

## Evaluation of Arterial Compliance in Polycythemia Vera Patients: Short and Long-Term Influence of Phlebotomy

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### Abstract

**Background:** Thrombosis is a major cause of morbidity and mortality in polycythemia vera. Hypercoagulability is principally due to hyperviscosity of the whole blood, an exponential function of the hematocrit. PV is also associated with endothelial dysfunction that can predispose to arterial disease. Reduction of the red cell mass to a safe level by phlebotomy is the first principle of therapy in PV. This therapy may have some effect on the arterial compliance in PV patients.

**Objectives:** To estimate the influence of phlebotomies on large artery (C1) and small artery compliance (C2) in PV patients by using non-invasive methods.

**Methods:** Short-term hemodynamic effects of phlebotomy were studied by pulse wave analysis using the HDI-Pulse Wave CR2000 (Minneapolis, MN, USA) before and immediately after venesection (350–500 ml of blood). We repeated the evaluation after 1 month to measure the long-term effects.

**Results:** Seventeen PV patients were included in the study and 47 measurements of arterial compliance were performed: 37 for short-term effects and 10 for long-term effects. The mean large artery compliance (C1) before phlebotomy was 12.0 ml/mmHg x 10 (range 4.5–28.6), and 12.6 ml/mmHg x 10 (range 5.2–20.1) immediately after phlebotomy (NS). The mean small artery compliance (C2) before and immediately after phlebotomy were 4.4 mg/mmHg x 10 (range 1.2–14.3) and 5.5 mg/mmHg x 10 (range 1.2–15.6) respectively (delta C2–1.1,  $P < 0.001$ ). No difference in these parameters could be demonstrated in the long-term arm.

**Conclusions:** Phlebotomy immediately improves arterial compliance in small vessels of PV patients, but this effect is short lived.

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Polycythemia vera is a monoclonal myeloproliferative-myeloaccumulative disorder [1,2] due to the ability of PV erythroid progenitor cells to proliferate in the absence of erythropoietin [3]. The main complications of PV include thrombosis and hemorrhage [4,5] secondary to increased whole blood viscosity [6]. Blood viscosity is an exponential function of the hematocrit, mainly at the higher levels, creating the potential for vascular stasis [7-9]. The diminution in capillary flow in PV appears to represent the influence of both peripheral vasodilatation and increased blood viscosity, while major vessel venous thrombosis in PV represents the end stage of a process beginning in the very small vessels [10]. Reduction of the red cell mass and maintaining it at a safe

level by phlebotomy – hematocrit level < 45% in men [11] and < 42% in women, < 36% in pregnancy [6] – is the first principle of therapy in PV [12,13]. Venesection is a safe and immediately effective therapy; it restores coagulant activity toward normal by reducing blood viscosity [14,15], and improves blood flow, platelet function [16,17] and the balance between coagulation factor concentration and red cell number [18]. Such an effective therapy may affect the arterial compliance in PV patients; but to the best of our knowledge, the influence of isolated or repeated phlebotomies on arterial hemodynamic parameters has not been studied in PV patients. The present study was performed to estimate the influence of phlebotomies on arterial compliance in PV patients and to look for a possible correlation between arterial and hematologic parameters.

### Patients and Methods

The study received the authorization of the Barzilai Medical Center Ethics Committee and all patients signed an informed consent form after receiving an explanation about the purposes and methods of the study by one of the investigators.

Arterial compliance parameters were measured immediately before and after venesection (350–500 ml of blood) and repeated 1 month later when the hematocrit had stabilized below 45% in two consecutive examinations. Whenever needed, a second or third phlebotomy was performed and arterial compliance parameters were again measured. Other therapies for PV (hydroxyurea, interferon, aspirin) were continued during the study, according to clinical considerations.

The study was limited to adult PV patients, diagnosed according to Polycythemia Vera Study Group criteria [11]. We collected data on gender, age, height and weight, and computed body mass index (weight in kilograms divided by the square of the height in meters). BMI was then dichotomized as normal or overweight ( $\leq 25$  or  $> 25$ , respectively). We also recorded the patients' current smoking status (smoker or non-smoker) and the presence or absence of chronic hypertension.

At the start of each clinic visit, hematocrit was measured and phlebotomy (350–500 ml) was performed if the value was greater than 45% in men and 42% in women. We further categorized patients according to the volume of blood taken on phlebotomy

PV = polycythemia vera

BMI = body mass index

( $\leq 400$  ml or  $> 400$  ml). When phlebotomy was indicated, we measured large and small artery compliance and systemic vascular resistance before and immediately after the procedure, by means of non-invasive pulse wave analysis (HDI-Pulse Wave CR2000, Research Cardiovascular Profiling System, Minneapolis MN, USA).

