The Effect of Chronic Erythrocytic Polycythemia and High Altitude upon Plasma and Blood Volumes[1] (36580)

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Physiological chronic erythrocytic polycythemia is found generally in homeotherms residing at high altitude—the apparent result of the hypoxic environment. The effect of this phenomenon, however, upon the blood volume and its constituents has not been clearly established.

It is generally agreed that an increase in the body erythrocyte volume produces an increased blood volume, however, the effect upon the body plasma volume is not clear. Hurtado (1) concluded that only minor changes occurred in the plasma volumes of high-altitude natives. However, recently, Sanchez, Merion and Fegallo (2) found a large reduction, 27%, in plasma volumes of high-altitude natives which was inversely correlated with the hemotocrit.

In order to differentiate the specific effect of erythrocytic polycythemia from the general effects of high altitude upon the plasma volume, two kinds of physiological chronic erythrocytic polycythemias were compared. These were produced in female domestic fowl[3] (chickens): (a) hormonally, at sea level, or (b) by protracted high-altitude exposures.

Methods. Single-comb white leghorn adult chickens were used in these studies.[4] High-altitude data were collected from birds hatched and raised at the White Mountain Research Station, Barcroft Laboratory—elevation 12,500 feet.[5]

Chronic erythrocytic polycythemia was produced at sea level (at Davis, elevation 50 ft) in adult hens by androgen (testosterone) injections (im)—25 mg testosterone repository 3 times each week for 3 months (3).

Plasma volumes were directly determined from the dilution of intravenously injected human serum albumin labeled ^{131}I (4). Blood samples were taken 3 min after isotope injection, which is adequate time for complete vascular mixing in the chicken (5).

Blood and body erythrocyte volumes were determined indirectly from the plasma volume data and the peripheral hematocrit. The hematocrits were obtained by standard micro methods (6) with blood taken from the brachial (wing) vein. Inherently, blood volumes calculated by this method include inaccuracies because of incomplete erythrocytic (hematocrit) packing and plasma skimming in the peripheral circulation. However, these errors can be estimated from the following equation (6):

$$BV = \frac{PV}{100} - (HCT \times 0.90) \times 100, \quad (1)$$

Where

PV = blood volume (ml); and,
BV = plasma volume (ml); and,
HCT = hematocrit (%).

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[3] The female *Aves*—domestic fowl in particular—are unique for homeotherms in that their hematocrit may be significantly increased at sea level with androgen (testosterone) injections to a value comparable to that found in hens living at 12,500 ft (3).

[4] The animals involved in this study were maintained in accordance with the "Guide for Laboratory Animal Facilities and Care" as published by the National Academy of Sciences–National Research Council.

[5] The high-altitude studies were conducted at the White Mountain Research Station (located near Bishop, CA) which has laboratories at 4000, 10,150, 12,500, and 14,250 ft elevations. For further information regarding these facilities, contact the director: Professor Nello Pace, Department of Physiology, University of California, Berkeley, CA 94720.

TABLE I. Various Hematologic Parameters Are Compared for 3 Groups of Adult Female Chickens: (a) High Altitude (12,500 ft); (b) Androgen-Treated[a] Living at Sea Level; (c) Sea-Level Controls (No Treatment).[b]

Group	n	Body mass (kg)	HCT (%)	Plasma vol (ml)[c]	Erythrocyte vol (ml)[c]	Blood vol (ml)[c]
Controls	34	1.62 ± 0.04	29.9 ± 0.6	63.5 ± 2.0	23.2 ± 0.7	86.7 ± 2.5
High altitude (12,500 ft)	12	1.64 ± 0.09	42.7 ± 0.9	64.3 ± 2.6	40.2 ± 1.9	104.5 ± 4.3
Androgen treated[a]	17	1.60 ± 0.08	45.9 ± 0.7	52.9 ± 2.3	37.3 ± 1.7	90.2 ± 3.8
F ratio		0.10	177.1	6.38	59.2	6.19
p[d] <		ns	.01	.01	.01	.01

[a] For details regarding androgen treatment, see "Methods" in text.

