Increased asymmetrical dimethylarginine levels were found in a preclinical model and in patients with asthma, including children (3, 4).

Our group discovered that the entire class of proton pump inhibitors inhibits dimethylarginine dimethylaminohydrolase, an enzyme responsible for asymmetrical dimethylarginine degradation in cells. We have demonstrated that proton pump inhibitors increase plasma asymmetrical dimethylarginine level in animals and reduce NO production in human endothelial cells and saphenous veins (5). Because endothelial NO is an antiatherogenic molecule (6), and because asymmetrical dimethylarginine is associated with increased cardiovascular risk (7), the inhibition of dimethylarginine dimethylaminohydrolase by proton pump inhibitors might be expected to increase the risk for major adverse cardiovascular events. Indeed, we have recently reported that the use of proton pump inhibitors is associated with increased cardiovascular mortality (8).

As asymmetrical dimethylarginine is a nonselective NOS inhibitor, it is also possible that proton pump inhibitor-mediated accumulation of asymmetrical dimethylarginine may reduce activity of inducible NOS. Because inducible NOS participates in immune defense, its inhibition by proton pump inhibitors may reduce the clearance of pathogens. As Lang and colleagues pointed out, impaired defense against pathogens could be particularly problematic in poor metabolizers of lansoprazole.

The study by Lang and colleagues, as well as our work and that of others, raises concerns about the routine availability of proton pump inhibitors for purchase without a prescription. There are strong indications for the use of proton pump inhibitors, but these drugs may have serious adverse effects. We feel that they should be prescribed as necessary and used under the guidance of a medical professional.

Author disclosures are available with the text of this letter at www.atsjournals.org.

Reply: Worsening Asthma Control in Children Taking Lansoprazole: Possible Mechanisms

From the Authors:

We appreciate the interest of Dr. Sukhovershin, Dr. Ghebremariam, and Dr. Cooke in our recent report about worsening asthma control among children taking lansoprazole who have the *CYP2C19* poor metabolizer phenotype (1). The authors correctly point out that we found that these children developed worse asthma symptoms after 5 months of lansoprazole therapy. We speculated that prolonged acid suppression among poor metabolizers alters gastric flora and heightens host susceptibility to respiratory pathogens that are known to affect asthma control. In a previous report from our group (2), we showed that lansoprazole-treated children with the *CYP2C19* poor metabolizer phenotype had a significantly higher prevalence of self-reported sore throats and

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upper respiratory infections during the treatment period. We also found a nonsignificant trend between metabolizer phenotype and worse asthma symptoms after upper respiratory infections. The potential role of proton pump inhibitor (PPI)-induced acid suppression in causing worsening asthma control requires replication and further mechanistic study.

We were intrigued by the plausible hypothesis proposed by Sukhovershin and colleagues, which suggests that asymmetrical dimethylarginine (ADMA) becomes increased with PPI treatment. They propose that ADMA, which is a nitric oxide synthase inhibitor, may generate reactive oxygen species and impair immune defenses, leading to worse asthma. ADMA has been shown to be elevated in human asthma and also increases airway responsiveness when administered in a mouse model (3).

Among the 115 children who completed our 6-month study and provided fractional exhaled nitric oxide (FENO) measurements before and after treatment, neither lansoprazole treatment ($n = 63$) nor metabolizer phenotype affected the fold change from baseline of FENO. Fold changes from baseline FENO among placebo-treated, lansoprazole-treated poor metabolizers, and lansoprazole-treated extensive metabolizers were 1.1, 1.0, and 1.1, respectively ($P > 0.6$ for all pair-wise comparisons). Our results are consistent with past authors, who have also failed to show

significant correlations among airway ADMA and FENO (4). We did not measure ADMA in our study.

ADMA has been associated with changes in hemodynamic parameters that associate with cardiovascular risk (5, 6). To explore a possible link between PPI treatment and hemodynamic changes in a post hoc analysis, we determined the associations among PPI treatment status, metabolizer phenotype, and key hemodynamic measures before and after the intervention period. Using our original statistical approach, we found that increasing PPI exposure was not associated with changes in blood pressure, heart rate, pulse pressure, mean arterial pressure, mid blood pressure ([systolic blood pressure + diastolic blood pressure]/2), pulse pressure index, or rate pressure product (data not shown). However, we did see a weak trend between PPI exposure group and changes from baseline in systolic blood pressure (placebo 0.0 vs. lansoprazole-treated poor metabolizer +3.5; $P = 0.09$).

It is biologically plausible for excess PPI exposure to increase susceptibility to asthmagenic pathogens and increase ADMA, leading to altered NOS activity and airway inflammation. However, further research is needed to confirm these speculations. Despite the fact that long-term use of PPIs is common, current US Food and Drug Administration recommendations for dosing is limited to short-term use (up to 12 weeks).

We very much agree with Sukhovershin and colleagues that considering PPIs' multiple known adverse effects and limited research into long-term effects, judicious use of PPIs is warranted and should be conducted with close guidance from a medical professional.

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FEV₁ Can Be Associated with Reduced Values after Vigorous Exercise in Healthy Adolescents

To the Editor:

I read with great interest the study “Vigorous exercise can cause abnormal pulmonary function in healthy adolescents,” recently published by Abosaida and colleagues (1).

The study considered more than 50 healthy adolescents who underwent a constant and progressively increasing work rate exercise testing protocol on a cycle ergometer. The study was designed so that participants had at least 2 weeks between the test protocols to allow for complete recovery, but not more than a month, to reduce chances of participants showing a change in respiratory tests' outcomes unrelated to the experimental design, and in accordance with the American Thoracic Society guidelines (2).

The main result of the study was that 10 participants had a decrease in FEV₁ after vigorous exercise testing. Of these participants, three showed a decrease only after the constant work rate test, five only following the ramp test, and two after each testing protocol.

The article concludes that healthy adolescents demonstrate subtle bronchoconstriction after exercise.

I think that the effect of fatigue, and especially central command, could have been overlooked in this study. Also, this study shows association between vigorous exercise and decreased FEV₁, not causality, as the title suggests. It is possible that the cause of the observed FEV₁ reduction after vigorous exercise is not exercise-induced bronchoconstriction.

Table 2 in the article shows that participants with abnormal FEV₁ had a (not significant) reduction in exercise capacity in terms of work rate that they could sustain for a given heart rate. No significant difference was detected in any of the other physiological variables measured; this may depend on the complex nature of the cardiac and respiratory parameters measured such as heart rate and ventilation, especially at heart rates of 80–90% peak heart rate. These results could suggest that a greater fatigue may be experienced by participants presented in the abnormal FEV₁ group, irrespective of FEV₁ itself. For example, it is possible that different baseline fitness levels, not taken into account or not detectable by the exercise testing protocols used, may be associated with the reduced exercise capacity. For example, accumulation of blood lactate could help show whether this may be the case (3).