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Letters to *Blood*

TO THE EDITOR:

Reevaluation of excessive erythrocytosis in diagnosing chronic mountain sickness in men from the world's highest city

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Erythrocytosis is an increase in the number of circulating red blood cells especially resulting from a known stimulus (such as hypoxia).[1] Chronic mountain sickness (CMS) is defined as "a clinical syndrome that occurs to natives or life-long residents above 2500 m. It is characterized by excessive erythrocytosis (females hemoglobin concentration ([Hb]) $\geq$ 19 g·dL^{-1}; males [Hb] $\geq$ 21 g·dL^{-1}), severe hypoxemia, and in some cases moderate or severe pulmonary hypertension."[2(p149)] This syndrome is most prevalent among Andean high-altitude residents and is, presumably, the consequence of a loss of ventilatory acclimatization to altitude promoting hypoxemia and the excessive erythropoietic response leading to high [Hb], hematocrit, and blood viscosity.[3,4] CMS is diagnosed on the basis of a score that includes 7 clinical symptoms and 1 clinical sign, [Hb].[2] Measuring erythrocytosis more accurately by total red blood cell volume (RBCV) indicates that excessive erythrocytosis coincides with abnormally high RBCV expansion in CMS patients living at altitudes ranging from 3600 to 4500 m.[5-8]

La Rinconada, a gold mining town located at 5100 m in Southern Peru, is the highest city in the world. Chronically exposed to an inspired oxygen partial pressure of 77 mmHg,[9] its inhabitants face a unique physiological stress.[10] The severity of environmental hypoxia at 5100 m suggests a high prevalence of excessive erythrocytosis and severe hypoxemia, with a large percentage of the population exhibiting both signs. The use of excessive erythrocytosis as a clinical sign of CMS in such individuals at extremely high altitude may be questionable and may need to be reevaluated. It may be assumed that CMS patients at higher altitudes reach even higher levels of erythrocytosis than at lower altitudes. In support of this, the virtual absence of a ceiling for erythrocytosis is plausible, considering, eg, cobalt intoxication at an altitude where hematocrit was found to exceed 90%.[11] However, it remains unknown whether the magnitude of erythrocytosis associated with CMS increases with altitude. Alternatively, should non-CMS individuals living at 5100 m develop excessive erythrocytosis similar to that of CMS patients, excessive erythrocytosis would no longer be a hallmark of CMS at this extreme altitude.

To test the hypothesis that excessive erythrocytosis is a clinical sign for the diagnosis of CMS at extremely high altitude, we conducted RBCV measurements in non-CMS individuals and CMS patients in La Rinconada. How to define and diagnose CMS in such cases is clinically relevant for the ~60 000 inhabitants of the world's highest city.

The study was ethically approved by the Universidad Nacional Mayor de San Marcos, Lima, Peru (Protocol No. CIEI-2019-002), and each individual gave their written and oral consent for participation prior to inclusion. Thirty-six male residents from La Rinconada (5100 m, Peru) were recruited and categorized into no CMS (CMS$^-$; n = 12) and CMS (CMS$^+$; n = 24). Twenty-five male residents from Puno (3800 m, Peru) and 17 male sea-level residents from Lima (160 m; Peru) were also included. CMS was defined by the CMS Qinghai score with 0 to 5 for CMS$^-$ and $\geq$6 for CMS$^+$,[2] and a modified CMS score was calculated by excluding the [Hb] criterion.[12,13] RBCV, plasma volume, and blood volume were derived from total hemoglobin mass, assessed by the carbon monoxide rebreathing technique, as previously described.[14] Details on participant recruitment, CMS scoring, methods, and statistics are available in the supplemental Material, available on the *Blood* Web site.

