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The Association of High Burden Premature Ventricular Contractions with Esophageal/Upper GI Diseases

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Abstract: Six patients in our clinical program who were diagnosed with high burden (>10%) premature ventricular contractions (PVCs) and concomitant significant upper GI disease with no other significant cardiac history demonstrated a significant reduction in the burden of PVCs following surgical or procedural interventions of the upper GI tract (68.34% reduction, $p = 0.024$). Furthermore, in all cases, the origin of the PVCs was from the base of the right ventricular outflow tract (RVOT). This is the first report in the literature that we are aware of that makes the unique association that we propose a dual mechanism of action of the upper GI and vagally mediated PVCs and through direct, anatomical extrinsic triggering of the right ventricular outflow tract (RVOT) of the heart. These are very preliminary findings that warrant larger clinical and mechanistic studies that if confirmed, may define a new physiologic subset of PVCs for which we propose a new term, "E-PVCs".

Keywords: premature ventricular contractions; vagus nerve; esophageal disease; upper GI disease

Citation: Khimani, F.; Kulkarni, C.; Haase, E.; Moore, P.; Murdock, P.; Ramanathan, A.; Wolf, A.; Sathyamoorthy, M. The Association of High Burden Premature Ventricular Contractions with Esophageal/Upper GI Diseases. *Hearts* **2024**, *5*, 516–528. https://doi.org/10.3390/hearts5040038

Academic Editor: Matthias Thielmann

Received: 22 July 2024
Revised: 28 September 2024
Accepted: 13 October 2024
Published: 29 October 2024

1. Introduction

Premature ventricular contractions (PVCs) are common in the general population. In fact, if monitored for more than a few hours, PVCs are observed broadly, as demonstrated in a population-based cohort of adults aged 25–41 years old who had 24-h Holter monitoring. Of all participants, 69% had at least one PVC with a median count of 2 PVCs, and the 95th percentile had 193 PVCs [1]. In the Cardiovascular Health Study that followed patients for 14 years, patients aged 65 years and older in the general population underwent 24-h Holter monitoring and were found to have PVCs comprising a median of 0.011% of all heart beats [2]. Though PVCs are often viewed as benign by clinicians, a multiracial community-based cohort of more than 15,000 individuals revealed a higher risk of coronary artery disease events and death in those with the presence of a PVC [3]. The Cardiovascular Health Study also found that a higher frequency of PVCs was linked with a 5-year reduction in left ventricular systolic function (measured by left ventricular ejection fraction), increased risk for heart failure, and increased risk for death [2].

2. Physiologic Mechanisms of PVCs

The mechanism of PVCs is multifactorial, and is related to extrinsically triggered activity, automaticity, and reentry [4]. Triggered mechanisms include behavioral (sympathetic stress) or from underlying diseases, induced by increased intracellular calcium

in the plateau phase of the action potential during prolonged repolarization. PVCs generated in this setting may cause torsade's de pointes or acquired long QT syndrome [5]. The increased intracellular calcium is typically a result of activation of cAMP-dependent protein Kinase A, so this mechanism is often a target of induction or termination of PVCs. For example, caffeine can result in delayed after-depolarization due to calcium release from the sarcoplasmic reticulum [6]. On the other hand, adenosine inhibits the production of adenylyl cyclase, which in turn reduces cAMP release; therefore, it is useful in the termination of PVCs [7]. Catecholamines also play a role in the induction of calcium release, so beta-blockers (β-blocker) are a useful targeted therapy for triggered activity [8]. Likewise, non-dihydropyridine calcium channel blockers (CCB) prevent intracellular calcium accumulation via blockage of L-type calcium channels [8] and are sometimes utilized for therapy. PVCs related to automaticity are present with parasystole, occurring at the same cycle length [9]. The automaticity mechanism is multifactorial, ranging from an exaggeration of baseline cardiomyocyte automaticity to electric isolation like that seen in fibrosis. PVCs occurring through reentry require the presence of two electrical pathways and a temporary or permanent unidirectional block in one pathway. This may involve pathology in the fascicles that produces a fascicular PVC, or an area of fibrosis, where a series of cardiomyocytes are electrically connected creating slower conduction pathways, resulting in a PVC.

