Reply to Drs. Teppema, Berendsen, and Swenson

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TO THE EDITOR: We followed with great interest the recent exchanges between Drs. Teppema and Berendsen (4) on one hand and Dr. Swenson on the other hand regarding the mechanisms of effects of acetazolamide (AZ) in the prevention of Acute Mountain Sickness (AMS) (3).

One of the essential questions raised by both parts is the action of AZ on central and peripheral chemosensitivity, respectively. We would like to bring a small contribution to this passionate reflection by approaching this issue from the breathing stability angle. We recently described ventilatory oscillations in normal subjects submitted to physiological (exercise) and environmental (hypoxia) stresses (1, 2) and we analyzed the effect of oral AZ (500 mg/day on day before and on the test day vs. placebo) on this instability (2). In accordance with most studies, we noted an increase in minute ventilation (V̇E) and arterial O₂ saturation and a decrease in end-tidal CO₂ pressure (PETCO₂) during exercise in hypoxia, confirming the well-known effect of AZ on ventilation in hypoxia. Traits of breathing instability, such as magnitude of V̇E oscillations, were blunted under AZ (see Figs. 1 and 4 in Ref. 2). We also pointed out that AZ drastically enhanced ventilatory response to CO₂ (HcVR) (placebo: 2.46 ± 0.53, AZ: 3.78 ± 1.67 l·min⁻¹·mm·Hg⁻¹, P = 0.006) (see Table 2 in Ref. 2), whereas the ventilatory response to hypoxia was blunted or unchanged. In a previous study, we showed that breathing oscillations were positively related to HcVR, but only in hypoxic conditions (see Fig. 8 in Ref. 1). Moreover, AZ blunted the relationship between intensity of oscillations and HcVR (see Fig. 7 in Ref. 1). In fact, AZ increases the controller gain (HcVR) but inhibits the enhancing effects of controller gain on ventilatory oscillations. This latter data confirm the stimulant action of AZ on central chemoreceptors (mainly responsible for ventilatory response to CO₂) through metabolic acidosis but raise interrogations regarding the blunting of ventilatory oscillations. Furthermore, in our preliminary study (1), subjects with a higher ventilatory response to hypoxia showed a greater breathing instability, suggesting that carotid bodies were playing a predominant role in the genesis of ventilatory oscillations, and blunting of oscillations by AZ strongly suggests that AZ inhibits carotid bodies activity. These observations made during exercise in hypoxia may also confirm the blunting effect of AZ on periodic breathing during sleep. However, as mentioned by E. R. Swenson (3), no clear relationship has been evidenced between periodic breathing and AMS. From our observations of the effects of AZ on chemosensitivity to CO₂ and breathing instability, we hypothesize that the increase in ventilation by AZ is mostly due to an increase in the (central) response to CO₂ that overwhelms a decrease in the (peripheral) response to hypoxia. However, the blunting of ventilatory instability by AZ might be mediated through its action on carotid bodies.

AUTHOR CONTRIBUTIONS
E.H. drafted manuscript; E.H., F.J.L., and J.-P.R. edited and revised manuscript; E.H., N.V., F.J.L., and J.-P.R. approved final version of manuscript.

DISCLOSURES
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