Residence at 5100 m was associated with extremely high RBCV (Table 1; Figure 1). To our knowledge, the mean ($\pm$ standard deviation) RBCV of 77.5 $\pm$ 23.4 mL·kg^{-1} measured in non-CMS individuals in La Rinconada is the highest reported value among healthy high-altitude residents. In line with previous data,[5-8] CMS patients at 3800 m presented with excessive erythrocytosis, as shown by their higher RBCV and more severe hypoxemia when compared with non-CMS individuals (Table 1; Figure 1). By contrast, at 5100 m, similar high levels of RBCV in CMS patients and non-CMS individuals demonstrated excessive erythrocytosis in both subpopulations. Furthermore, hypoxemia shown in CMS patients was not more severe than that found among non-CMS individuals (Table 1). Consistent with these results were the similar concentrations of serum erythropoietin in both subpopulations at 5100 m (Table 1), which also

Table 1. Similar hematological profile in CMS patients and non-CMS residents at 5100 m

	Sea level (Lima)	3800 m (Puno)			5100 m (La Rinconada)			*P*				
	All CMS$^-$	All	CMS$^-$	CMS$^+$	All	CMS$^-$	CMS$^+$	Altitude (All)	Altitude (only CMS$^-$)	Altitude (only CMS$^+$)	CMS 3800 m	CMS 5100 m
Participant characteristics												
N	17	25	17	8	36	12	24					
Age, y	28 (23 to 35)	32 (23 to 50)	24 (22 to 32)	51 (49 to 52)	42 (35 to 47)*	39 (36 to 47)*‡	43 (35 to 47)	.005	.017	.002	<.001	.591
Body weight, kg	69 (64 to 75)	69 (63 to 74)	65 (63 to 73)	72 (63 to 83)	71 (65 to 76)	70 (66 to 73)	72 (65 to 77)	.658	.732	.896	.307	.481
Height, m	1.69 (1.66 to 1.71)	1.67 (1.63 to 1.69)	1.68 (1.63 to 1.69)	1.66 (1.62 to 1.67)	1.64 (1.61 to 1.69)	1.64 (1.61 to 1.72)	1.64 (1.61 to 1.67)	.051	.481	.896	.143	.534
BMI, kg·m^{-2}	24.1 (23.2 to 25.0)	24.6 (22.3 to 26.9)	24.6 (22.2 to 26.2)	25.7 (24.0 to 30.5)	25.8 (24.4 to 27.5)	24.8 (24.1 to 26.1)	26.7 (24.4 to 28.0)	.118	.485	.983	.162	.159
Duration of stay, y	—	32 (23 to 50)	25 (23 to 32)	50 (50 to 51)	13 (8 to 20)†	10 (10 to 20)‡	14 (6 to 18)	<.00001	<.001	<.0001	<.001	.942
[Hb], g·dL^{-1}	13.6 (13.4 to 14.4)	18.8 (18.2 to 20.8)*	18.5 (18.0 to 19.0)*	21.4 (20.2 to 23.3)	23.0 (21.7 to 24.4)*†	22.3 (20.0 to 23.9)*‡	23.4 (22.3 to 24.4)	<.00001	<.00001	.043	.047	.180
SpO_2, %	98 (98 to 98)	92 (88 to 94)*	93 (92 to 94)*	86 (82 to 90)	80 (77 to 85)*†	83 (80 to 86)*‡	79 (77 to 83)	<.00001	<.00001	.006	.002	.117
CMS score with [Hb]	0 (0 to 2)	2 (1 to 7)	1 (0 to 2)	8 (8 to 10)	9 (5 to 12)*†	5 (4 to 5)*‡	11 (9 to 13)	<.00001	<.001	.175	<.0001	<.00001
CMS score without [Hb]	0 (0 to 2)	1 (0 to 5)	1 (0 to 2)	8 (5 to 9)	6 (2 to 9)*†	2 (2 to 2)‡	8 (6 to 10)	<.00001	.019	.381	<.0001	<.00001
Hematological characteristics												
Hematocrit, %	43.8 (43.0 to 46.3)	56.0 (55.0 to 65.0)*	55.3 (54.5 to 56.3)*	65.5 (63.8 to 68.4)	73.4 (68.7 to 78.0)*†	69.5 (64.0 to 76.2)*‡	74.0 (71.3 to 78.0)	<.00001	<.00001	.003	.007	.240
EPO, mIU·mL^{-1}	8.9 (7.2 to 11.0) (n = 11)	13.5 (8.5 to 16.3) (n = 12)	13.1 (8.2 to 14.2) (n = 9)	15.8 (14.3 to 20.0) (n = 3)	24.0 (19.6 to 48.6)*† (n = 35)	21.7 (16.0 to 36.6)*‡ (n = 12)	25.3 (20.6 to 52.4) (n = 23)	<.0001	.004	.118	.229	.224
RBCV, mL·kg^{-1}	34.0 (29.5 to 36.6)	42.2 (36.1 to 56.1)*	39.9 (34.6 to 42.2)*	58.8 (50.8 to 66.2)	69.8 (57.2 to 92.7)*†	72.3 (58.7 to 95.6)*‡	69.7 (55.4 to 92.1)	<.00001	<.00001	.098	.001	.712
PV, mL·kg^{-1}	40.7 (35.8 to 49.6)	29.3 (28.2 to 33.7)*	29.3 (27.6 to 33.7)*	29.6 (28.3 to 32.2)	26.7 (23.0 to 32.6)*	28.9 (25.5 to 34.7)*	24.8 (21.5 to 31.9)	<.00001	<.0001	.074	.954	.081
BV, mL·kg^{-1}	77.2 (68.5 to 80.1)	75.5 (63.7 to 86.5)	70.2 (62.9 to 75.5)	88.5 (80.3 to 93.5)	97.6 (81.2 to 124.3)*†	100.2 (90.2 to 120.4)*‡	94.8 (75.6 to 124.3)	<.0001	<.0001	.602	.004	.365
Hb_{mass}, g·kg^{-1}	10.8 (9.4 to 11.3)	13.3 (12.2 to 18.1)*	12.7 (11.8 to 14.0)*	18.8 (16.1 to 22.7)	22.7 (18.1 to 29.5)*†	22.5 (18.8 to 30.6)*‡	22.7 (17.2 to 29.3)	<.00001	<.00001	.164	.003	.814

