

## Case Report: The Effect of Proton Pump Inhibitor Administration on Hemodynamics in a Cardiac Intensive Care Unit

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### ABSTRACT

Ex vivo studies have suggested that high dose proton pump inhibitors (PPI) may have negative inotropic effects in myocardial tissue. We sought to investigate this concept in a real-world clinical setting. In this case series, we enrolled critically ill patients in the coronary and cardiothoracic intensive care units who had a preexisting pulmonary artery (PA) catheter in place for hemodynamic monitoring and were on a PPI for prespecified clinical indications. Hemodynamic measurements were made at baseline and then at 15 minute intervals for 1 hour after PPI administration. A total of 18 patients were evaluated; 72% were male with a mean age of 59.9 years. A total of 9 patients were evaluated on 2 consecutive days, yielding 26 patient-exposures to the medication. The majority of patients (72%) were receiving 1 or more inotropic agents ( $n = 6$ ), a vasopressor ( $n = 4$ ), or both ( $n = 4$ ). When compared to baseline values, there was no significant change in mean arterial pressure (baseline  $80 \pm 11$  mm Hg), heart rate ( $87 \pm 11$  bpm), or Fick cardiac index ( $2.7 \pm 1.8$  L/min/m<sup>2</sup>). Mean PA pressure did decrease transiently at 45 minutes following PPI administration ( $28.5 \pm 7.7$  mm Hg at baseline vs  $26.5 \pm 7.5$  mm Hg,  $P = 0.017$ ), but is unlikely to be of clinical significance. In conclusion, these data suggest that IV PPIs do not immediately impact important hemodynamic parameters and are likely safe in a high-risk intensive care setting.

### Introduction

Proton pump inhibitors (PPIs) are one of the most widely used medications in the United States. The mechanism of action of PPIs involve inhibition of the H<sup>+</sup>/K<sup>+</sup> adenosine triphosphatase (ATPase; ie, proton pump), which is the final step in the acid secretion pathway in gastric tissue. The H<sup>+</sup>/K<sup>+</sup> ATPase has also been isolated in myocardial and vascular smooth muscle cells. Ex vivo data suggest that in myocardial tissue, this enzyme may regulate homeostasis of H<sup>+</sup> and K<sup>+</sup>, and its suppression could cause cellular acidosis, interfere with Ca<sup>2+</sup> responsiveness in the muscle cells, and thereby depress myocardial contractility.<sup>1</sup> It is not clear if the negative inotropic effect observed in these in vitro studies translates into clinically relevant consequences in acutely ill patients. We accordingly sought to evaluate the acute hemodynamic impact of PPI administration in these patients.

### Methods

After obtaining University of Michigan institutional review board approval, we evaluated patients in the coronary and cardiothoracic intensive care units between October 2007 and January 2008. Patients included were receiving an intravenous (IV) PPI for an approved indication (gastroesophageal reflux, prior gastrointestinal ulcer disease, high

risk for gastritis) and had a pulmonary artery (PA) catheter in place. The decision to place a PA catheter was made by the primary team, independent of and prior to study enrollment. Patients were excluded if they were hemodynamically unstable within 12 hours of the index PPI dose, required rapid titration of vasopressor or inotropic agents, or had an acute change in oxygenation status. Informed consent was obtained from the patient directly or from an official patient designate.

Hemodynamic data were obtained prior to, and then 15, 30, 45, and 60 minutes after a PPI was administered. In all cases, 40 mg of pantoprazole was given as an IV injection per unit protocol. Data collected included heart rate (HR), blood pressure (BP), pulse oximetry, right atrial pressure, PA pressure, pulmonary capillary wedge pressure if available, pulmonary artery oxygen saturation, and thermodilution cardiac output when available. Mean arterial pressure (MAP) and mean PA pressures were calculated for each time point. Complete blood count, comprehensive metabolic profile, height, and weight were recorded the day of study participation. From these data, a Fick cardiac output and index were calculated.<sup>2</sup> Other data recorded included concurrent medications and doses, presence of diabetes, chronic kidney disease (creatinine >1.5 mg/dL), hypertension, and liver failure. A paired *t* test was used to compare each value of the measured variables

to baseline values. Data are presented as mean  $\pm$  standard deviation. A *P* value of  $<0.05$  was considered significant.

**Results**

A total of 18 patients were evaluated; 72% were male with a mean age of 59.9 years. Each patient was evaluated following 1 or 3 doses of an IV PPI on separate consecutive days, depending on the clinical course, for a total of 26 patient-exposures to this medication. Patients had been assigned to an intensive care setting for a variety of clinical indications; 4 patients were postoperative following mitral or tricuspid valve repair, 5 patients had recent coronary artery bypass grafting, 4 patients had acute type A aortic dissection (2 of whom had recent aortic repair), and 5 patients had nonischemic or ischemic cardiomyopathy and were awaiting transplant or left ventricular assist device implantation. The majority of patients (72%) were receiving 1 or more inotropic agents ( $n = 6$ ), a vasopressor ( $n = 4$ ), or both ( $n = 4$ ) at the time of evaluation. Comorbid conditions in this population included hypertension ( $n = 12$ ), diabetes ( $n = 4$ ), and chronic kidney disease ( $n = 6$ ). A total of 6 patients required mechanical ventilation and 3 patients were on continuous hemodialysis (Table).