[b] Shown are mean values ± standard errors and an analysis of variance evaluation. n = number of animals per group; HCT = hematocrit; F ratio = analysis of variance statistical calculation.

[c] Methods of determination are found in text.

[d] Statistical probability (ns = not significant)—degrees of freedom, numerator = 2 and denominator = 60.

The factor, 0.90, was derived from data obtained at this laboratory (7). It is quantitatively similar to the factor, 0.88, established by Cohen (8) for the duck.

Results. The body mass, hematocrit, and various absolute blood volumes for groups of (a) high altitude, (b) sea-level androgen treated, and (c) sea-level controls—adult female chickens (all approx. 1 year of age) are summarized and compared in Table I. Analyses of variance indicate that significant differences are present between group values for all parameters except body mass. Statistical and quantitative comparisons between groups are shown in Table II.

Androgen treatments or high-altitude exposure produced similar increases in the hematocrits (+43 to +54%) of adult female chickens. Both procedures also increased the body erythrocyte volumes by approximately the same magnitude (+61 to +73%). These two procedures, however, affected the plasma volumes differently. No change in plasma volume was found at high altitude, but there was a significant reduction (—17 to —18%) in the androgen-treated birds, compared with either the sea-level controls or the high-altitude birds (Table II). This reduction in plasma volume resulted in a significant decrease (—14%) in total blood volume of the androgen-treated birds compared with the high-altitude birds, but no significant differ-

TABLE II. Statistical and Quantitative Comparisons of Various Hematologic Parameters Using 3 Groups of Adult Female Chickens as Shown in Table I.

Group comparison		df[a]	HCT	Plasma vol	Erythrocyte vol	Blood vol
High altitude vs controls	p <[b]	44	.001	ns[c]	.001	.001
	Δ%[d]		+42.8		+73.3	+20.5
Androgen vs controls	p <	49	.001	.01	.001	ns
	Δ%[d]		+53.5	—16.7	+60.8	—
Androgen vs high altitude	p <	27	.01	.01	ns	.05
	Δ%[d]		+7.5	—17.7	—	—13.7

[a] df = degrees of freedom (total n—2).

[b] p < = statistical probability of chance occurrence.

[c] ns = not statistically significant, $p > 0.05$.

[d] Δ% = {(high altitude—control) ÷ (control)} × 100.

TABLE III. Comparison of High-Altitude Chicken Blood Volumes (This Report) with High-Altitude Native (Human) Values (% body mass).[a]

Parameter	Sanchez, Merion and Fegallo (2) (14,200 ft)	Hurtado (1) (14,900 ft)	Reynafarje (10) (14,900 ft)	This report (12,500 ft)
Blood vol[b]	+14	+26	+27	+20
Plasma vol	−27	− 7	+ 6	+ 1
Erythrocyte vol	+83	+64	+49	+72
HCT	+47	+27	+39[c]	+43

[a] Shown as percentage change from sea-level values. HCT = hematocrit.

[b] Values relative to body mass.

[c] Hemoglobin value (HCT not available).

ence was evident between them and the sea-level controls.

Discussion. A comparison was made of the data obtained at high altitude (12,500 ft) for chickens with previously reported human values obtained at elevations of 14,000 to 15,000 ft using values mathematically related to body mass (% body mass; Table III). These calculations are appropriate since the somatic relationship of blood volume is approximately isogonic—proportional to body weight (9)—and the body sizes of the experimental groups were quite uniform (Table I). These altitude-induced changes in the chicken, as percentage differences from sea-level values, are similar, both quantitatively and qualitatively, to those reported by Hurtado (1) and Reynafarje (10)—that is, no significant changes were found in plasma volumes. However, Sanchez, Merion and Fegallo (2) reported a 27% reduction in plasma volumes at high altitude, a finding similar to the response of chickens to androgen treatment (Table II).