Participant characteristics of male residents at sea level, 3800 m, and 5100 m. Individuals were categorized with the CMS Qinghai score including the [Hb] criterion. The effect of altitude was assessed with a Kruskal-Wallis test including all participants and also with CMS$^-$ only or with CMS$^+$ only. Pairwise comparisons using a Mann-Whitney *U* test with Bonferroni correction were performed with *$P < .05$ vs sea level; †$P < .05$ vs 3800 m all; ‡$P < .05$ vs 3800 m CMS$^-$. The observed tendency toward an effect of altitude on height ($P = .051$) may be explained by the fact that growth is delayed in Andean highlanders due to a combination of undernutrition, poor health, and chronic hypoxia.[23] However, the absence of a difference in BMI suggests comparable development between populations. The effect of CMS at 3800 m or 5100 m on participant and hematological characteristics was assessed with a Mann-Whitney *U* test. Values are presented as median and interquartile range.

BMI, body mass index; EPO, serum erythropoietin concentration; Hb_{mass}, total hemoglobin mass; SpO_2, arterial oxygen saturation by pulse oximetry.

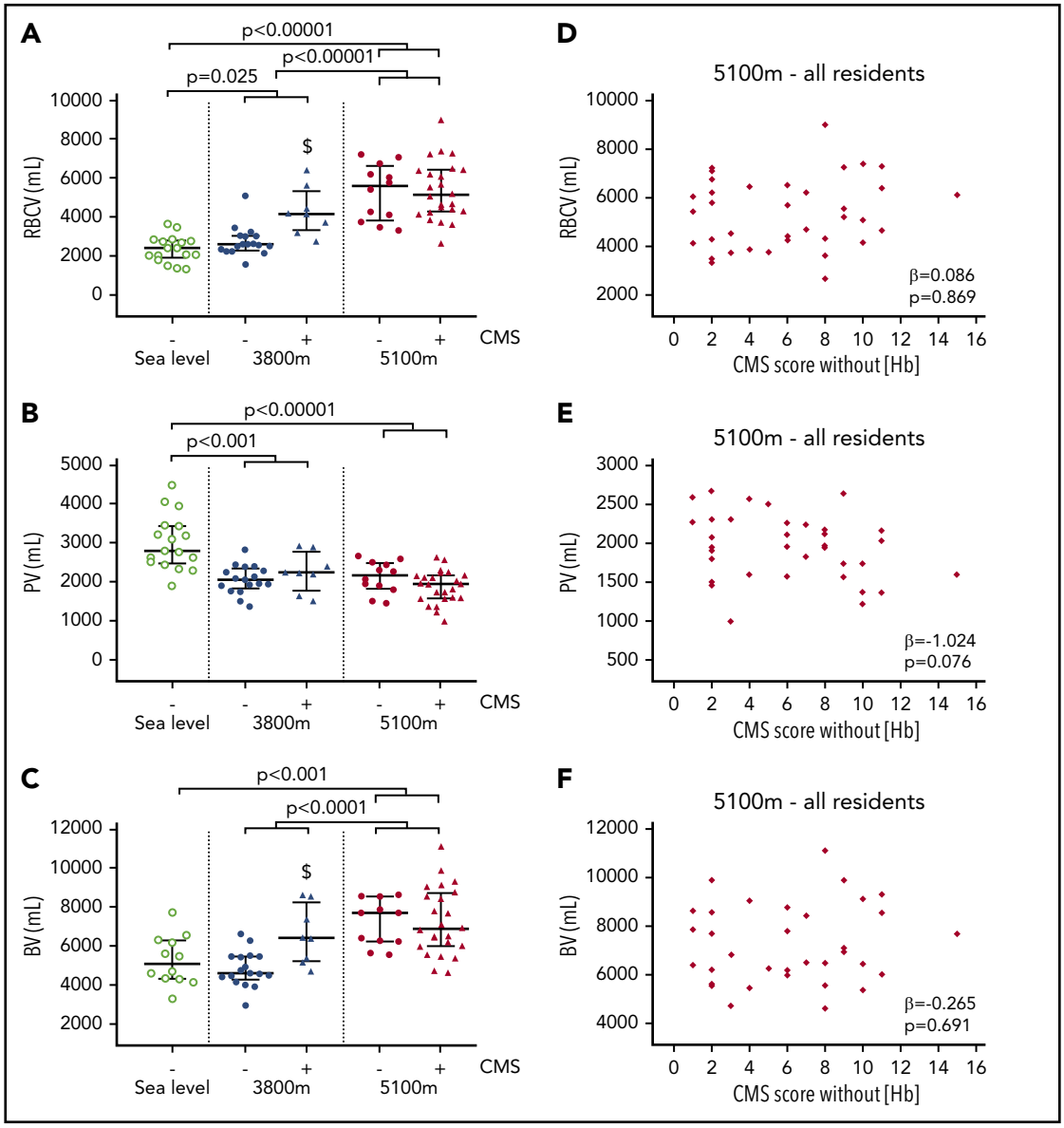

Figure 1. No association between excessive erythrocytosis and CMS score at 5100 m. (A-C) Individual intravascular volumes of participants categorized into no CMS (CMS^-) and CMS (CMS^+) with the CMS score including the [Hb] criterion. Erythrocytosis was determined by RBCV measurement. The effect of altitude was assessed with a Kruskal-Wallis test including all participants. Pairwise comparisons using a Mann-Whitney *U* test with Bonferroni correction were performed and visualized with brackets above the graphs. The effect of CMS at 3800 m or 5100 m was assessed with a Mann-Whitney *U* test with $\$P < .01$ vs CMS^-. Lines indicate median and interquartile range. (D-F) Individual intravascular volume data from all residents at 5100 m showing associations of intravascular volumes with the CMS score excluding the [Hb] criterion. Linear regression analysis was performed with β indicating the age-adjusted regression