TO THE EDITOR: We appreciate the numerous comments (see Ref. 4) on our Viewpoint (2), which demonstrates the interest of muscle physiologists for the topic. A number of commentators pointed toward the fact that our model did not sufficiently account for the high interindividual variability in the response to high altitude. We completely agree with the latter point. We previously found as well that the physiological responses to hypoxic exposure were highly variable between subjects, but were consistent within subjects (3). As mentioned in one comment, the reduction in energy intake at altitude probably contributes to this high interindividual variability, with some subjects being more sensitive than others to the loss of appetite. An approach suggested to control for this high variability is to use %desaturation as measurement for “internal” hypoxic dose (5) instead of the “external” hypoxic dose, i.e., altitude, as used in the hypoxic dose model. This is a valuable suggestion, because hypoxia-induced decreases in arterial Po2 are highly correlated with drops in intramuscular PO2 (8), which among others triggers muscle atrophy. Nevertheless, this “saturation hours” parameter could have its limitations as well. For instance, an important part of the adaptations to chronic hypoxia is the alleviation of the initial decrease in SpO2 (7). Thus, because it is not a fixed variable throughout time, at which point during data from our laboratory (3), we found no relation (r < 0.2; not significant) between the initial decrease in SpO2 after 6 h at ~5,000 m and the increase in markers of protein catabolism at rest such as REDD1, LC3II/I ratio, and pAMPK. As this was an acute study, future long-term studies are warranted to determine if individual initial adaptations to hypoxia in terms of SpO2, tissue oxygenation or anabolic signaling can predict long-term effects, such as skeletal muscle atrophy.

Another recurrent point in the commentaries is that our model likely only holds true when a minimal altitude of ~5,000 m is reached, because this is approximately the cut-off point at which physiologically relevant hemoglobin desaturation occurs. Importantly, when subjects do not remain passive, but are involved in resistance training for instance, hypoxia-induced inhibition of skeletal muscle anabolism can be induced at lower altitudes and hypoxic doses than the suggested 5,000 km·h. It is known that muscle contractions induce a drop in intramuscular Po2 far greater that the one that can be achieved by environmental hypoxia alone (8). Thus it is not surprising that, during chronic hypoxic exposure, the combination of a lower intramuscular Po2 during exercise with a lower PaO2 during recovery blunts muscle protein synthesis acutely (1) and reduces the increase in cross-sectional area (6) usually observed at sea level.

On the basis of our model, the literature, and the commentaries provided, we can conclude that the human body copes extremely well with low oxygen environments in terms of preservation of skeletal muscle mass. Nevertheless, a 40-day sojourn at 5,000 m is likely a turning point above which desaturation occurs to such an extent that intramuscular Po2 drops are sufficiently large and repetitive to induce muscle catabolism.

AUTHOR CONTRIBUTIONS
G.D. and L.D. interpreted results of experiments; G.D. drafted manuscript; G.D. and L.D. edited and revised manuscript; G.D. and L.D. approved final version of manuscript.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES

