was linked to an increased chance of developing cardiac arrhythmia on its own. Acid stimulation of the oesophagus has been demonstrated to increase vagal afferent traffic and may play a role in the onset of atrial fibrillation paroxysms [22, 23]. This could be explained by increased vagal tone, as well as atrial inflammation, which may play a role in the development of AF.

Frustaci et al. demonstrated the existence of atrial inflammation in patients with known paroxysmal lone AF [24] with the identification

of myocarditis in 66% of right atrial septal biopsies taken from 12 patients with lone AF. Statin use was linked to a reduction in AF paroxysms, which supported this theory **[25]**. Furthermore, previous reports of atria-esophageal fistulas caused by percutaneous Tran's catheter ablation show the close closeness of these two structures and the possibility for inflammatory transmission **[26]**. The near proximity of the oesophagus and atria may theoretically provide a pathway for triggering atrial fibrillation paroxysms due to the inflammatory response associated with chronic GERD.

Few studies have been conducted over the past decade to investigate the role of GERD in AF. Weigl et al. **[27]** 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 two months after being endoscopically diagnosed with reflux esophagitis. In 78 percent of patients, at least one PAF-related symptom decreased or disappeared completely. Antiarrhythmic medicines were also stopped in five individuals, and no one needed a higher dose or a new prescription for an antiarrhythmic medication.

The association between intraesophageally decreases in pH and the onset of AF has also been described. Gerson et al. **[17]** studied three patients with symptoms of both palpitations and reflux who underwent simultaneous Holter and 24-hour pH monitoring while off acid suppressive therapy. On acid suppressive medication, all three patients reported a reduction in arrhythmia symptoms, with a substantial link between a drop in intraesophageal pH and the start of atrial fibrillation on Holter monitoring noted in two of the three patients.

Regarding to the link between GERD and AF, certain observational evidence may point to potential explanations. For starters, GERD may cause vagal nerve activation **[8]**. Also accumulating evidence suggested that the induction of AF may be related to vagal nerve over stimulation **[28]** and vagal nerve-mediate parasympathetic stimulation **[29]**. As a result, overstimulation of the vagal nerve, which has been reported in patients with GERD, could be to blame for the link between GERD and an increased risk of AF. Second, while the exact processes of AF are unknown, they have been

linked to inflammation [24]. The close anatomical relationship between the esophagus and the atria in addition to the local inflammatory process observed in GERD [30] theoretically provide a mechanism by which GERD initiates AF via the close positioning of the esophagus and the atria. Third, GERD may induce an autoimmune response that contributes to AF **[31]**. Fourth, acid stimulation of the lower esophagus could cause a significant reduction in coronary blood flow in patients with coronary artery disease **[32]** and chronic atrial ischemia has been proposed to predispose individuals to AF **[33]**.

The link between GERD and AF could be explained by patients who have an undetected hiatal hernia. Finally, AF may be clinically silent, causing it to be overlooked. GERD may be linked to clinically significant cardiac arrhythmia, according to our findings. There is still a need for studies that take clinically silent AF into account.

Although the exact mechanism by which GERD causes cardiac arrhythmia is unknown as most previous publications have discussed the link between GERD and AF as we mentioned before these two disorders are frequently seen in clinical practice. Unfortunately, no previous data have addressed the link between GERD and other types of cardiac arrhythmia to compare our finding with.

Meanwhile, many previous studied have addressed the link between GERD and coronary heart disease in general. Johansson et al. (2003) reported that the relative risk of myocardial infarction (MI) in GERD patients was 1.4 (95% CI, 1.0–1.9). The increased risk of MI was limited to the immediate days after GERD disease diagnosis. This indicates that prodromal ischaemic symptoms were misinterpreted as reflux symptoms **[34].**

The study of Chen et al., (2016) reported that GERD is associated with increased CHD development after adjustment of all confounding factors **[35]**.

