Proton Pump Inhibitors are Associated with Focal Arrhythmias

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ABSTRACT. Proton pump inhibitors (PPIs) are powerful H⁺/K⁺-adenosine triphosphatase (ATPase) blockers commonly used to treat gastrointestinal illness. H⁺/K⁺-ATPase is present in myocardial tissue, and PPIs may affect intracellular calcium. We sought to test the hypothesis that PPIs are proarrhythmic. We evaluated PPI use in 80 patients with focal tachycardias attributed to an automatic or triggered rhythm: 40 consecutive focal atrial tachycardia (AT) and 40 consecutive right ventricular outflow tract ventricular tachycardia (RVOT VT) patients. Controls included patients with re-entrant rhythms attributed to anatomic abnormalities: 40 consecutive AV nodal re-entrant tachycardia and 40 consecutive atrial–ventricular reciprocating tachycardia patients. Twenty patients (13%) were taking a PPI. Fifteen (19%) focal arrhythmia patients compared with 5 (6%) of the controls were taking a PPI (p = 0.034). The proportion of focal AT patients on PPIs alone was significantly greater than controls (p = 0.009). After adjusting for potential confounders, PPI use was associated with a 3.6 greater odds of focal arrhythmia (95% CI, 1.2–11.1 greater odds, p = 0.025), a 4.5 greater odds of focal AT (95% CI, 1.3–15.7 greater odds, p = 0.018), and a nearly significant 3.5 greater odds of RVOT VT (95% CI, 0.89–13.9 greater odds, p = 0.074). PPI use is associated with focal arrhythmias.

KEYWORDS. atrial tachycardia, right ventricular outflow tract ventricular tachycardia, proton pump inhibitor, focal arrhythmia.

Introduction

Proton pump inhibitors (PPIs) are potent inhibitors of the gastric H⁺/K⁺-adenosine triphosphatase (ATPase) pump, widely used for the treatment of gastrointestinal (GI) illness. They are the most efficacious acid-suppressing drugs to treat esophagitis and gastroesophageal reflux disease (GERD) and play an important role in both the acute and the chronic treatment of peptic ulcer disease. Available both by prescription and over the counter, they are among the most commonly used drugs in the USA.

Tissue studies have demonstrated that H⁺/K⁺-ATPase is expressed in myocardium, and both animal and human tissue studies have shown that PPIs have electrophysiologic effects, potentially by increasing intracellular calcium concentrations.

Aberrations in calcium handling may play an important role in arrhythmias that arise due to triggered activity or enhanced automaticity. The most common arrhythmias attributed to increased automaticity or triggered activity are focal atrial tachycardia (AT) and right ventricular outflow tract (RVOT) automaticity. We hypothesized that PPI use would be associated with arrhythmias attributed to increased automaticity or triggered activity.

Methods

We performed a case–control study restricted to patients undergoing invasive electrophysiology studies in the same electrophysiology laboratory. Conservatively assuming that approximately 3% of the baseline general population use PPIs and that a clinically meaningful difference in PPI use between those with and without...
focal arrhythmias would be approximately 15%, we estimated that 80 patients per group would be sufficient to provide 80% power with a two-tailed alpha of 0.05.

The 80 cases consisted of 40 consecutive focal AT patients and 40 consecutive RVOT automaticity patients. To provide a comparable control group, patients referred to the same electrophysiology laboratory (with a goal of reflecting the same catchment area, demographics, socioeconomic, and insurance status) for arrhythmias not due to increased automaticity were included: 80 controls consisted of 40 consecutive patients with atrioventricular nodal re-entrant tachycardia (AVNRT) and 40 consecutive atrioventricular reciprocating tachycardia (AVRT) patients. AVNRT or AVRT patients exhibiting focal AT or ventricular tachycardia (VT) were excluded. Patient selection was limited to those with data available in a clinical database that was initially implemented in 2004 (patients underwent these procedures between 2004 and 2008).

RVOT automaticity cases were identified based on previously established criteria, including the presence of symptomatic frequent premature ventricular contractions and/or VT determined to be arising from the RVOT by both 12-lead surface electrocardiogram (with a typical left bundle branch, inferior axis morphology) and intracardiac mapping during invasive electrophysiology study.12 In order to exclude re-entrant tachycardia in the RVOT automaticity patients, the arrhythmia had to exhibit behavior characteristic of focal arrhythmias: induced spontaneously, with isoproterenol, or burst pacing, and without evidence of low voltage/endomyocardial scar, entrainment during pacing, or consistently induced with ventricular extra-stimuli.

To distinguish AT, AVNRT, and AVRT, results of the electrophysiology study were used: all patients underwent placement of standard right atrial, His, right ventricular, and coronary sinus multielectrode catheters under fluoroscopic guidance; determination of the arrhythmia mechanism was performed with standard intracardiac recordings and pacing maneuvers.16 Patients with macro re-entrant AT or AT attributed to micro re-entry based on entrainment and mode of induction were not included.

