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Could Hypoxia increase the prevalence of thrombotic complications in Polycythemia Vera?

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Abstract

Background—Thromboses represent a major cause of morbidity and mortality in Polycythemia Vera (PV) but the contributing mechanisms are not fully described.

Patients and methods—To evaluate whether environmental conditions such as altitude/hypoxia could impact thromboses history, we retrospectively analyzed thrombosis history in 71 PV patients living at an elevation of 5,000 feet or more in the SLC area (SLC) and 166 PV patients living near sea level in the Baltimore area (BLM). The SLC cohort was older with a longer disease duration. No significant differences in type of anticoagulation therapy or prothrombotic factors were present between the two cohorts. After adjusting for age, sex and disease duration, SLC patients experienced an estimated 3.9-fold increase in the odds of a history of thromboses compared to BLM patients (95% confidence interval 1.8-7.6; $p = 0.0004$). A history of cardiovascular event was present in 58% of the SLC patients compared to 27% of the BLM patients ($p < 0.0001$). Before diagnosis thromboses occurred in 18% and 4% of the SLC and BLM groups respectively ($p = 0.003$). No correlation between *JAK2*^{V617F} allele burden and thrombosis was observed in this study.

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Author Contributions: Dr. Prchal had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs. Zangari, Prchal, Tolomelli, Lee contributed equally to this work.

Study concept and design: Dr. Zangari first raised a possibility of increased thrombosis in Salt Lake City based on his experience with other hematological patients compared to his experience at Little Rock, Arkansas. Together with Dr. Prchal, Dr. Zangari set up to study the effect of high altitude in PV.

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Conclusion—This retrospective study suggests that even moderate hypoxia associated with 5,000 feet elevation should be considered as independent prothrombotic risk factor. This observation needs to be confirmed by prospective studies.

Introduction

Polycythemia Vera (PV) is the most common primary polycythemia with an estimated incidence of 2.3 per 100,000 persons/year (1, 2). This myeloproliferative neoplasm is characterized by clonal proliferation of hematopoietic precursors that leads to an increased erythrocyte mass unrelated to erythropoietin (EPO) levels and increased platelet and granulocyte counts. Long-term consequences include splenomegaly, hyperuricemia with secondary gout, erythromelalgia, neurological manifestations, aquagenic pruritus, hemorrhage, and the risk of evolution to myelofibrosis, myelodysplasia and acute leukemia. Thrombotic complications are the major cause of morbidity and mortality and are reported as the presenting symptom in 12 to 49% of patients (1, 2). Deep venous thrombosis, myocardial infarction, acute coronary syndrome, Budd-Chiari syndrome, pulmonary embolism, stroke and transient ischemic attacks often have been explained by the hyperviscosity from the increased hematocrit and/or thrombocytosis (3, 4). However, these etiologies have recently been challenged (5, 6) and other contributing mechanisms have not been excluded. For example, the European Collaborative Study on Low-Dose Aspirin in Polycythemia Vera showed that the rate of major thrombotic events was approximately doubled in patients older than 65 years of age and four-fold higher in individuals with an additional thrombotic history (7). Leukocytosis has been reported as independent risk factor for arterial thrombosis (5, 8, 9). The presence of *JAK2*^{V617F} mutation and/or the burden of mutated alleles have been suggested to be associated with thrombotic complications in PV (10) even though a prospective study has not confirmed the finding (11). Thus, the pathophysiology of thrombosis in PV is not yet entirely explained.

Chronic hypoxia induces many physiological responses to compensate for the decreased tissue oxygen supply, including erythropoietin (EPO) production that may result in secondary erythrocytosis and pulmonary hypertension. Chuvash polycythemia, an autosomal recessive genetic disorder with augmented hypoxia sensing, shares features with both primary and secondary polycythemia. These patients are homozygous for the R200W loss-of-function mutation in the *Von Hippel Lindau* (*VHL*) tumor suppressor gene, a negative regulator of the alpha subunit of hypoxia inducible factors (HIFs) (2, 8). Chuvash polycythemia patients have elevated HIF-1 and HIF-2 levels at normoxia resulting in increased EPO production and elevated red blood cell mass; yet the mechanisms of augmented erythropoiesis are not fully explained (2, 8, 12). Chuvash polycythemia is characterized by an increased morbidity and mortality largely due to thrombotic complications which appear unrelated to the hematocrit level. These considerations suggest either that inherited augmented hypoxia-sensing or environmental extrinsic conditions could play a significant role in the pathogenesis of cardiovascular complications in PV (13).