Sanchez, Merion and Fegallo (2) noted this discrepancy between their data and those of prior reports. This was attributed to the different techniques they used in measuring blood volumes. They also reported a significant inverse correlation between relative plasma volume and hematocrit values (correlation coefficient $r = -0.693$; $p < .01$) in the high-altitude natives. No similar significant relationship was found in the high-altitude data reported herein (correlation coefficient $= -0.37$; $p > .05$).

A possible reason for the inverse relationship between hematocrit:plasma volume in high altitude subjects may be an age effect, which apparently was not considered by Sanchez, Merion and Fegallo (2). Their high-altitude natives had an age range of 20–54 years (mean of 36 years), compared to 20–26 years (mean of 24 years), for their sea-level group. Variation in their reported hematocrit (HCT, % PCV) and relative plasma volumes (PV, ml/kg) appear to be closely correlated with age (A, years): (a) age vs hematocrit ($r = 0.81$) and (b) age vs relative plasma volume ($r = 0.73$). Regression analyses of these data indicate the relationships:

$$PV = 53.2 - 0.55A, \quad (2)$$

$$HCT = 38.8 + 0.64A. \quad (3)$$

A comparison of blood volumes reported by Sanchez, Merion and Fegallo (2) for sea-level subjects, for high-altitude natives, and for older high-altitude residents is given in Table IV. The values for the younger high-altitude natives are similar to those reported by Hurtado (1) and by Reynafarje (10), indicating only a minor reduction in plasma volumes in young persons at high altitude.

This age effect upon plasma volume and hematocrit apparently is not found at sea level, although this apparently has not been completely resolved (11–13). It would appear, however, that age effects on these parameters are pronounced at high altitudes —apparently a specific environmental response.

The inverse relationship between hematocrit:plasma volume (2) appears to be a response similar to the reduction in plasma volume found in the androgen-treated birds

TABLE IV. Comparison of Blood Volumes (% Body Mass) of Young and Middleaged High-Altitude Natives with Sea-Level Subjects—Data of Sanchez, Merion and Fegallo (2).[a]

Parameter	Age (years)	
	Mean = 22 (range 20–30)	Mean = 45 (range 35–54)
Blood vol[b]	+9	+18
Plasma vol	−8	−40
Erythrocyte vol	+36	+112
HCT	+24	+61

[a] Shown are percentage changes from sea-level values—mean age 24 years. HCT = hematocrit.

[b] Values relative to body mass.

(Table II).

It appears, therefore, that the vascular system of the body may account for an increase in red blood cell mass by either (a) reduction in plasma volume or (b) no change in plasma volume resulting in differential changes in total blood volumes. The latter apparently occurs in animals residing at high altitudes. The former appears to be a response to physiological polycythemias initiated by stimuli other than or in addition to high altitude.

Conclusion. Chronic erythrocytic polycythemias were produced in adult female domestic fowl (chicken): (a) hormonally (by androgen injection) at sea level, or (b) by protracted high-altitude (12,500 ft) exposure. Plasma volumes were determined directly by injected ^{131}I human serum albumin dilution methods. Total body erythrocyte and blood volumes were calculated from plasma volumes and adjusted peripheral hematocrits. Androgen treatment or high-altitude exposure similarly increased the hematocrits approximately 45% and the body erythrocytic volumes approximately 65%. These two procedures, however, affected the plasma volumes differently. No change in plasma volume was found at high altitude; however, there was a significant (17%) reduction in plasma volume in the androgen-treated birds as compared with either the sea-level controls or the high-altitude birds. It appears, therefore, that the vascular system of the body accounts for an increase in erythrocytic mass by either (a) a reduction in plasma volume or (b) no change in plasma volume, in which case differential changes occur in total blood volumes.

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