Idiopathic PVCs have often been linked to increased sympathetic nervous system activity [10]. Gillis et al. demonstrated that increased ventricular irritability in cats was associated with increased firing of the sympathetic nervous impulses in the cardiac system [11]. Estes and Izlar showed that ventricular tachycardia episodes in a patient were terminated by bilateral cardiac sympathectomy [12]. Although the impact of the sympathetic nervous system has been extensively studied, the role of the parasympathetic system in PVCs is still largely unexplored. The currently available data thus far indicates that some patients have vagally suppressible PVCs, while others have vagally inducible PVCs. Weiss et al. demonstrated that 5 out of 10 patients had a statistically significant decrease in PVCs with phenylephrine-induced increase in reflex vagal tone [13]. However, in the same study, atropine, a muscarinic antagonist that blocks cardiac vagal nerve activity, also reduced the burden of PVCs. He et al. suggested that PVCs were evoked by sudden fluctuations in autonomic balance, and when separated by type, fast rate-dependent PVC (F-PVC) might be facilitated by sympathetic activation, while slow rate-dependent PVC (S-PVC) might be induced by vagal activation [14]. In this case series, patients are presented with pathologies (gastroesophageal reflux disease (GERD), achalasia, and gastric lap-band placement) in the distal esophagus that may have triggered a neural reflex mediated by the vagus nerve. The reflex allows changes in gastric and esophageal mechanoreceptors to send powerful vagal-mediated inhibition to the lower esophagus and lower esophageal sphincter, which results in lower parasympathetic vagal input to the alimentary and cardiovascular systems [15]. We postulate that this mechanism results in a high burden of S-PVCs via suppression of the parasympathetic nervous system.

3. Cardio-Physiologic Consequences of PVCs

The electromechanical coupling of cardiac function hinges upon the orchestrated stimulation initiated by the sinoatrial (SA) node, which causes the sequential contraction of atrial myocardium. Following this, a transient delay at the atrioventricular (AV) node facilitates ventricular filling, crucial for optimizing cardiac output. Subsequently, the propagated electrical impulse traverses the bundle of His and Purkinje fibers, stimulating ventricular contraction. This process is known as excitation–contraction coupling (ECC) [16].

The synchronization of ECC is paramount because it ensures adequate ventricular filling, which is requisite for optimal stroke volume [17]. Premature ventricular contractions disrupt this synchrony, precipitating ventricular depolarization prior to complete diastolic filling, thereby compromising stroke volume [18], and when PVC burden is significant, decrease cardiac output [19]. This hemodynamic disturbance can result in reduced arterial

pressure, impeding tissue perfusion, and precipitating clinical manifestations such as palpitations, syncope, and fatigue (Figure 1) [20,21].

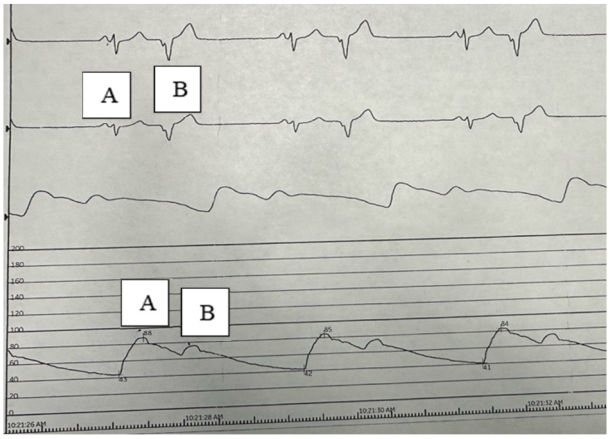

Figure 1. In this particular hemodynamic tracing from a catheter placed in the ascending aorta, note that the typical anterograde conducted sinus beat (labeled A) with a corresponding arterial systolic pressure is 88 mmHg (labeled A). In a Post PVC beat (labeled B), the arterial pressure declines to 70 mmHg, representing a 21% decrease in perfusion pressure.

4. Clinical Features and Therapies

PVCs are typically diagnosed as an incidental finding or during evaluation of clinical symptoms, including palpitations, chest discomfort, presyncope, dyspnea, and fatigue [22]. The discomfort experienced by patients is usually due to the strong heartbeat that follows the increased filling time after the PVC. Patients may also present with abrupt syncope, and very rarely, sudden arrhythmic death from PVC-induced ventricular fibrillation. On physical exams, one may find apparent bradycardia ascertained by a palpable pulse alone, occurring from a poorly perfused PVC. PVCs are diagnosed via a 12-lead electrocardiogram (ECG). The gold standard for assessing PVC frequency used to be a 24-h Holter monitor; however, recent evidence has demonstrated that due to substantial daily variation, the duration of monitoring should be extended (>5 days) [23].

Current guidelines suggest that management of PVCs may be pursued if the patient is symptomatic, presents with a high burden of PVC, or has PVCs accompanied by structural heart disease. First-line medical therapy involves either β-blockers, calcium CCBs, or flecainide [24]. However, patients with F-PVC are more likely to benefit from this treatment, likely because it is mediated by the sympathetic nervous system [25]. In general, catheter ablation procedures have a success rate of 80–95%, while β-blockers only have a success rate between 12–24% [26]. If pharmacologic treatment is ineffective for higher burden (>15%), catheter ablation is considered, providing superior effectiveness but also requiring acquiescence to procedural risks [27–29]. Patients who are opposed to cardiac ablation, have failed the procedure, or are unfavorable candidates may be trialed on additional antiarrhythmics [27–29].

