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CORRESPONDENCE

Making a virtue out of an evil: Are red blood cells from chronic mountain sickness patients eligible for transfusions?

To the Editor:

Chronic Mountain Sickness (CMS) manifests in high-altitude residents above 2500 m, characterized by symptoms associated with elevated hematocrit levels typically ranging between 60% and 80% caused by excessive erythrocytosis (EE). This results in elevated hemoglobin, exceeding 21 g/dL for men and 19 g/dL for women, and the presence of signs and symptoms among the following: headache, tinnitus, breathlessness and/or palpitations, sleep disturbances, cyanosis, vein dilation, and paresthesia.[1] A comprehensive assessment of symptom severity is captured through the *Qinghai index* score system.[1] For an in-depth exploration of diagnosis, comorbidities, and risk factors, refer to Villafuerte and Corante's comprehensive review from 2016.[2] The sole definitive remedy for CMS involves a permanent relocation to lower altitudes; however, this option is unattainable for most patients due to socio-economic constraints. While medications such as enalapril or acetazolamide and noninvasive interventions like exercise training, show promise in alleviating symptoms, they do not evolve into established long-term effective treatments. In contrast, a commonly employed approach for CMS management involves phlebotomy, typically extracting 1–2 units (450–900 mL) of blood,[3] which is subsequently discarded. Despite the observed improvement in oxygenation and symptom relief for CMS patients through phlebotomy[4] the merit of this treatment is a subject of contentious debate.[2] The controversy arises from the phlebotomy-induced decrease in iron stores and iron depletion, which causes an increase in pulmonary arterial pressure.[5] The transient reduction in hemoglobin levels (lasting a few weeks) is followed by a potential rebound effect, leading to higher hemoglobin values compared with pre-phlebotomy levels.[2] Nevertheless, when phlebotomy is administered regularly, incorporating plasma volume management and ensuring adequate nutritional supplementation of iron and amino acids, it emerges as a pragmatic disease management option aligned with the practical needs of patients. Our study aimed to delve deeper into the characterization of CMS patients, focusing particularly on the properties of their red blood cells (RBCs).

We investigated 62 male volunteers residing permanently in La Rinconada, Peru, 5100 m above sea level. Following the prevailing international consensus,[1] a diagnosis of CMS was established when the Qinghai CMS score was ≥6, with the presence of EE. We identified 36 individuals as CMS patients and 26 as healthy controls. The scores were 9.9 ± 3.1 for CMS patients and 5.2 ± 2.5 for controls. Age was not different between those with CMS (46.7 ± 9.5 years) and controls (42.5 ± 12.6; $p = .14$). The body mass index was uniform at 27.6 ± 3.3 kg/m^2 for both groups. Figure 1 illustrates a markedly significant elevation in hematocrit and hemoglobin concentration among CMS patients compared with controls (Figure 1A,B, respectively). This surge in hematocrit contributes to a noteworthy increase in blood viscosity in CMS patients compared with their healthy counterparts (Figure 1C). Consistent with prior studies, CMS patients exhibited significantly reduced arterial oxygen partial pressure (PaO_2) and oxygen saturation (SpO_2) compared with controls (Figure 1D,E, respectively). Additionally, the relative reticulocyte count was substantially higher in CMS patients than in controls (Figure 1F), suggesting that CMS is predominantly driven by an elevated rate of erythropoiesis. Total blood volume measurements, as shown in Figure 1G, did show significant differences between CMS patients and controls. Therefore, the effects of phlebotomy in CMS patients on fluid regulations would require the assessment of optimal isovolumic plasma-like replacement strategies to avoid cardiovascular issues.[6]

Additionally, we delved into the biophysical characteristics of RBCs from CMS patients in comparison to controls, with the findings detailed in Figure 1H–P. Mean RBC volume and mean RBC hemoglobin concentration are presented in Figure 1H,I, respectively. While not statistically significant, variations in these parameters may be influenced by the distinct count of reticulocytes (Figure 1F), given their 24% higher volume and 16.7% lower hemoglobin concentration compared with mature RBCs.[7] Microscopic examination of RBCs did not unveil any discernible differences in shape between CMS patients and controls. Representative images are displayed in Figure 1J. We replicated the viscosity

measurements presented in Figure 1C, normalizing the hematocrit to 40%. Notably, no discernible differences were observed between CMS patients and controls, as depicted in Figure 1K. RBC deformability, a critical parameter for assessing the quality of RBCs for transfusion purposes,[8] was evaluated using ektacytometry. We present mean values of shear stresses in the range between 0.3 and 30 Pa (Figure 1L) and individual deformation values at a shear of 3 Pa (Figure 1M). In Figure 1L,M, no significant differences were observed between CMS patients and controls. Similarly, RBC aggregation indices (M and M1) presented in Figure 1N,O,

