



Reply to Yasuma *et al.*

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From the Authors:

We thank Yasuma and colleagues for their interest in our study recently published in the *Journal* in which we demonstrated that prostaglandin I₂ (PGI₂) analogues increased the percentage of circulating T regulatory cells (Tregs), the mean fluorescence intensity (MFI) of Foxp3 within the Tregs, and the MFI of CD44 on the Tregs while decreasing the ratio of T effector cells to Tregs in patients with pulmonary arterial hypertension (1). The authors commented on the potential differential effects that different PGI₂ analogues may have on Treg generation in humans. Eight patients were treated with epoprostenol and four were treated with treprostinil during the study. It is important to note that the patients in this study received a room-temperature stable formulation of epoprostenol or a room-temperature stable formulation of treprostinil (2, 3). In response to the concerns of Yasuma and colleagues that these different analogues may have differential effects, we have separated the data for each of our endpoints based on treatment. We found significant increases in Treg percentage (Figure 1A) and Foxp3 MFI (Figure 1B) in patients treated with epoprostenol, but not those treated with treprostinil, after grouping the patients based on treatment received. No differences in CD44 MFI (Figure 1C) or in the ratio of CD4⁺ T effector cells to Treg (Figure 1D) were observed after grouping patients based on treatment received. However, we are underpowered for this subgroup analysis, and there may be selection bias in treatment recommendations that cannot be accounted for by the low number of subjects in each group. Therefore, we cannot confidently conclude whether there are differential effects on Treg generation and function by the different PGI₂ analogues.

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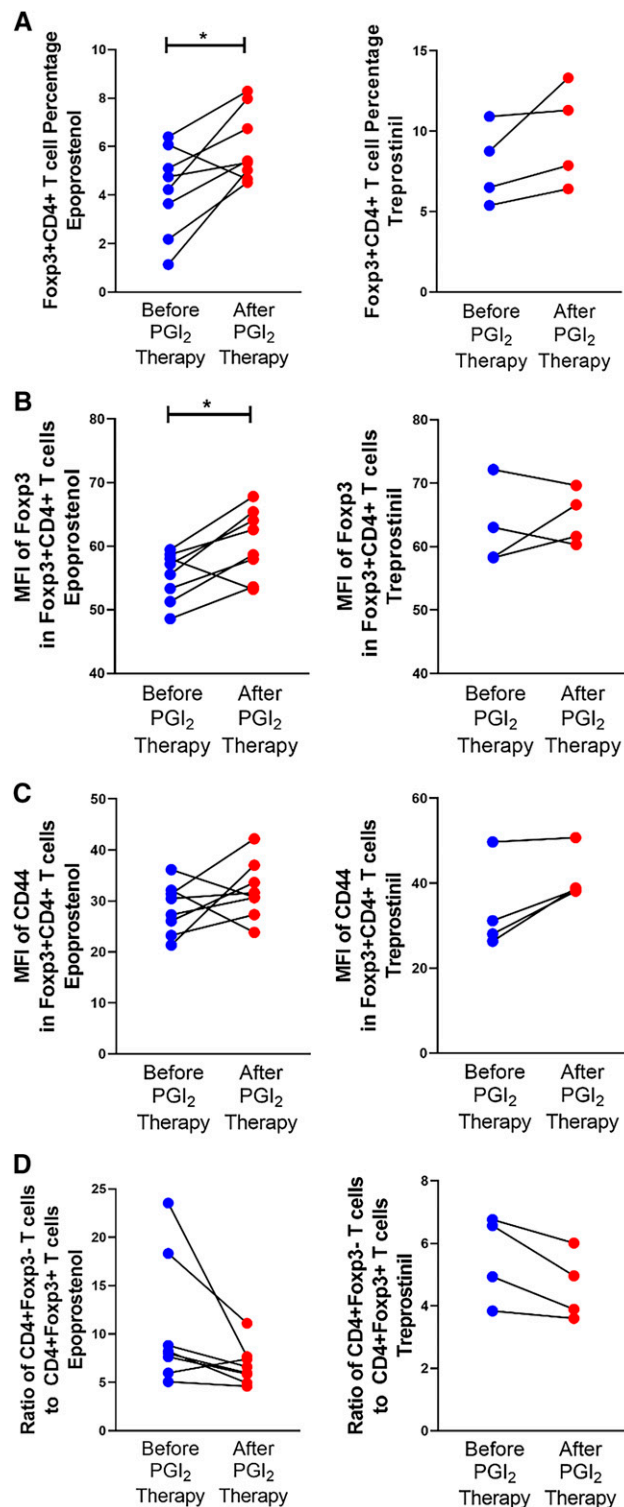