A complete list of all medications was recorded from each patient prior to the procedure. Additional demographic information and medical history were obtained by chart review.

Normally distributed continuous variables are expressed as means ± SD and were compared using t-tests. Not normally distributed continuous variables are expressed as medians and interquartile ranges (IQR) and were compared using the Wilcoxon rank sum test. Categorical variables were compared using the χ² test. Multivariable analysis was performed with logistic regression analysis, and covariates/potential confounders were selected for inclusion in the regression model based on important demographics (e.g. age, race, and sex) and those covariates significantly associated with both the predictors and outcomes of interest with p values <0.10. Two-tailed p values <0.05 were considered statistically significant.

Table 1: Baseline characteristics of cases and controls

<table>
<thead>
<tr>
<th></th>
<th>Focal arrhythmia</th>
<th>Control</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>n = 80</td>
<td>n = 80</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>48 (62%)</td>
<td>42 (55%)</td>
<td>0.38</td>
</tr>
<tr>
<td>Black</td>
<td>6 (8%)</td>
<td>3 (4%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>15 (19%)</td>
<td>19 (25%)</td>
<td></td>
</tr>
<tr>
<td>Latino</td>
<td>3 (4%)</td>
<td>8 (10%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>6 (8%)</td>
<td>5 (6%)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25 ± 6</td>
<td>26 ± 6</td>
<td>0.33</td>
</tr>
<tr>
<td>Hypertension</td>
<td>21 (26%)</td>
<td>21 (26%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2 (3%)</td>
<td>4 (5%)</td>
<td>0.41</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>3 (4%)</td>
<td>1 (1%)</td>
<td>0.31</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>4 (5%)</td>
<td>2 (3%)</td>
<td>0.41</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Aspirin</td>
<td>19 (24%)</td>
<td>14 (18%)</td>
<td>0.33</td>
</tr>
<tr>
<td>Prednisone</td>
<td>3 (4%)</td>
<td>6 (8%)</td>
<td>0.30</td>
</tr>
<tr>
<td>Warfarin</td>
<td>1 (1%)</td>
<td>4 (5%)</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Results

The baseline characteristics of the cases and controls are shown in Table 1: the controls were more often male, but no other statistically significant differences were found. Focal arrhythmia patients were on a median of three medications (IQR, 1–5) whereas the controls were on a median of two medications (IQR, 0–5, p = 0.21). Twenty-six of the RVOT automaticity patients had VT (six with a history of sustained VT), and the remainder had RVOT premature ventricular contractions.

Twenty patients (13%) were taking PPIs. The baseline characteristics of those receiving and those not receiving PPIs are shown in Table 2. Those receiving PPIs were older, had more hypertension, more end-stage renal disease requiring hemodialysis, and were more often receiving prednisone. Patients taking PPIs were on a median of five medications (IQR, 3.5–10), whereas patients not taking PPIs were on a median of two medications (IQR, 0.5–4, p <0.001). The indication for PPI use could be identified in 14 of the 20 patients: 10 had GERD, one had dyspepsia, one had inflammatory bowel disease, one had “gastritis,” and one had a non-specific “GI etiology.”

Compared to controls, a statistically significantly larger proportion of focal arrhythmia patients were on PPIs (Figure 1). AT patients alone were statistically significantly more often on PPIs than were controls. Although RVOT automaticity patients alone were more often on PPIs than controls, this was not statistically significant.

Among those with RVOT automaticity, PPI use was not associated with VT (as opposed to only premature ventricular contractions); spontaneously induced or overdrive pacing induced arrhythmias; having more than one focus; termination of tachycardia with adenosine; and did not appear to differ by location. Five out of six (83%) of the RVOT automaticity patients on PPIs exhibited isoproterenol-sensitive tachycardia versus 13
out of the 34 (38%) RVOT automaticity patients not taking PPIs (p = 0.041).

Among the AT patients, the tachycardia (or dominant AT if more than one focus was observed) was mapped to the following locations: seven (16%) along the crista terminalis, 12 (28%) along the right atrial septum (including para-Hisian), two (5%) from the mitral annulus, seven (16%) from the coronary sinus, two (5%) from the right atrial appendage, one (2%) from the tricuspid annulus, eight (18%) from the right posterior wall, one (2%) from the right lower pulmonary vein, three (7%) from the left posterior wall, and one (2%) from the left atrial appendage. PPI use was not found to be associated with location, mode of induction, sustained versus non-sustained tachycardia, isoproterenol or adenosine sensitivity, or having more than one focus.

After adjustment for potential confounders, PPI use remained significantly associated with focal tachyarrhythmias (Figure 2). After the same adjustment, PPI use was significantly associated with AT alone and exhibited a trend toward an association with RVOT automaticity alone (Figure 2). Although the total number of medicines did not meet the pre-specified criteria for inclusion in the multivariate model, a separate analysis was done including this covariate, given the possibility that the total number of medicines used might represent an important confounder: after adjusting for age, sex, race, and number of medicines, patients taking PPIs still had a significantly greater odds of having a focal arrhythmia than patients not taking PPIs (odds ratio 5.2, 95% CI, 1.4–19.2, p = 0.014).