We compared mean compliance and resistance values before and after phlebotomy using paired *t*-tests. Analysis was carried out for both the overall study population, and for specific strata of gender, visit number, smoking status, hypertension, and BMI category. Statistical significance was set at  $P < 0.05$ .

## Results

We examined 17 patients during 47 visits. Phlebotomy was indicated and performed in 37 visits. Patient characteristics are shown in Table 1, and overall paired analyses for hemodynamic parameters in Table 2 (short-term) and Table 3 (long-term).

In the short-term analysis, mean post-phlebotomy measurements were better for both large and small vessel compliance when compared to pre-phlebotomy parameters. There was no significant difference in mean measurements for systemic vascular resistance.

Upon stratification of the paired analysis, small vessel compliance showed a significant improvement shortly after phlebotomy in both men and women ( $P = 0.03$  and  $0.02$ , respectively), and among non-smokers ( $P < 0.001$ ). Compliance of both small and large arteries showed post-phlebotomy improvement in hypertensive patients; the small number of normotensive patients included in the study ( $n=3$ ) precluded analysis of this stratum. Upon analysis stratified by BMI, small vessel compliance demonstrated significant improvement in both the normal and overweight categories ( $P = 0.039$  and  $0.007$ , respectively). Both large artery elastic index and small artery elastic index showed improvement after phlebotomies  $> 400$  ml, but not after those  $\leq 400$  ml.

In the long-term analysis (1 month post-phlebotomy), no statistically significant difference was observed in the arterial compliance parameters after phlebotomy compared to the pre-phlebotomy measurements. The small number of measurements could account for this result.

## Discussion

Thrombosis and bleeding are the major causes of morbidity and mortality in PV. Thrombotic risk increases with advanced age, prior history of thrombosis, hypercholesterolemia and smoking. Large vessel arterial thrombosis in PV involves the cerebral, coronary and peripheral arterial circulations, while microcirculatory disturbances may cause erythromelalgia and digital ischemia. Aggressive phlebotomy is still the mainstay of PV therapy to maintain a target hematocrit level below 45% in men and 42% in women.

In this pilot prospective clinical study of the effect of phlebotomy on arterial compliance among 17 PV patients, we demonstrated an immediate beneficial effect of aggressive phlebotomy ( $> 400$  ml) on arterial compliance for both large

**Table 1.** Patients' characteristics (n=17)

Males	10 (59%)
Age (yrs)	Median 66 (range 48–82)
Hematocrit (%)	Median 49.3 (range 45–63)
Body mass index (kg/m <sup>2</sup> )	Median 25.4 (range 19.2–32.6)
Current smokers	3 (18%)
Hypertension	14 (82%)
Diabetes mellitus	3 (18%)
Ischemic heart disease	4 (24%)
History of stroke	2 (12%)
Hydroxyurea treatment	6 (35%)

**Table 2.** Paired analyses of mean hemodynamic parameters, before and immediately after phlebotomy (n=37)

	Before (ml/mmHg x 10)	After (ml/mmHg x 10)	<i>P</i>
Large artery elastic index	11.58 ± 4.59	12.64 ± 4.95	0.046
Small artery elastic index	4.35 ± 3.50	5.50 ± 4.76	0.001
Systemic vascular resistance	1736.59 ± 548.51	1659.97 ± 378.21	0.104

**Table 3.** Paired analyses of mean hemodynamic parameters, before and 1 month after phlebotomy (n=10)

	Before (ml/mmHg x 10)	After (ml/mmHg x 10)	<i>P</i>
Large artery elastic index	10.96 ± 4.68	13.71 ± 5.92	0.28
Small artery elastic index	3.88 ± 2.91	4.66 ± 2.71	0.66
Systemic vascular resistance	1849.71 ± 558.75	1730.43 ± 635.38	0.85

and small vessels, without influence on systemic vascular resistance. Phlebotomy was found to be equally beneficial in men and women, and among hypertensive patients and non-smokers. However, the immediate improvement observed on the arterial compliance was not maintained in the tests repeated 1 month after phlebotomy. Nevertheless, the long-term results should be interpreted with caution, since the lack of statistical significance may reflect a low study power rather than a true lack of effect. This issue should be resolved with additional long-term observation of similar patients.

The study was not designed to compare the basic parameters of PV patients with healthy controls, although these data could be of interest to improve our understanding of the mechanisms leading to thrombotic complications in this disease. Our findings confirm the beneficial role of phlebotomy in the treatment of patients with PV, not only by improving viscosity but also by acting on arterial compliance. In the light of these results, we may justify the policy of frequent and aggressive phlebotomies in PV patients in order to prevent the development of vascular complications.

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