To our knowledge, environmental conditions have not been examined as potential modifying factors for the development of thrombotic events in cancer patients. Salt Lake City (SLC), Utah, is located in a valley at ~5,000 feet of altitude and surrounded by populated mountains reaching 9,000 feet. This relatively hypoxic environment is appreciated by physiologic sensors and is reflected in a mean hemoglobin concentration that is 0.6-1.3 g/dL higher than the average value in the US (14). To analyze the effect of relative hypoxia on PV-associated thrombosis, we retrospectively compared the prevalence of thrombotic complications in patients dwelling in SLC with those inhabiting at sea level in Baltimore (BLM), MD.

Patients and Methods

We reviewed the clinical history of 237 PV patients from 2005 to 2010. Seventy-one individuals inhabited the SLC area at an average elevation of ~ 5,000 feet above sea level or more, and 166 were living in the BLM area located at sea level. The clinical and laboratory characteristics of the subjects are summarized in Table 1. The median age at diagnosis was 67 years in SLC and 53 years in BLM; 32% of the subjects in SLC were women compared to 64% in BLM. The median disease duration for patients at the time of our analysis was 7.8 years in SLC and 5.6 years in BLM. The diagnosis of PV was based on the Polycythemia Vera Study Group and WHO Criteria and all patients were positive for *JAK2*^{V617F} mutation (15, 16, 17). Genomic DNA was isolated from purified granulocytes using the Puregene DNA purification kit (Gentra, MN, USA) in both Baltimore and Salt Lake City. The *JAK2*^{V617F} mutational burden in neutrophil genomic DNA was determined by a quantitative allele specific polymerase chain reaction (AS-PCR) at both the University of Utah and at ARUP Laboratories (Salt Lake City) (18), and by a quantitative real-time PCR assay using allele-specific probes in Baltimore (19). The median time to diagnosis for *JAK2*^{V617F} mutational burden was 4.8 years in Salt Lake City, and 5.6 years in Baltimore (concordance of assays as in ref. 20) (20).

All patients signed an Institutional Review Board approved Informed Consent that indicated their medical records were available for our analysis. Collected information included: *JAK2* allelic burden, thromboses history, age at 1st thrombosis, WBC count, use of anticoagulant and/or anti-platelet-therapy and type of thrombotic events. In this analysis we considered all the following thrombotic event types: transient ischemic attack (TIA), acute coronary syndrome (ACS), cerebrovascular accident (CVA), deep venous thrombosis (DVT), pulmonary embolism (PE), abdominal and sagittal vein thrombosis, miscarriage, and minor occlusive events such as erythromelalgia.

Statistical Analysis

Categorical variables were compared among groups by the χ^2 test. Continuous numeric variables were expressed as medians and compared among groups by the Kruskal-Wallis test. Statistical significance was set at 0.05 ($p < 0.05$). The relationship of thrombosis history to study site was examined in univariate and multivariate logistic regression models.

Results

A total of 237 patients were included in this retrospective analysis, 71 from SLC and 166 from BLM (Table 1). The SLC patients were predominantly males (68%) while those in BLM were predominantly females (64%). The SLC patients were older (mean age: 67 years) than the BLM patients (mean age: 53 years) ($p < 0.0001$). Over half of the patients in both cohorts (SLC and BLM) had received ASA but less than 25% had received warfarin with no significant difference between groups. The mean disease duration in SLC patients (7.8 years) was statistically longer ($p = 0.021$) compared to the Baltimore PV individuals (5.6 years). The white blood cell (WBC) count of $11.7 \times 10^9/L$ in the SLC group was considerably lower than the count of $15.3 \times 10^9/L$ observed in the BLM group ($p = 0.003$).

Eighty-six patients (36%) experienced a thrombotic event, 41 cases (58%) in SLC group and 45 cases (27%) in the BLM cohort ($p < 0.0001$) (Table 1). The mean age at the first thrombotic event was similar between the two groups of patients (60 years in SLC vs 57 years in BLM) ($p = 0.3$). Thrombotic complications were higher in the SLC cohort irrespective of the age distribution (Fig 1a). When stratified by sex, 15 of 23 (65%) SLC female patients had a history of thrombosis compared with 34 of 106 (32%), BLM females ($p = 0.003$). Twenty-six of 48 (54%) SLC males had a thromboses history compared with 11

of 60 (18%) BLM males ($p=0.0001$). SLC patients experienced a 3.7-fold increase in the odds of history of thromboses compared to BLM subjects after adjusting for age, sex, white blood cell count and disease duration, (95% CI 1.8-7.6, $p=0.0004$) (Table 2).

Thrombotic events preceding the diagnosis of PV were observed in 13 patients (18%) in the SLC cohort and 7 patients (4%) in the BLM cohort (Table 1). After adjusting for age at diagnosis and gender, SLC patients showed a 2.5-fold increase in the odds of history of thromboses before the diagnosis of PV compared to the BLM subjects (95% CI 1.0-6.1, $p=0.048$). The SLC patients also demonstrated a significantly lower WBC counts after adjusting for age, sex and disease duration ($p=0.003$).