When compared to baseline values, there was no significant change in systemic blood pressure or cardiac index (Figure). Similarly, the mean HR at baseline ( $87 \pm$

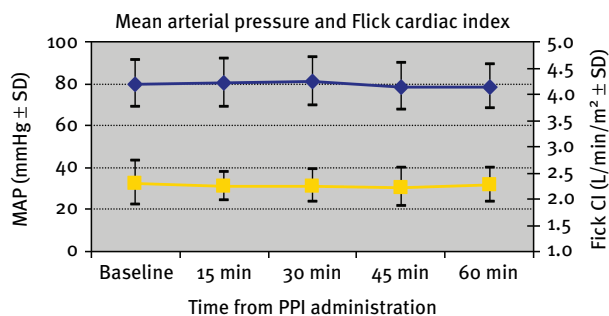


Figure 1. Mean arterial pressure and Fick cardiac index values for 1 hour following IV PPI administration (the data points in blue reflect mean arterial pressure and the data points in maize reflect cardiac index).

17 bpm) did not change significantly in the hour following IV PPI administration. Baseline right atrial pressure ( $11.5 \pm 4.2$  mm Hg) and pulse oximetry ( $96.2\% \pm 2.2\%$ ) values did not change significantly after drug administration (*P* = not significant for all time points). Mean PA pressure did decrease transiently at 45 minutes following PPI administration ( $28.5 \pm 7.7$  mm Hg at baseline vs  $26.5 \pm 7.5$  mm Hg, *P* = 0.017) but this decrease is unlikely to be of clinical significance.

**Discussion**

Proton pump inhibitors are commonly used medications in the intensive care setting. The safety of these medications in patients with intrinsic cardiac disease has not been well studied. Their use accounts for a large portion of the net pharmaceutical expenditures in the U.S.<sup>3</sup> In the inpatient and intensive care unit settings, these drugs are commonly used in oral and intravenous formulations as prophylaxis against stress-induced gastritis, ulcers, and gastrointestinal bleeding in high-risk patients.<sup>4</sup> Proton pump inhibitors may also be a particularly important intervention after cardiac surgery.<sup>5</sup>

Schillinger et al have evaluated the effects of PPIs (specifically pantoprazole) on myocardial tissue specimens from humans and rabbits.<sup>1</sup> Human tissue was derived from 8 patients undergoing heart transplantation (failing ventricular tissue) and 16 patients undergoing cardiac surgery (nonfailing atrial tissue). In both specimen types, there was a dose-dependent effect of decreased isometric twitch force with pantoprazole exposure and partial reversibility after drug washout. This effect was not mediated by changes in pH (related to H<sup>+</sup>/K<sup>+</sup> inhibition) but seemed to be mediated by impaired calcium uptake and reduced myofilament responsiveness. At very high concentrations of pantoprazole there was near complete inhibition of cardiac contractility and these effects seemed to occur within minutes.

Table 1. Baseline Demographic and Clinical Characteristics of All Patients Evaluated

	n = 18
Age (mean $\pm$ SD; years)	59.9 $\pm$ 16
Gender n (%) male	13 (72.2%)
Indication for ICU and PA catheter monitoring, n (%)	
Postoperative valve surgery	4 (22.2%)
Postoperative CABG	5 (27.7%)
Type A dissection	4 (22.2%)
Cardiomyopathy	5 (27.7%)
Concurrent medications, n (%)	
Inotropic agents	6 (33.3%)
Vasopressors	4 (22.2%)
Inotropic agents + Vasopressors	4 (22.2%)
Comorbid conditions	
Hypertension	12 (66.6%)
Diabetes	4 (22.2%)
Chronic kidney disease	6 (33.3%)

Given the widespread use of these medications in routine clinical practice, it was important to assess if these effects have clinical relevance. It was expected that based on the significant underlying cardiovascular disease and cardiac dysfunction in our study population, these patients would be at high risk for acute hemodynamic compromise in the setting of a drug with potential negative chronotropic and inotropic effects. However, we were unable to demonstrate any adverse hemodynamic effects immediately after IV PPI administration.

This study was limited by a small sample size, heterogeneity of the patient population, and uncontrolled use of concomitant medications. Inotropic agents were used in the majority of patients and their effects may have mitigated the negative inotropy and contractility seen in vitro. However, these differences in clinical conditions and variation in use of inotropic agents reflect real-world intensive care settings where these drugs are most likely to be used. In addition, these patients had relatively stable hemodynamics and inotropic agent doses were not being actively titrated at the time of data collection. Finally, despite a small sample size, we calculated a greater than 80% power to detect a difference in cardiac index of 0.2 L/min/m<sup>2</sup>. Finally, most

patients were on either an IV or oral PPI prior to enrollment in the study. Therefore, we cannot rule out a conditioning effect due to prior exposure.

In conclusion, these data suggest that IV proton pump inhibitors at currently employed doses do not immediately impact important hemodynamic parameters and are likely safe in a high-risk intensive care setting.

## References

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