There were pathophysiological mechanisms that might underlie the association between CHD and GERD. Firstly, in linked angina, exposure of the esophageal mucosa to acid and reduced lower esophageal sphincter pressure might compromise myocardial perfusion resulting from coronary spasm and cause arrhythmia through sympathetic

activation **[36-40]**. Also, myocardial ischemia can induce esophageal relaxation or dysmotility of the lower esophageal sphincter **[41]**. Secondary, many visceral pain receptors are polymodal and sensitive to mechanical distension, changes in temperature and acid. Esophageal and cardiac afferent sensory innervations entering the spinal cord can overlap, and thus stimulation of the heart or esophagus might be perceived and summed up over the dermatomes corresponding to either organ **[42]**. Thirdly, the association between GERD and sleep disturbances is interactive and bidirectional **[43]**, and it is well known that sleep apnea increases the risk of a cardiovascular event **[35]**. Finally, PPI use can reduce the metabolism of antiplatelet agents to their active form and hence reducing the cardioprotective effects of these drugs **[44-46]**. Also PPIs impairing the absorption of vitamin B12, this might increase homocysteine and hence reduce the contractility of myocardial tissue **[47]**. Moreover, the study of Chen et al., (2016) reported that PPI use might have an important effect on CHD, as the author found that the risk of CHD among the patients treated for > 1 year was greater than that of patients treated for less than 1 year **[35]**.

However, further investigations are needed to determine if GERD is a risk factor for increasing development of CHD and/or cardiac arrhythmia.

Limitations to this study include the cross-sectional nature that intimidate the external validity of the study.

Conclusion and Recommendations:

A hypocaloric diet containing olive oil should be In conclusion, there was a link discovered between GERD and the frequency of reflux episodes, as well as the incidence of cardiac arrhythmia and/or the expression of cardiac ischemia. Also diabetic smoker patients and patients with S-T depression are associate with increased reflux episodes.

Ethical Considerations:

Prior to the study's execution, the Ethical Committee of Assiut University's Faculty of Medicine gave its approval (IRB no. 08-31-016). After a thorough description of the study's objectives and methodology, all participants were asked to sign a written informed consent form. Anonymity and confidentiality were guaranteed. Every patient was told that he or she might join or leave the research at any time without facing any consequences. There were no implicit incentives or consequences. Data from the study is available upon request. The study conformed with the guidelines of the Helsinki Declaration **[15]**.

Highlights:

This study provide possible association between GERD and cardiac arrhythmia.

This finding needs to be confirmed in future prospective studies.

REFERENCES

1. Moayyedi P, NJ. Talley, Gastro-oesophageal reflux disease. *The Lancet* 2006; 367(9528): p. 2086-2100.

2. Hungin S, Molloy-Bland M, Scarpignato C. Revisiting Montreal: New Insights into Symptoms and Their Causes, and Implications for the Future of GERD. *The American Journal of Gastroenterology* 2019; 114(3): p. 414-421.

3. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *American Journal of Gastroenterology* 2013; 108(3): p. 308-328.

4. Hershcovici T, Fass R. Nonerosive Reflux Disease (NERD) - An Update. *Journal of neurogastroenterology and Motility* 2010; 16(1): p. 8-21.

5. Modlin IM, Hunt RH, Malfertheiner P, Moayyedi P, Quigley, Eamonn Martin, et al. Diagnosis and management of non-erosive reflux disease–the Vevey NERD Consensus Group. *Digestion*, 2009. 80(2): p. 74-88.

6. Dent J. Gastro-oesophageal reflux disease. *Digestion* 1998; 59(5): p. 433-445.

7. WHO, Department of Health Statistics and Informatics in the Information, Evidence and Research Cluster of the World Health Organization (WHO). *Global health risks: mortality and burden of disease attributable to selected major risks*, 2016.

8. Kontos MC. Evaluation of the Emergency Eepartment Chest Pain Patient. *Cardiology in Review* 2001; 9(5): p. 266-275.

9. Udelson JE, Beshansky JR, Ballin DS, Feldman JA, Griffith JL, Heller GV, et al. Myocardial perfusion imaging for evaluation and triage of patients with suspected acute cardiac ischemia: a randomized controlled trial. *JAMA* 2002; 288(21): p. 2693-2700.

10. Chahal PS, Rao SS. Functional chest pain: nociception and visceral hyperalgesia. *Journal of Clinical Gastroenterology* 2005; 39(5): p. S204-S209.

11. Liuzzo JP, Ambrose JA. Chest pain from gastroesophageal reflux disease in patients with coronary artery disease. *Cardiology in Review* 2005; 13(4): p. 167-173.