5. Genetic Associations

The genetic mechanisms contributing to PVCs encompass variations within genes encoding cardiac ion channels that are responsible for the intricate electrical signaling within cells. Notably, genetic mutations in genes such as SCN5A, which is integral to sodium channels, and KCNQ1/KCNE1, which form potassium channels, are key contributors to PVC development. These mutations have the potential to disrupt the finely orchestrated cardiac rhythm, thereby precipitating the premature contractions characteristic of PVCs. However, PVCs can also be influenced by non-genetic factors such as structural heart disease, electrolyte imbalances, and stimulants, further underscoring the intricate blend of factors at play [30]. Within this genetic landscape, SCN5A serves as a critical determi-

nant, encoding the sodium channel Nav1.5 that plays a pivotal role in orchestrating the rapid depolarization phase during the cardiac action potential. Genetic variations within SCN5A have the potential to perturb the flow of sodium ions, culminating in irregular electrical activity and the emergence of arrhythmias like PVCs. KCNQ1 and its interacting partner KCNE1 form the potassium channel Kv7.1, indispensable for efficient repolarization of cardiac cells. Genetic mutations affecting these genes can potentially prolong the repolarization phase, creating an environment conducive to arrhythmias [30–32].

To probe these genetic contributions, a study of 100 post-MI patients included clinical genetic assessments alongside a range of more common cardiac diagnostic evaluations. As depicted in Figure 2, the examination of genetic polymorphisms revealed significant findings within the SCN5A, KCNE1, and KCNQ1 genes. Specifically, polymorphisms like H558R in SCN5A, S38G in KCNE1, and intronic variations in KCNQ1 were identified. Remarkably, these polymorphisms were closely linked to anomalies in the QT interval, characterized by both QT prolongation and an increase in QT dispersion. Despite these associations, the study's intriguing outcome illuminated that these genetic variations, while influencing repolarization patterns, did not manifest a direct correlation with complex ventricular arrhythmias, sudden cardiac arrest, or sudden cardiac death in post-MI patients [32]. These collective findings underscore the intricate relationship between genetic predisposition, the intricate cardiac electrophysiological landscape, and the development of PVCs and related conditions. While genetic variations significantly contribute to the subtle nuances of repolarization patterns and gastrointestinal dysfunctions, the genesis of PVCs emerges from a complex interplay involving genetic factors, acquired conditions, and external triggers. This intricate interplay highlights the layered complexity in the origination and progression of cardiac arrhythmias and related conditions, epitomizing the multifaceted nature of these events.

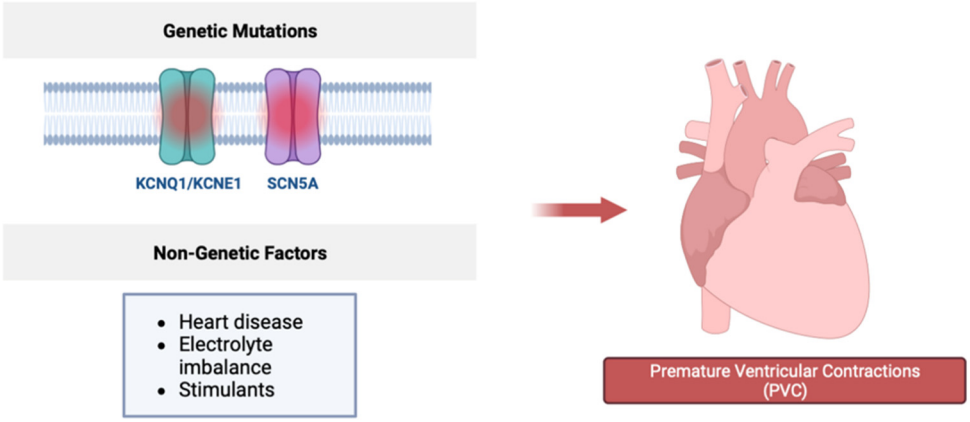

Figure 2. Genetic factors including mutations in the SCN5A gene, encoding essential components of voltage gated sodium channels, or KCNQ1/KNCE1, which encode components of potassium channels, may be responsible for PVC formation. Other non-genetic factors that contribute to PVC formation include structural heart disease, electrolyte imbalance, and stimulant use.

In this report, we present six cases where we observed a significant reduction in PVCs following esophageal/upper GI procedures and/or surgery, presenting evidence for the first time, to our knowledge, of this novel association between cardiac electrophysiology and gastrointestinal anatomical diseases.

6. Methods

6.1. Clinical Subject Selection

After obtaining IRB approval from the TCU IRB, we reviewed the charts of subjects who had high PVC burden (defined in this study as >10%) who also had concomitant upper GI disease requiring procedural or surgical intervention. We reviewed their clinical

symptoms, progress, and cardiac data pre- and post-procedure, with a focus on continuous rhythm monitoring (Holter) data.