All analyzed subjects were carriers for *JAK2*^{V617F} mutation. The mean allele burden in the BLM cohort was 66% and it was statistically higher ($p=0.0002$) than in the SLC cohort (49%). We performed univariate and multivariate analysis of all the known predictor factors for thrombosis in the entire group of patients (Tables 3, 4). In multivariate analysis age, location and gender were all found statistically significant, but *JAK2* allele burden was not associated to thrombosis in the entire PV group and not appreciable different in the subjects with or without thrombosis in either location ($p=0.30$).

As shown in Figure 1b, CVA was the most common type of event in SLC, accounting for the 24% of the total thrombotic episodes. In our study, SLC males ($n=48$) had a higher risk (OR 15, 26 95% CI 1, 87-124, 14 $p=0.01$) of arterial thromboses (acute coronary syndrome and CVA) compared with BLM males ($n=59$). SLC females ($n=23$) had also an increased risk (OR 3, 65 95% CI 1, 35-9, 85 $p=0.01$) of venous thrombotic episodes (portal, hepatic and mesenteric veins and DVT/PE) compared to BLM females ($n=107$). The frequency of TIAs and sagittal vein thromboses was similar in both cohorts. Odds ratios for individual thrombotic events after adjusting for age, gender and disease duration are presented in Table 5. There were differences in rates of abdominal venous thromboses but no significant differences in the type of cardiovascular events among two groups.

Discussion

Increased blood viscosity due to high hematocrit as well as quantitative and qualitative platelet and leukocyte abnormalities are considered to have a major role in the pathogenesis of the PV associated thrombophilia (1, 3, 4). However, other major contributing factors to PV thromboses still need to be delineated and one potential factor could be an augmented hypoxic signaling. We investigated the possible role of relative hypoxia in the SLC area as one of the contributing factors to thromboses in PV. We retrospectively analyzed two groups of PV patients, one living in SLC at ~5,000 feet and more above sea level and another living in BLM close to sea level. Under hypoxic conditions, multiple physiologic compensatory mechanisms take place to adapt tissues to a lower oxygen partial pressure, including elevated EPO (2, 21). It is tempting to consider that hypoxia driven upregulation of HIF-family transcription factors could also be involved in the thrombotic tendency in PV patients living at high altitudes despite the well-documented suppression of erythropoietin production in PV. Consistent with other reports, we observe a considerable percentage of thrombotic events in both cohorts manifested before the diagnosis of PV. In the prospective multicenter ECLAP study, 35.8% of patients developed a thrombotic event before and only 10% after enrollment (22); similar findings were reported in the GISP with a 22% incidence of major thromboses prior to diagnosis and a much lower incidence after PV diagnosis was established (23). These reports resemble what we observed in the SLC cohort where a positive history of thrombotic events was documented in 58% of patients, of which 18% occurred before PV diagnosis ($n=13$). In the BLM cohort the total rate of thromboses was

overall markedly lower (27%) with only 4% of patients (n=7) reporting thrombotic events before the diagnosis.

These findings suggested a possible role of relative hypoxia in the pathogenesis of thrombotic complications.

Both the BLM and SLC cohorts consisted of entirely positive subjects for *JAK2*^{V617F} mutation. The mean allele burden was higher in the BLM cohort (66%) than the SLC cohort (36%; $p=0.0002$). Although the presence of the mutation has been considered to be a co-factor for increasing the rate of thromboses (24), our multivariate analysis failed to show an association of JAK2 with cardiovascular complications in the entire group or in each separate cohort.

As the WBC count has been previously described as an independent prothrombotic factor in PV patients (8), we analyzed its possible contribution in developing thrombosis among patients living in SLC. In a multivariate analysis, we found a higher prevalence of thrombosis despite the considerably lower WBC count ($11.7 \times 10^9/L$) in SLC compared with the BLM cohort ($15.3 \times 10^9/L$) ($p=0.003$).

The reported male to female ratio in PV is 1.2 to 2.2(1, 25, 26), in our study is more representative of the SLC region population. By univariate analysis, female gender was associated with an increased risk of abdominal vein thrombosis and in multivariate analysis female gender remained as an independent risk factor for the history of thrombosis. Previously in literature (4), and more recently by us (27), a relationship between gender and thrombotic complications has been described. Interestingly, the BLM cohort mainly represented by women (64%), had a lower rate of thrombosis in comparison with the cohort in SLC. Our multivariate analysis of all the known prothrombotic factors in the entire group of patients suggested that location (SLC) was the prominent element indicating hypoxia as a possible driving factor in cardiovascular complications developed by PV patients.