12. Dobrzycki S, Baniukiewicz A, Korecki J, Bachórzewska G, Prokopczuk P, Musial W, et al. Does gastro-esophageal reflux provoke the myocardial ischemia in patients with CAD? *International Journal of Cardiology* 2005; 104(1): p. 67-72.

13. Faul F, et al. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods* 2007; 39(1): p. 175-191.

14. IBM_SPSS, Statistical Package for Social Science. Ver.24. Standard version. Copyright © SPSS Inc., 2012-2016. *NY, USA*. 2016. 2016.

15. Association WM. World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. *Bulletin of WHO* 2001; 79(4): p. 373-374.

16. Chen PS, Tan AY. Autonomic nerve activity and atrial fibrillation. *Heart Rhythm* 2007; 4(3): p. S61-S64.

17. Gerson L, Friday K, Triadafilopoulos G. Potential relationship between gastroesophageal reflux disease and atrial arrhythmias. *Journal of Clinical Gastroenterology* 2006; 40(9): p. 828-832.

18. Gillinov AM, Rice TW. Prandial atrial fibrillation: off-pump pulmonary vein isolation with hiatal hernia repair. *The Annals of Thoracic Surgery* 2004; 78(5): p. 1836-1838.

19. Kunz JS, Hemann B, Edwin AJ, Jackson J, Wu T, Hamm C. Is there a link between gastroesophageal reflux disease and atrial fibrillation? *Clinical Cardiology: An International Indexed and Peer-Reviewed Journal for Advances in the Treatment of Cardiovascular Disease* 2009; 32(10): p. 584-587.

20. Jervell O, Lødøen O. The gastrocardiac syndrome. *Acta Medica Scandinavica* 1952; 142(S266): p. 595-599.

21. Bunch TJ, Packer DL, Jahangir A, Locke GR, Talley NJ, Gersh, BJ, et al. Long-term risk of atrial fibrillation with symptomatic gastroesophageal reflux disease and esophagitis. *The American Journal of Cardiology* 2008; 102(9): p. 1207-1211.

22. Bajwa A, Hollerbach S, Kamath MV, Upton AR, Fitzpatrick D, Fallen EL, et al. Neurocardiac response to esophageal electric stimulation in humans: effects of varying stimulation frequencies. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* 1997; 272(3): p. R896-R901.

23. Ramet J. Cardiac and respiratory reactivity to gastroesophageal reflux: experimental data in infants. *Neonatology* 1994; 65(3-4): p. 240-246.

24. Frustaci A, Chimenti C, Bellocci F, Morgante E, Russo MA, Maseri A. Histological substrate of atrial biopsies in patients with lone atrial fibrillation. *Circulation* 1997; 96(4): p. 1180-1184.

25. Siu CW, Lau CP, Tse HF. Prevention of atrial fibrillation recurrence by statin therapy in patients with lone atrial fibrillation after successful cardioversion. *The American Journal of Cardiology* 2003; 92(11): p. 1343-1345.

26. Pappone C, Oral H, Santinelli V, Vicedomini G, Lang CC, Manguso F, et al. Atrio-esophageal fistula as a complication of percutaneous transcatheter ablation of atrial fibrillation. *Circulation* 2004; 109(22): p. 2724-2726.

27. Weigl M, Gschwantler M, Gatterer E, Finsterer J, Stollberger C. Reflux esophagitis in the pathogenesis of paroxysmal atrial fibrillation: results of a pilot study. *Southern Medical Journal* 2003; 96(11): p. 1128-1133.

28. Kanoupakis EM, Manios EG, Mavrakis HE, Kaleboubas MD, Parthenakis FI, Vardas PE. Relation of autonomic modulation to recurrence of atrial fibrillation following cardioversion. *The American Journal of Cardiology* 2000; 86(9): p. 954-958.

29. Hou Y, Scherlag B, Lin J, Zhang Y, Lu Z, Truong K, et al. Ganglionated plexi modulate extrinsic cardiac autonomic nerve input: effects on sinus rate, atrioventricular conduction, refractoriness, and inducibility of atrial

fibrillation. *Journal of the American College of Cardiology* 2007; 50(1): p. 61-68.