coefficient calculated from log-transformed data. β and *P* values for regression analysis with the CMS score including the [Hb] criterion were as follows: RBCV: $\beta = 0.506$, $P = .130$; PV: $\beta = -0.762$, $P = .041$; BV: $\beta = 0.292$, $P = .499$. For panel (E), the *P* value of the regression analysis was $P = .111$ when the individual with a score of 15 was removed from the analysis. (G) The distribution of CMS symptom severity between the 2 cities with different altitude with $^*P < .001$ between 3800 m (Puno) and 5100 m (La Rinconada). The numbers on the right of the graph indicate the symptoms' severity. BV, blood volume; PV, plasma volume.

illustrates the strong persistent erythropoietic drive among the healthy residents of La Rinconada. Our finding that excessive erythrocytosis may not be a clinical sign for the diagnosis of CMS at very high altitude implies that, in these circumstances, any CMS diagnosis would have to rely uniquely on symptoms included in the current diagnostic criteria. Moreover, including [Hb] in the score may complicate the diagnosis, as according to our observations in residents of La Rinconada, the non-CMS individuals had a median score of 5 (Table 1). Such a score could be interpreted as borderline mild CMS phenotype and highlights the difficulties in distinguishing between cases and controls in such a population. This score in fact reflected the high prevalence of [Hb] $\geq$ 21 g·dL^{-1} rather than symptoms. The CMS score without [Hb] did however demonstrate the overall low symptomatology among healthy non-CMS individuals of La Rinconada (Table 1).

To explore the effect of age on RBCV across altitude levels and CMS status, we conducted a multivariable analysis (see supplemental Material). Altitude was associated with RBCV independently of age and CMS status, whereas no independent association was found between CMS and RBCV. The age was also independently

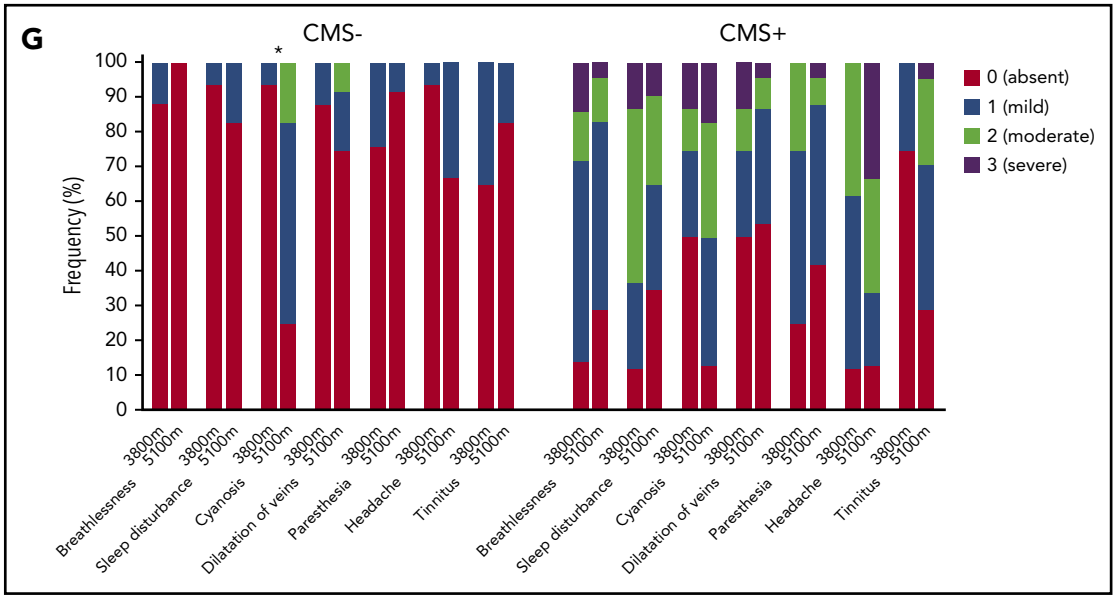

Figure 1. (Continued).

associated with RBCV, consistent with the increasing hematocrit[15] or [Hb][16] with age at high altitude.