6.2. Statistics

Descriptive statistics were utilized to summarize patient characteristics and PVC burden distributions. The primary analysis focused on assessing the mean reduction in PVC burden post-intervention. A paired *t*-test or Wilcoxon signed-rank test was employed to compare baseline and post-intervention PVC burden. Statistical significance was determined at a threshold of $p < 0.05$ (see Table 1 and Appendix A).

Table 1. Reduction in PVC burden by 68.34% [$p = 0.024$] in this patient series after Esophageal/Upper GI interventions.

Age	Sex	GI Pathology	Esophageal Intervention	Baseline PVCs (%)	Post Intervention PVCs (%)	% Decline	*p*-Value
60	F	Hiatal hernia	LINX repair	26.00	<0.01	99.96	
46	F	Achalasia	Esophageal dilation	17.00	<1.0	94.11	
62	F	Lap-band	Lap-band removal	20.00	10.70	46.50	
74	M	Esophageal stenosis	Esophageal dilation	12.29	7.70	37.34	
67	F	Hiatal hernia	Hernia repair	12.4	2.6	79.03	
69	M	Esophageal stenosis	Esophageal dilation	23.7	11.0	53.5	
						68.34%	**0.024**

Ordinary least squares interrupted time series analysis was also employed to examine the temporal trends in PVC burden before and after esophageal interventions. It considers potential confounders and provides insight into the longitudinal effects of interventions on PVCs. This was made possible by the data in Table 1 and draw.io software (https://app.diagrams.net/).

6.3. EKG Analysis

Based on current understanding, the RVOT's anterior location places it closer to leads V1 and V2 compared to the LVOT, which results in ventricular arrhythmias originating from the RVOT displaying a deeper S wave and a smaller R wave in these leads. In contrast, the more distant position of the LVOT leads to ventricular arrhythmias that present with a higher R wave and a smaller S wave in V1 and V2. This principle was applied when interpreting the EKG to suggest an RVOT origin of the PVC burden, with a reported sensitivity of 95.1% and a specificity of 85.5% [33].

7. Case Descriptions

7.1. Subject 1—Index Case

A 60-year-old female with no previous cardiac history presented with an abnormal heart rate reading of 40 bpm and persistent palpitations. Her relevant history included gastroesophageal reflux disease and gastritis with no family history of arrhythmias or sudden cardiac death. Her initial cardiac evaluation in another program showed a 12-lead EKG with sinus rhythm without proarrhythmic features and normal conduction intervals but with frequent, unifocal RVOT basal PVCs. An initial echocardiogram and nuclear perfusion stress test were reported as normal, the index Holter demonstrated a unifocal PVC burden of 26%, and she did not tolerate an initial trial of β-blockers. She had severe GERD secondary to a large hiatal hernia that was refractory to conservative therapies, and subsequently underwent a LINX surgical procedure, which is a magnetic sphincter augmentation system (MSA) used in the treatment of refractory GERD [34]. She established care in our program, and in a follow-up visit after the LINX, she reported a significant

decline in her palpitations. Curious, we repeated a Holter study, showing a <1% burden of PVCs, followed by a Holter one year later demonstrating a <0.01% burden of PVCs. There were no interval changes in medications, laboratory data, or clinical conditions that accounted for this difference. We believed that her PVCs may have been associated with her esophageal pathology and began observing other patients for similar patterns in an IRB approved study.

7.2. Subject 2

A 46-year-old female with history of achalasia and hypothyroidism presented with palpitations. Her resting 12-lead EKG demonstrated sinus rhythm with no proarrhythmic features and normal conduction intervals, but frequent PVCs that appeared to originate from the base of the right ventricular outflow tract. Her echocardiogram demonstrated a structurally and functionally normal heart, and her stress echocardiogram was without ischemia and notable for exercise phase suppression of PVCs. Her index Holter monitor demonstrated a PVC burden of 17%. During this time, the patient elected to undergo an esophageal dilation to treat her achalasia. At a subsequent follow-up visit with us, our patient reported a significant improvement in her symptomatic palpitations. A repeat 7-day patch Holter revealed a near resolution of PVCs with a burden of <1%. There were no interval changes in medications, laboratory data, or clinical conditions.

7.3. Subject 3

A 62-year-old female with a history of hypothyroidism and remote history of a lap-band presented with intermittent palpitations and moderate to severe reflux. Her resting 12-lead EKG demonstrated sinus with no proarrhythmic features and normal conduction intervals with frequent PVCs originating from the base of the RVOT [Figure 3]. A Holter demonstrated a 20% unifocal PVC burden, and her echocardiogram demonstrated a structurally and functionally normal heart. A high-resolution coronary computed tomography angiogram (CCTA) demonstrated no obstructive epicardial coronary artery stenosis, myocardial bridging, or coronary anomalies. The study did identify a dilated fluid-filled esophagus concerning obstruction at the level of gastric lap-band. We trialed a β-blocker, without any significant symptom relief, and eventually referred her for surgical removal of her lap-band, which resulted in a significant reduction in her symptomatic palpitations. A repeat Holter showed a decline in PVCs to 10.7% and we anticipate a further reduction in PVCs in her next study.