In keeping with the suggestion from our data that even mild to moderate chronic hypoxia may be a contributing prothrombotic factor in PV, the constitutive increase of hypoxia sensing due to upregulated levels of HIF-1 and HIF-2 in Chuvash polycythemia, produces the transcription of a myriad of HIF-1 and HIF-2 target genes including *EPO*, the transferrin receptor and *VEGF*. These changes are associated with a marked increase of thrombotic complications, not related with either hemoglobin/hematocrit or phlebotomy (13).

The condition is associated with a marked increase of thrombotic complications, which do not correlate with either with hemoglobin/hematocrit nor phlebotomy (13). However, it needs to be considered that there is a substantial individual variability in the response to hypoxia, making the ultimate outcome of effect of hypoxia unpredictable in an otherwise unselected individual (28, 29). These presumably genetic factors accounting for the variable hypoxic response remain to be defined. Some of these factors have been selected in certain populations such as Tibetan and Andean highlanders (30) and their function is being currently elucidated (31). Thus, the hypoxic exposure would be expected to result in varied activation of HIF regulated pathways found in subjects with heterogeneous genetic background as reported in US athletes (32). It is tempting to speculate that the different levels of HIFs activation in a hypoxic environment may correlate with the diverse thrombotic risk encountered in PV subjects. Further prospective studies are needed to confirm these data.

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Figure 1a.
Frequency of the 1st thrombosis in each range of age.

Figure 1b.
Percentage of thrombotic types on total thrombotic events in SLC and in BLM.

Table 1

Demographic table.

	Salt Lake City PV Cohort (N=71)	Baltimore PV Cohort (N=166)	P value
Women, number (%)	23 (32%)	106 (64%)	P<0.0001
Age at diagnosis (years), mean (SD)	67 (13)	53 (15)	P<0.0001
Age at first thrombosis (years), mean (SD)	60 (14) ^a	57 (17) ^b	P=0.3
Disease duration (years), mean (SD)	7.8 (7.0)	5.6 (5.9)	P=0.021
Aspirin use, number (%)	49 (69%)	94 (65%) ^c	0.5
Coumadin use, number (%)	15 (21%)	18 (11%)	0.036
WBC mean (1000/ul), mean (SD)	11.7 (7.4)	15.3 (10.7) ^d	P=0.003
Thrombosis before diagnosis, number (%)	13 (18%)	7 (4%)	P=0.037
JAK2 V617F alleleburden, mean (%), (SD)	49 (36) ^e	66 (20)	P=0.0002
Total Thrombosis history, number (%)	41 (58%)	45 (27%)	P<0.0001

^aN = 36^bN = 40^cN = 145^dN = 165^eN = 70

Table 2

Independent associations of clinical parameters and geographic location with total history of thrombosis by logistic regression.

	Odds ratio of thrombosis	95% confidence interval	P
Age	1.2	1.0 – 1.5	0.075
Female gender	2.1	1.1 – 3.9	0.021
Disease duration	0.9	0.5 – 1.4	0.6
White blood cell count (increase by 1000/ μ L)	0.99	0.96 – 1.02	0.5
Salt Lake City	3.7	1.8 – 7.6	0.0004

Table 3

Univariate Analysis of all the known predictor factors for thrombosis in the entire group of patients.

Predictor	Odds ratio	P-value
Age	1.34	0.001
Located in Utah	3.67	0.000012
JAK 2	0.98	0.028
Disease Duration (years)	0.999	0.96
WBC (per measurement unit)	0.98	0.21

Table 4

Multivariate Analysis of all the known predictor factors for thrombosis in the entire group of patients.

Predictor	Odds ratio	P-value
Age	1.24	0.045
Located in Utah	3.14	0.003
JAK 2	0.994	0.29
Disease Duration (years)	0.994	0.81
WBC (per measurement unit)	0.996	0.79
Male	0.45	0.01

Table 5

Odds ratio for event in SLC patients compared to BLM patients after adjustment for age, sex, and disease duration.

	Odds ratio of thrombosis	95% confidence interval	P
TIA	2.7	0.8 – 9.2	0.1
Microvascular	1.5	0.1 – 20.0	0.8
ACS	2.8	0.8 – 10.4	0.1
CVA	2.6	0.8 – 8.5	0.1
Abdominal vein	3.5	1.1 – 11.3	0.037
DVT/PE	1.6	0.5 – 5.1	0.4
Sagittal vein thrombosis	3.3	0.1 – 83.7	0.5
Miscellaneous^I	6.5	0.8 – 51.6	0.1

Abbreviation: TIA, transient ischemic attack; ACS, acute coronary syndrome; CVA, cerebro-vascular accident; DVT, deep venous thrombosis; PE, pulmonary embolism.

^I Miscarriages and erythromelalgia