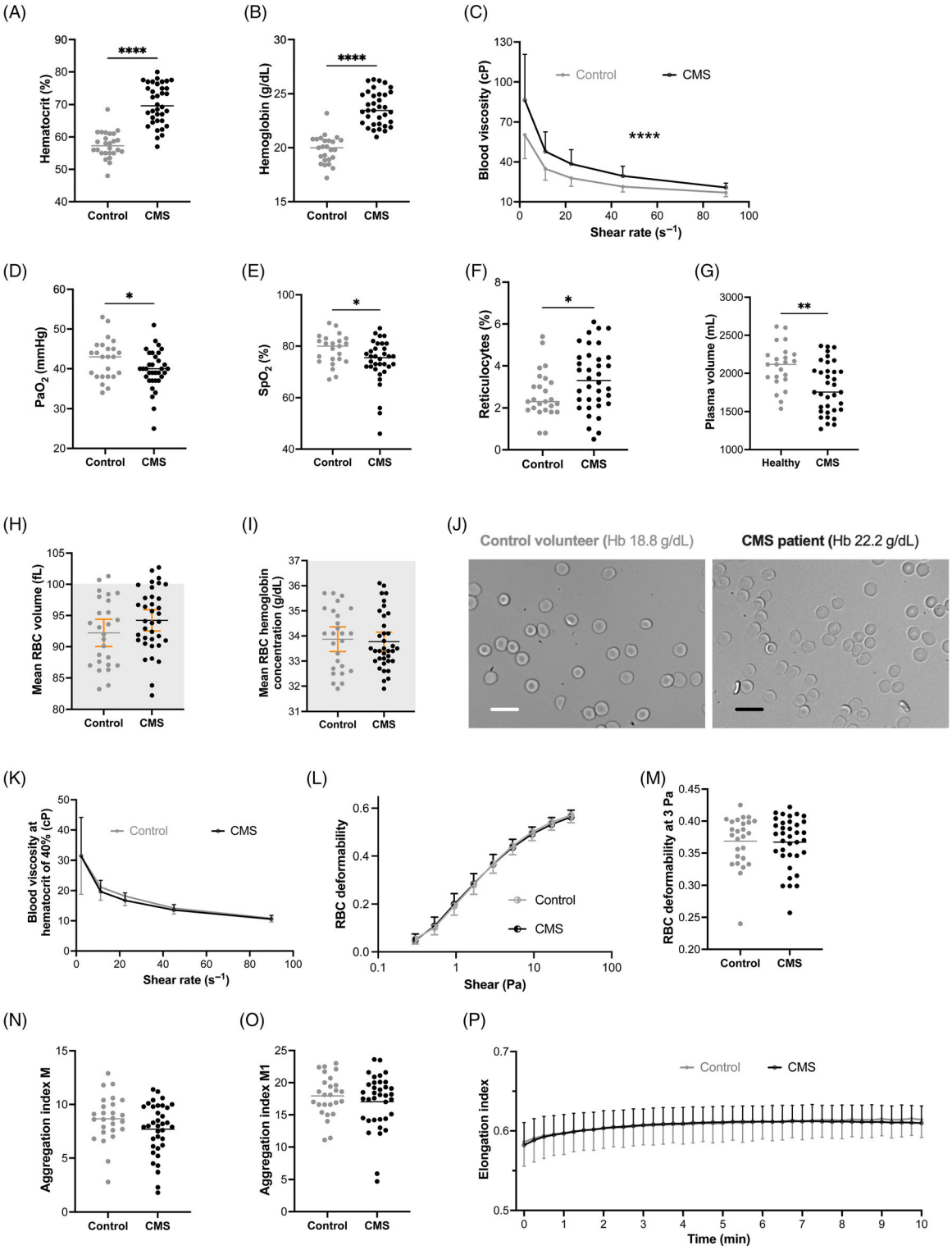

FIGURE 1 Legend on next page.

respectively, exhibited no discernible differences between CMS patients and controls. This corresponds with feedback from clinicians in intensive care units and internal medicine whom we consulted; they did not note a heightened occurrence of thrombotic events in CMS patients. Finally, as a measure of RBC stability, we monitored the elongation index (at a constant shear of 30 Pa) over a 10-min duration (Figure 1P). Even in this time course, no significant differences were detected between CMS patients and controls.