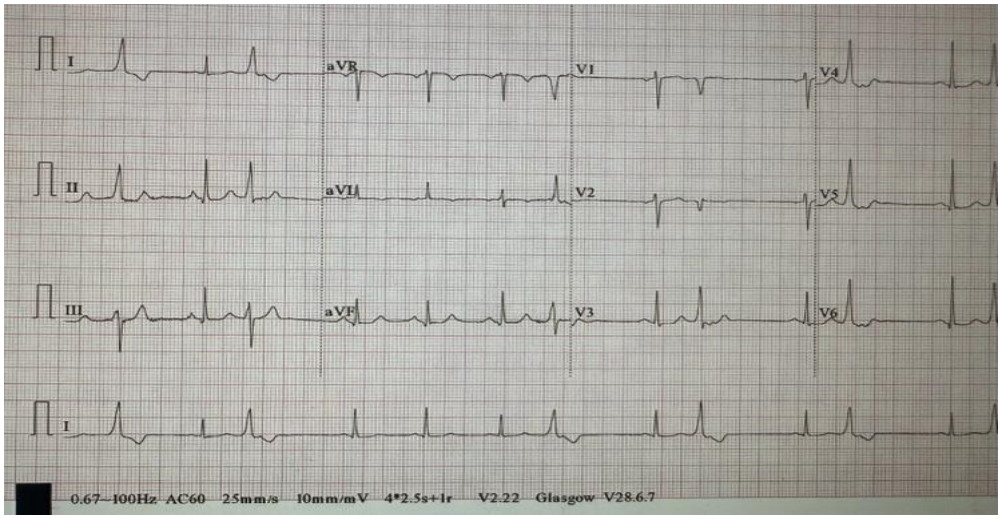

Figure 3. An EKG from one of the subjects demonstrating sinus rhythm with frequent PVCs that appear to originate from the base of the RVOT.

7.4. Subject 4

A 74-year-old African American male with a history of gastritis, hypercholesterolemia, hypertension presented with occasional palpitations, dysphagia, and chest discomfort. His EKG demonstrated sinus with no proarrhythmic features and normal conduction intervals without PVCs. An initial 7-day Holter monitor revealed a PVC burden of 12.3%. An echocardiogram demonstrated mild aortic valve insufficiency, but normal LV (Left Ventricle) dimensions and intracardiac pressures. He underwent a CCTA demonstrating an elevated calcium score (>500) and moderate to severe angiographic disease; subsequent cardiac catheterization revealed no significant intraluminal coronary artery disease with calcium being largely extraluminal. We advised conservative management of his PVCs. Given his ongoing dysphagia, we referred him to our GI colleagues, who identified esophageal disease requiring esophageal dilation resulting in amelioration of all symptoms. A repeat 7-day Holter monitor post-esophageal dilation revealed a decline in PVC burden to 7.7%.

7.5. Subject 5

A 67-year-old female patient with a history of reflux was referred to our practice for evaluation of palpitations and angina. Her initial EKG demonstrated sinus with frequent PVCs originating from the base of the RVOT. Her echo demonstrated a structurally and functionally normal study. Given her symptom profile and overall risk assessment, we elected for non-invasive coronary anatomical and flow risk assessment with a high-resolution CCTA, which demonstrated angiographically normal coronaries with normal flow. An index 7-day patch Holter demonstrated a high burden of unifocal PVCs matching EKG morphology at 12.4% and no other arrhythmias. She did not respond to initial β-blocker therapies. Her CT demonstrated a large hiatal hernia, and after additional GI evaluation, she was referred for surgical intervention. After surgery, she noted a clinical improvement in her palpitations, and a repeat Holter examination demonstrated a decline in PVC burden to 2.6%.

7.6. Subject 6

A 69-year-old African American established patient in our practice with a history of HTN, hiatal hernia s/p repair noted chest pressures with anginal type features. His EKG demonstrated sinus with frequent PVCs originating from the base of the RVOT, his repeat echo demonstrated no changes from a prior structurally and functionally normal study. A Holter demonstrated a 24% unifocal PVC burden without other arrhythmias. We proceeded with a high-resolution CCTA, which demonstrated angiographically normal coronaries with normal flow and no significant extraluminal coronary artery calcium. We suspected an esophageal etiology of his symptoms and after GI evaluation, he underwent an esophageal dilation. He noted an immediate improvement in palpitations and resolution of chest pains. A repeat Holter demonstrated a decline in PVC burden to 11%.