Analysis of symptoms did not evoke a pattern specific to very high altitude, as the distribution of symptoms did not differ between CMS patients at 3800 m and those at 5100 m (Figure 1G). Nonetheless, the higher prevalence of symptoms like cyanosis and headache in la Rinconada, independently of CMS (supplemental Table 1), should be accounted for in the diagnosis.

Although excessive erythrocytosis may not characterize CMS at very high altitude, our data suggest that exaggerated plasma volume contraction may be more informative, as indicated by the trend toward a lower plasma volume among CMS patients at 5100 m (Table 1). In such individuals, plasma volume also tended toward an association with the CMS score not including [Hb] (Figure 1E) and was associated with the score including [Hb] (legend to Figure 1). Data showing decreased plasma volume in CMS patients[5] as well as the recent suggestion that maintaining high plasma volume may play a key role in successfully adapting to high altitude[17] support our observation. An accentuated plasma volume contraction would contribute to the elevated blood viscosity reported in CMS patients.[18,19] High viscosity is related to clinical manifestations, such as headache and tinnitus,[20] symptoms that are included in the CMS score. Nevertheless, in the absence of robust statistical differences, our observation on plasma volume should be interpreted with caution.

In conclusion, excessive erythrocytosis as identified via direct RBCV determination was found to not be a clinical sign of CMS among the residents of the world's highest city. This finding reorients the diagnosis of CMS at very high altitude toward a score using only the symptoms. The dissociation between excessive erythrocytosis and CMS in severe chronic hypoxia may help the understanding of other human hematological disorders, such as Chuvash erythrocytosis, in which the role of elevated hematocrit as the principal determinant of thrombotic risk is under question.[21,22]

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Authorship

Contribution: C.L., I.H., P.R., and S.V. conceived and designed the research; A.-K.M.L., A.P., E.S., L.O., and M.U.-R. performed experiments; L.O. analyzed data; C.L., L.O., and P.R. interpreted results of experiments; L.O. prepared the figures; C.L., L.O., and P.R. drafted the manuscript; A.P., C.L., E.S., F.C.V., I.H., M.U.-R., L.O., P.R., and S.V. edited and revised the manuscript; and A.-K.M.L., A.P., C.L., E.S., F.C.V., I.H., M.U.-R., L.O., P.R., and S.V. approved the final version of the manuscript.

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Footnotes

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TO THE EDITOR:

No evidence of SARS-CoV-2 transfusion transmission despite RNA detection in blood donors showing symptoms after donation

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Since December 2019, a novel human coronavirus, SARS-CoV-2, has emerged from China where the first cases of COVID-19 were described.[1,2] It is the third highly pathogenic coronavirus introduced in humans from animal reservoirs[3,4] and has spread worldwide, leading to an unprecedented pandemic. By August 2020, more than 20 million cases have been reported worldwide, including almost 0.8 million deaths. France has reported more than 200 000 cases and 30 000 deaths with an epidemic peak at week 14 (30 March-5 April).[5] SARS-CoV-2 is mostly transmitted through airborne droplets,[6-8] with a reproduction number (R_0) varying between 2.5 and 3.5 before the implementation of control measures.[9-11] COVID-19 incubation is short (5.7-5.9 days)[12] and mostly asymptomatic or with moderate symptoms, but 20% to 25% of infected individuals develop severe symptoms, some of them needing intensive care.[6,13,14] First reported data suggested the presence of SARS-CoV-2 RNAemia in