While the hematological parameters illustrated in Figure 1A–G are characteristic of CMS patients, all mechanical and rheological factors, including RBC aggregation properties, deformability, and stability, as detailed in Figure 1H–P, exhibit no significant differences between CMS patients and their healthy counterparts. In essence, the mechanical and rheological properties of RBCs from CMS patients closely resemble those of controls. Considering that blood bank products are processed as blood constituents—not whole blood—these physical properties of RBCs are most relevant. In light of these findings, we propose that blood obtained through phlebotomy for treating CMS patients holds the potential as a viable source for blood transfusions. This is in line with a similar proposal, where venesections of well-managed hereditary hemochromatocytosis patients are suggested for blood product development.[9] Considering the scarcity of blood supply, particularly in low and medium-income countries in the Andes region such as Ecuador, Peru, or Bolivia,[10] which also have a high incidence of CMS, a systematically scheduled phlebotomy for CMS patients—assuming controlled substitution of plasma, iron, and amino acids—would have a dual benefit. It not only enhances the well-being of patients and enables their active participation in various aspects of life, including physical labor, but also addresses the critical need for blood supplies for transfusion purposes. Moreover, within the health system, monetary benefits derived from blood donations could serve as a financial offset for CMS patient treatment including the necessary nutritional supplements. Despite a cultural aversion among the Andean population to needle pricks, some high-altitude mines have instituted regulations stipulating specific hemoglobin thresholds for miners to be deemed fit for work. Consequently, clandestine phlebotomy practices have become prevalent. In consideration of this context, implementing a supervised and controlled phlebotomy program within the framework of disease management might emerge as a practical treatment approach, characterized by a reasonable level of effort and feasibility.

Certainly, the suggestion to employ RBCs from CMS patients for transfusions, as proposed through the in vitro investigations of blood samples illustrated in Figure 1H–P, warrants validation through clinical trials. Nonetheless, the information conveyed in this letter lays a robust foundation for initiating such clinical studies. This proposition could be effectively integrated into a randomized controlled trial, assessing both the safety and efficacy of phlebotomy as a treatment for CMS. It is noteworthy that such a trial has not been conducted before,[2] and its execution is now imperative, especially considering the estimated 7 million patients worldwide affected by CMS.[1]

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CONFLICT OF INTEREST STATEMENT

There is no conflict of interest to declare.

PATIENT CONSENT STATEMENT

The study was conducted in accordance with the Declaration of Helsinki and upon signing of informed consent by all participants.

FIGURE 1 Basic hematological comparison and biomechanical properties of red blood cells from CMS patients compared with healthy high-altitude controls. (A) hematocrit (Hct) classically measured using the microcentrifuge method (12 000 rpm for 10 min); (B) hemoglobin (Hb) concentration from a blood gas analyzer (ABL80, Radiometer, Denmark); (C) blood viscosity measured rates using a cone plate viscometer (Brookfield DVII+, CPE-40 spindle, USA) at shear rates ranging from 2.25 to 90 s^{-1}; (D) arterial oxygen partial pressure (PaO_2) measured on an arterial blood sample obtained from a radial artery puncture (i-STAT, Abbott Point of Care, Princeton, New Jersey); (E) oxygen saturation (SpO_2) measured with a pulse oximeter by a finger sensor (Nellcor OxiMax N-65, Medtronic, Ireland); (F) reticulocyte count based on complete blood count (BC-51250 analyzer, Mindray, China); (G) blood volume determined using the CO-rebreathing technique (OpCO, Detalo Instruments; and ABL80, Radiometer, Copenhagen, Denmark); (H) mean RBC volume; (I) mean RBC hemoglobin concentration, (H,I) the orange error bars represent the 95% confidence interval of the plotted values and the gray areas show the 95% interval of healthy males at sea level; (J) microscopic wide-field images of RBC from a representative CMS patient (right) and a representative high-altitude control (left). The scale bars represent 20 μm. Images are taken with a modified CyScope (Sysmex, Germany) to allow inverse operation (×40 objective, CMOS camera). One μL of packed fresh RBC collected in EDTA-tubes was diluted 1:20 000 in physiological solution and imaged after sedimentation in a "18-well μ-Slide" (ibidi, Germany); (K) blood viscosity was measured as in panel (C) but with a normalized hematocrit of 40% (dilution with autologous blood plasma); (L,M) RBC deformability determined by ektacytometry (LoRRca Maxis, Mechatronics, The Netherlands) at various shear stresses, (L) semi-logarithmic plot of the RBC deformability over a shear range from 0.3 to 30 Pa, (M) individual RBC deformation values at a shear stress of 3 Pa; (N,O) aggregation indices, M (stasis) and M1 (very low shear), respectively, samples were measured by light transmission (Myrenne Aggregomater, Germany) at a standardized hematocrit of 40%; (P) Measurement of the elongation index (at a constant shear of 30 Pa) over time measured with LoRRca Maxis (RR Mechatronics, The Netherlands) following the manufacturer instructions; (H–P) no significant differences were found between the population of CMS patients and healthy high-altitude controls. Significance levels are indicated by stars with * referring to $p < .05$, ** to $p < .01$ and **** to $p < .0001$.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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