In each subject, obstructive sleep apnea was confirmed to be absent either by documented sleep study or by clinical criteria, or if present, adequately treated by continuous positive airway pressure.

8. Discussion

The autonomic nervous system has been hypothesized to play a significant role in pathogenesis, maintenance, and interference in ventricular arrhythmias. The vagus nerve contributes to the formation of the esophageal plexus, innervating the smooth muscle of the esophagus, and notably gives off cardiac branches, regulating heart rate through the parasympathetic nervous system. One case study reports the association between cardiac arrhythmias and vagus nerve stimulation in patients with GERD symptoms [35] by discussing a patient with GERD-like symptoms that developed PVCs, postulating that the pathophysiology of PVC was secondary to reflux stimulating the vagus nerve resulting in this arrhythmia.

The vagus nerve is the tenth cranial nerve and is a major component of the parasympathetic nervous system, which is responsible for slowing the heart rate and reducing cardiac output [36]. The right and left vagi originate in the medulla oblangata, passing through the jugular foramen, traveling alongside the carotid through the superior thoracic aperture into the thoracic cavity [37]. There, they join into the anterior and posterior vagal trunks of the esophageal plexus. The vagal trunks course around the esophagus and innervate the heart at the level of the atria, where they directly communicate with the SA and AV nodes [37] (Figure 4A). The AV node subsequently communicates with the bundle of His, thereby controlling ventricular heart rate. It is important to note that the precise anatomical relationships can vary somewhat among individuals, and there may be some variability in the proximity of the vagus nerve branches and the right ventricle. When stimulated, the vagus nerve releases the neurotransmitter acetylcholine, and subsequently binds to muscarinic receptors largely in the SA and AV node, leading to both a negative chronotropic and inotropic effect. The primary effects of vagal stimulation on the heart, including changes in heart rate and conduction, are generally associated with its interactions with the AV node [36]. While a principle use of vagal nerve stimulation is for cessation of epileptic disorders, vagal nerve stimulation has also been shown to help with various cardiac abnormalities including heart failure, dysrhythmia, and cardiac arrest. The use of vagal nerve stimulators showcases the vital role that the vagal nerve plays in cardiac function [36].

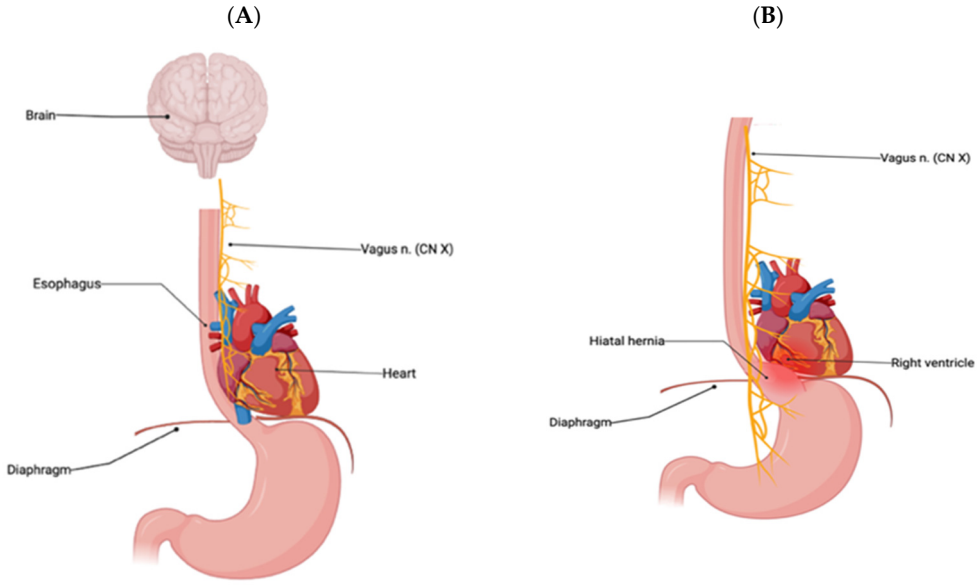

Figure 4. (**A**). Normal anatomic relationships of diaphragm, esophagus, vagus nerve, and heart. Note the very close anatomical proximity of the anterior esophagus to the vagus nerve to the posterior aspect of the right heart, in particular, the posterior aspect of the right ventricular outflow tract. (**B**). A hiatal hernia compressing the vagal nerve along with closer proximity to the right ventricle and posterior aspect of the RVOT in this altered anatomical state [38–40].

A portion of the vagus nerve continues past the heart, following the path of the esophagus to innervate some of the contents of the abdominal cavity. The vagal nerve esophageal plexus courses around the esophagus, directly innervating the esophagus and governing its peristalsis [38]. The anterior and posterior vagal trunks pass into the abdomen through the esophageal hiatus of the diaphragm at the level of T10, sharing this opening with the esophagus [39] (Figure 4A). Hiatal hernias are a protrusion of a portion of the stomach through the esophageal hiatus into the thoracic cavity. This can cause increased pressure on the vagal nerve, particularly as the size of the hernia increases. This can propel the vagal nerve cranially, leading to increased pressure on and irritation of the vagal nerve by the hiatal hernia [40,41] (Figure 4B).