### Discussion

We found that PPI use was significantly more common in patients with focal tachyarrhythmias than controls. After adjusting for potential confounders, PPI use was associated with a nearly fourfold greater odds of focal tachyarrhythmia. This finding was consistent with both the AT and the RVOT automaticity groups alone exhibiting a greater proportion of PPI use than the control group. After adjusting for potential confounders, PPI use was associated with a statistically significant fivefold greater odds of focal AT.

![Figure 1: Proportion of patients in the control and focal arrhythmia groups (both in black) on proton pump inhibitors; proportions of the two groups that comprise the focal arrhythmia group, right ventricular outflow tract (RVOT) automaticity alone, and focal atrial tachycardia (AT) alone (both in gray) on proton pump inhibitors are also shown. P values represent comparisons denoted by brackets.](image)
For more than a decade, animal studies have demonstrated evidence of H+/K+-ATPase activity in myocardium. In isolated myocyte preparations from rats and guinea pigs, PPIs have been shown to alter cellular electrophysiology, attributed to either decreased intracellular pH (blocking H+ efflux) or K+ depletion (blocking K+ influx). Most recently, this protein has been shown to be present in human myocardium. In that study, PPIs resulted in increased intracellular Ca\(^{2+}\) attributed to a PPI-dependent inhibition of sarcoplasmic reticulum Ca\(^{2+}\) ATPase (SERCA), resulting in a reduction in sarcoplasmic reticulum uptake of Ca\(^{2+}\).

Several arrhythmias are known to be associated with increased intracellular calcium, including the genetically mediated catecholaminergic polymorphic ventricular tachycardia and digoxin toxicity. Like the Na+/K+-ATPase targeted by digoxin, H+/K+-ATPase is also a potassium-dependent p-nitrophenylphosphatase. Intracellular Ca\(^{2+}\) regulation is crucial to normal myocardial automaticity, and common forms of triggered and automatic arrhythmias, such as AT and RVOT automaticity, may arise from abnormal intracellular Ca\(^{2+}\) concentrations. For this first clinical study examining the potential relationship between PPI use and arrhythmias, we chose well-defined arrhythmias that have no known etiology, could not be attributed to anatomic or structural abnormalities (such as the presence of an accessory pathway, dual AV nodal physiology, or scar-based re-entry), and that could be related to aberrations in intracellular physiology. Common focal tachyarrhythmias best met these criteria.

Although focal AT and RVOT automaticity are relatively common among arrhythmia patients, they are quite rare in the general population, making a prospective cohort study of PPI use potentially unwieldy, particularly for a first investigation into a possible association. We therefore performed a case–control study, with controls selected from consecutive patients arising from the same catchment area/referral base as the cases. Arrhythmias in the control group all had an underlying re-entrant mechanism due to an abnormal anatomic substrate (dual AV nodal physiology or an accessory pathway) rather than abnormal cellular electrophysiology.

Several findings provided some internal consistency in support of the hypothesis that PPIs may increase the risk for focal tachyarrhythmias. First, among those with RVOT automaticity, PPI use was more common in those with isoproterenol-sensitive ectopy, a finding generally attributed to increased cyclic adenosine monophosphate-mediated triggered activity. Of note, this observation is limited by the fact that administration of isoproterenol was determined by the discretion of the treating physician and dictated primarily by the clinical scenario in the electrophysiology laboratory. In addition, although not statistically significant, PPI use was more common in AT patients than in RVOT automaticity patients, a finding that fits with the observation that H+/K+-ATPase activity was found to be substantially greater in the atria than the ventricles in a rat model.

This study has several limitations. First, we cannot exclude the possibility that GI disease (such as GERD) increases the risk for focal tachyarrhythmias and that PPIs are simply a marker of this disease. However, such a finding has not previously been described. As this is an observational case–control study, we also cannot exclude the possibility that residual confounding by some other unknown factor is responsible for our positive findings. Finally, this is not a particularly large study; however, it
involves an investigation into specialized and relatively rare patients. As explained in the methods section, the study was powered to detect an effect size of 15%, one felt to be clinically meaningful. Whereas smaller numbers of participants will affect power (and therefore prevent any firm conclusions regarding characteristics of arrhythmia within each group by PPI status), they should not result in spurious positive findings. In fact, the statistically significant findings are more remarkable given the relatively small numbers, and the 95% confidence intervals provide all of the necessary information regarding the “confidence” of those estimates. Taking all of these limitations together, the findings of this study should be considered preliminary. Future prospective studies will be needed to confirm these results.

Conclusions

In the first study to examine the relationship between PPI use and arrhythmias, we found that PPIs were associated with a significantly greater odds of focal tachyarrhythmias. Although evidence from isolated myocyte and cardiac tissue studies provides biologic plausibility to support these findings, prospective studies are needed to exclude confounding as a potential explanation.

References