30. Rieder F, Cheng L, Harnett KM, Chak A, Cooper GS, Isenberg G, et al. Gastroesophageal reflux disease–associated esophagitis induces endogenous cytokine production leading to motor abnormalities. *Gastroenterology* 2007; 132(1): p. 154-165.

31. Maixent JM, Paganelli F, Scaglione J, Levy S. Antibodies against myosin in sera of patients with idiopathic paroxysmal atrial fibrillation. *Journal of Cardiovascular Electrophysiology* 1998; 9(6): p. 612-617.

32. Chauhan A, Mullins PA, Taylor G, Petch MC, Schofield PM. Cardioesophageal reflex: a mechanism for "linked angina" in patients with angiographically proven coronary artery disease. *Journal of the American College of Cardiology* 1996; 27(7): p. 1621-1628.

33. Nishida K, Qi XY, Wakili R, Comtois P, Chartier D, Harada M, et al. Mechanisms of atrial tachyarrhythmias associated with coronary artery occlusion in a chronic canine model. *Circulation* 2011; 123(2): p. 137-146.

34. Johansson S, Wallander MA, Ruigomez A, Garcia-Rodriguez LA. Is there any association between myocardial infarction, gastro-oesophageal reflux disease and acid-suppressing drugs? *Alimentary Pharmacology & therapeutics* 2003; 18(10): p. 973-978.

35. Chen CH, Lin CL, Kao CH. Association between gastroesophageal reflux disease and coronary heart disease: A nationwide population-based analysis. *Medicine*, 2016. 95(27).

36. Chauhan A, Petch MC, Schofield PM. Effect of oesophageal acid instillation on coronary blood flow. *The Lancet* 1993; 341(8856): p. 1309-1310.

37. Manisty C, Hughes-Roberts Y, Kaddoura S, Cardiac manifestations and sequelae of gastrointestinal disorders. *British Journal of Cardiology* 2009; 16(4).

38. Garcia-Pulido J, Batel PH, Hunter WC, Douglas JE, Thomas E. Esophageal contribution to chest pain in patients with coronary artery disease. *Chest* 1990; 98(4): p. 806-810.

39. Singh S, Richter JE, Hewson EG, Sinclair JW, Hackshaw BT. The contribution of gastroesophageal reflux to chest pain in patients with coronary artery disease. *Annals of Internal Medicine* 1992; 117(10): p. 824-830.

40. Mehta AJ, de Caestecker JS, Camm AJ, Northfield TC. Gastro-oesophageal reflux in patients with coronary artery disease: how common is it and does it matter? *European Journal of Gastroenterology & Hepatology* 1996; 8(10): p. 973-978.

41. Liu Y, He S, Chen Y, Xu J, Tang C, Tang Yi, et al. Acid reflux in patients with coronary artery disease and refractory chest pain. *Internal Medicine* 2013; 52(11): p. 1165-1171.

42. Foreman RD, Ohata CA. Effects of coronary artery occlusion on thoracic spinal neurons receiving viscerosomatic inputs. *American Journal of Physiology-Heart and Circulatory Physiology* 1980;. 238(5): p. H667-H674.

43. Fujiwara, Y, Arakawa T, Fass R. Gastroesophageal reflux disease and sleep disturbances. *Journal of Gastroenterology* 2012; 47(7): p. 760-769.

44. Sossalla S, Schotola H, Schmitto J, Toischer K, Sohns C, Schwörer H, et al. Effects of different proton pump inhibitors on cardiac contractility in isolated human failing myocardium. *The Journal of Cardiovascular Surgery* 2011; 52(3): p. 437-444.

45. Schillinger W, Teucher N, Sossalla S, Kettlewell S, Werner C, Raddatz D, et al. Negative inotropy of the gastric proton pump inhibitor pantoprazole in myocardium from humans and rabbits: evaluation of mechanisms. *Circulation* 2007; 116(1): p. 57-66.

46. Chou TC. New mechanisms of antiplatelet activity of nifedipine, an L-type calcium channel blocker. *BioMedicine*, 2014. 4(4): p. 1-8.

47. Ito T and Jensen RT. Association of long-term proton pump inhibitor therapy with bone fractures and effects on absorption of calcium, vitamin B2, iron, and magnesium. *Current gastroenterology reports*, 2010. 12(6): p. 448-457.

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