Our study presents a series of six subjects with esophageal disease who had an otherwise idiopathic PVC burden, that notably appeared to originate from the base of the RVOT by 12-lead EKG criteria in all subjects. In all cases, a standard evaluation excluded cardiac structural abnormalities or pulmonary pathologies. We observed that when these patients' esophageal diseases were treated with procedural or surgical intervention, there was a spontaneous reduction in PVC burden by Holter monitoring as noted in Figure 5. After these esophageal/upper GI interventions, we observed a 68.34% mean reduction in PVC burden in this cohort, as well as a decline in symptoms reported by the patients. Given our observation, we sought to explain this reduction in PVC burden by hypothesizing possible mechanisms by which treating esophageal disease subsequently improves cardiac conduction.

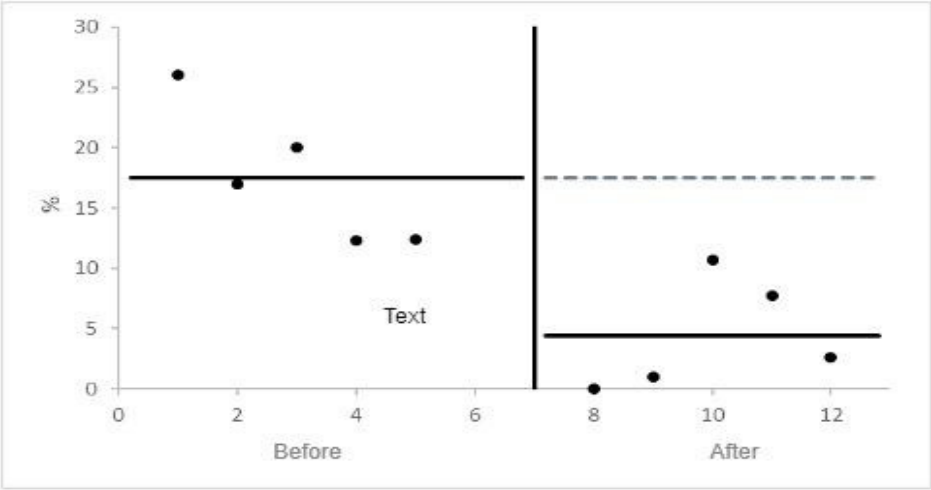

Figure 5. PVC burden before and after Upper GI/esophageal interventions by Ordinary Least Squares Interrupted Time Series Analysis.

The esophagus, vagus nerve, and the right ventricle are all adjacent structures and so it stands to reason that pathology in one could have detrimental effects on the other structures. There are reports of esophageal pathology stimulating vagal nerve parasympathetic action on the heart. For example, deglutition syndrome or swallow syncope is a condition in which patients with gastrointestinal disease such as hiatal hernia, achalasia, and esophageal cancer had syncopal episodes following the ingestion of foods or liquids [42]. The pathophysiological mechanism of swallow syncope is thought to be vagal stimulation from increased esophageal pressure causing reflex bradycardia and hypotension [43]. However, some reports describe deglutition syndrome resulting in complete heart block or supraventricular tachycardia [44,45]. With larger paraesophageal hernias, there can be increased pressure on the left atrium and therefore decreased cardiac output [40].

Other studies have shown a correlation between hiatal hernia with GERD and atrial fibrillation (AF) [46]. The treatment of hiatal hernia and GERD by either surgical intervention or proton pump inhibitor was found to relieve AF in several cases [46–48]. While the exact mechanism is currently not known, one proposed mechanism for the association between GERD and AF is that esophageal inflammation releases cytokines that stimulate the vagus nerve, affecting cardiac rhythm [49]. Another hypothesis is that a hiatal hernia can physically irritate the vagus nerve or heart by direct contact, thereby causing dysrhythmia [35]. Though there have been discussions of atrial arrhythmias due to gastrointestinal disorders, there is a paucity in the literature discussing ventricular arrhythmias and upper GI disorders.

Our patients all demonstrated PVCs in relation to upper GI disorders, as evidenced by relief of cardiac symptoms after treatment of GI disease. One commonality is that all of these patients' GI dysfunction can lead to an increase in esophageal size, especially post-prandially. The increased esophageal size places direct anatomical pressure on the

vagal nerve, leading to vagal nerve stimulation resulting in parasympathetic cardiac effects (Figure 4B). Two of the patients in our study underwent esophageal dilation, with complete relief of PVCs symptoms after, suggesting that direct effects on the vagal nerve played a role in their symptomatic PVCs. While we cannot ascertain if this anatomical pressure caused stimulation or inhibition, we believe that pressure on the vagus nerve leads to stimulation of mechanoreceptors resulting in bradycardia-induced PVCs [50]. All of our patients experienced a significant decline and/or symptomatic relief of PVCs after a surgical intervention that almost surely decreased mechanical pressure on the vagus nerve [51].