Figure 1. Effect of the prostaglandin I₂ analogues epoprostenol or treprostinil on (A) T regulatory cell (Treg) (Foxp3⁺CD4⁺) percentage, (B) Foxp3 mean fluorescence intensity in Tregs, (C) CD44 mean fluorescence intensity in Tregs, and (D) ratio of T effector cells (CD4⁺Foxp3⁻) to Tregs (CD4⁺Foxp3⁺). Analysis was performed with a paired *t* test. **P* < 0.05. MFI = mean fluorescence intensity; PGI₂ = prostaglandin I₂.

We appreciate this question and will consider this while planning a larger follow-up study. ■

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

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Outcome and Cognition in Home Noninvasive Ventilation: A More Decisive Factor?

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To the Editor:

The implementation of home noninvasive ventilation (NIV) in patients with chronic respiratory failure (CRF) is a complex process. It requires patient engagement to overcome paramount challenges mostly due to reduced interaction time. Furthermore, physiological issues in these patients impact cognitive performance, hindering the acquisition of skills for using home NIV.

In light of these factors, the results presented in the article by Patout and colleagues in the *Journal* (1) provide valuable insights into the potential relationship between cognitive function and home NIV treatment in this clinical setting. The findings underscore the intricate interplay between cognition and CRF.

There are several aspects of the study's methodology and interpretation of results that warrant careful examination. The study

heavily relies on the Montreal Cognitive Assessment (MoCA) as the primary measure of cognitive function. Although the MoCA and the widely used Mini Mental State Examination employ a 30-point scale and are quickly completed, the MoCA is more sensitive in evaluating executive function and is better at detecting mild disease than the Mini Mental State Examination (2). However, the potential limitations of the MoCA tool in capturing nuanced cognitive changes and distinguishing between specific cognitive domains have been well documented (3). For instance, Pugh and colleagues (4) suggested an optimal cutoff score of 24, rather than 26, to identify mild cognitive impairment. Other factors, such as natural fluctuations in cognitive performance over time or potential practice effects, could contribute to the observed MoCA score variations. Consequently, the absence of additional neuropsychological tests or measures targeting specific cognitive domains weakens the study's ability to comprehensively evaluate cognitive function.

Second, the study's focus on cognitive improvement is noteworthy. Cognitive impairment was unrelated to disease etiology but was associated with more severe breathlessness and lower education levels. However, the absence of data on other potential outcomes, such as changes in patients' daily functioning, health-related quality of life, or clinical outcomes, restricts the broader implications of the findings. A comprehensive assessment of the multifaceted impact of home NIV treatment on patients' well-being and overall health would yield a more comprehensive understanding of the intervention's effects. In essence, even though cognitive improvements were observed, the clinical significance of these enhancements in daily functioning and health-related quality of life was not thoroughly explored. Moreover, the study did not consider potential external factors that could influence cognitive function, such as medication, comorbidities, or lifestyle adjustments. This is very important for its clinical implications.

The absence of baseline polysomnographic assessments limits insights into sleep-related variables contributing to cognitive impairment, as acknowledged by the authors. Furthermore, without a control group, the precise impact of home NIV treatment on cognitive enhancement remains unclear. To establish causality, a controlled experimental framework with a well-matched control group receiving standard care is needed.

Therefore, although the article offers valuable insights into the cognitive implications of home NIV treatment for patients with CRF, methodological limitations exist. Comprehensive patient outcome assessment examining intervening variables would enhance the study's contribution and validity, especially considering that it is the first to explore cognitive function before and after home NIV in patients with CRF. ■

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

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