Curiously, all of our patients' PVCs appeared to originate from the base of RVOT. In normal anatomy, there is no relationship between the esophagus and RVOT in the mediastinum. However, in the setting of significant esophageal dilation or a large hiatal hernia, posterior–anterior directed compression from the esophagus/upper GI abnormality directed against the right ventricle resulting in RVOT irritation is theoretically feasible. This affected tissue in the RVOT may potentially create a reentry circuit, which is a known cause of PVCs [4]. All of our patients' RVOT basal PVCs resolved with procedural GI management, lending to our hypothesis that esophageal/upper GI anatomical abutment of the RV induced a potential reentry circuit leading to these stereotypic PVCs. Remediation of the esophageal/upper GI disorder directly relieved this mechanical pressure on the RVOT, resulting in the consistently observed reduction in PVCs.

9. Limitations

Limitations of our study include a very small sample size of retrospective cases that require significantly larger clinical studies and more definitive mechanistic investigation before generalization to a larger population. Our study simply makes an association between esophageal disorders and PVCs and does not prove causality between the two disorders. Furthermore, there may be a natural fluctuation in PVC burden; patients are often evaluated with high symptoms and PVC burden with a reduction over time, which may simply be due to regression to the mean. However, the novelty of the data reported in this paper should generate interest in pursuing these larger studies to confirm this novel and preliminary finding. Additionally, these patients are being followed as subjects currently and we anticipate a follow-up paper with these monitoring/clinical results. In several of our subjects, there was a residual burden of PVCs remaining after GI intervention, suggesting more than one pathway of PVC pathogenesis in these subjects.

10. Conclusions

In our series of patients, we observed a significant reduction or near resolution of premature ventricular contractions (PVCs) following procedural or surgical interventions for esophageal diseases. While these findings are promising, they are based on preliminary observations and should be interpreted with caution. We propose a dual mechanistic hypothesis: one involving vagal mediation within the lower esophagus and another suggesting that esophageal or upper gastrointestinal (GI) pathology could mechanically induce PVCs by directly affecting the right ventricular outflow tract (RVOT). Given the exploratory nature of this study, further research is essential to substantiate these mechanisms. Larger clinical studies and detailed mechanistic investigations are necessary to confirm these findings and fully understand their implications. If future research supports our hypothesis, the assessment of esophageal and upper GI pathologies could become an integral part of the diagnostic and therapeutic approach for patients with high-burden PVCs. This would lead to the classification of a potentially new subcategory of PVCs, which we would term esophageal PVCs (E-PVCs).

Author Contributions: Conceptualization, M.S.; methodology, M.S.; formal analysis, M.S., F.K., E.H., C.K., P.M. (Paul Murdock), P.M. (Peyton Moore), A.R. and A.W.; investigation, F.K., E.H., C.K. and M.S.; data curation, F.K., E.H., C.K., P.M. (Paul Murdock) and M.S.; writing—original draft preparation F.K., E.H., C.K., P.M. (Paul Murdock) and P.M. (Peyton Moore); writing—review and editing, M.S., F.K., E.H, C.K., P.M. (Paul Murdock), P.M. (Peyton Moore), A.R. and A.W; visualization,

P.M. (Peyton Moore); supervision, M.S.; project administration, M.S.; funding acquisition, M.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance following approval of Institutional Review Board of Texas Christian University (protocol code IRB#2022-204 and 12 August 2022).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study and is stored at CCMS-FW.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to patient privacy considerations.

Acknowledgments: The authors wish to thank the staff of Consultants in Cardiovascular Medicine and Science—Fort Worth for clinical subject and records coordination.

Conflicts of Interest: The authors declare no conflicts of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

Appendix A

Difference Scores Calculations

Treatment 1

N_1: 5

$df_1 = N - 1 = 5 - 1 = 4$

M_1: 17.54

SD_1: 5.74

SEM_1: 2.5

Treatment 2

N_2: 5

$df_2 = N - 1 = 5 - 1 = 4$

M_2: 4.4

SD_2: 4.6

SEM_2: 2.06

p-value Calculation

$dof = n - 1 = 4$

$X_D = 13.14$

$S_{XD} = \sqrt{1/(n-1)\,\Sigma(X_{Di} - X_D)^2} = 7.38$

$t = X_D/(S_D/\sqrt{n}) = 13.14/(7.38/\sqrt{5}) = 3.98$

The calculated t exceeds the critical value (3.98 > 2.78) so the means are statistically significant ($p < 0.05$) [52].

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