Hemodilution Reduces Clinic and Ambulatory Blood Pressure in Polycythemic Patients

Giovanni Bertinieri, Gianfranco Parati, Luisa Uljan, Cinzia Santucci, Paolo Massaro, Roberto Cosentini, Giuseppe Torgano, Alberto Morganti, Giuseppe Mancia

Abstract—Limited information is available for humans on whether blood viscosity affects total peripheral resistance and, hence, blood pressure. Our study was aimed at assessing the effects of acute changes in blood viscosity on both clinic and 24-hour ambulatory blood pressure (BP) values in 22 normotensive and hypertensive patients with polycythemia, clinic and 24-hour ambulatory BPs were measured before and 7 to 10 days after isovolumic hemodilution; this was performed through the withdrawal of 400 to 700 mL of blood, with concomitant infusion of an equivalent volume of saline-albumin solution. Hematocrit, plasma renin activity, plasma endothelin-1, right atrial diameter (echocardiography), and blood viscosity were measured under both conditions. Plasma renin activity and right atrial diameter were used as indirect markers of blood volume changes. Plasma endothelin-1 was used to obtain information on a vasomotor substance possibly stimulated by our intervention, which could counteract vasomotor effects. Isovolumic hemodilution reduced hematocrit from 0.53±0.05 to 0.49±0.05 (P<.01). Plasma renin activity, plasma endothelin-1 and right atrial diameter were unchanged. Clinic blood pressure was reduced by hemodilution (systolic, 144.3±5.4 to 136.0±3.9 mm Hg [mean±SEM]; diastolic, 87.0±2.8 to 82.1±2.6 mm Hg, P<.05 for both) and a reduction was observed also for 24-hour average ABP (systolic, 133.6±2.9 to 129.5±2.7 mm Hg; diastolic, 80.0±2.0 to 77.3±1.7 mm Hg, P<.05 for both). The reduction was consistent in hypertensive patients (n=12), whereas in normotensive patients (n=10) it was small and not significant. Both clinic and 24-hour average heart rates were unaffected by the hemodilution. Thus, in polycythemia, reduction in blood viscosity without changing blood volume causes a significant fall in both clinic and 24-hour ambulatory BPs; this is particularly true when, as can often happen, blood pressure is elevated. This emphasizes the importance this variable may have in the determination of blood pressure and the potential therapeutic value of its correction when altered. ([Hypertension. 1998;31:848-853.])

Key Words: blood viscosity ■ hemodilution ■ blood pressure monitoring, ambulatory ■ hemorheology

B P is determined by cardiac output and peripheral vascular resistance. The latter depends to a large degree on the caliber and length of arterioles. It also depends, however, on blood viscosity, with which it bears a linear relationship over a wide range of values.1

Although studied extensively in animals,2–5 the effects of blood viscosity on human BP have received only limited attention except for (1) the epidemiological evidence that there is a relationship between hematocrit and BP levels in both normotensive and hypertensive subjects6–11 and (2) the clinical evidence of an increased prevalence of hypertension in subjects with secondary erythrocytosis and polycythemia.16,17 In particular, no information is available on the BP effects of interventions that reduce blood viscosity (ie, whether this maneuver induces a sustained reduction in BP levels).

We addressed this issue by measuring clinic and ambulatory BPs before and after a reduction in blood viscosity obtained through isovolumic hemodilution. We also measured plasma endothelin-1 to obtain information on the secretion of a humoral factor possibly increased by hemodilution18–22 and thus potentially opposing the effect of reduced blood viscosity on vascular resistance. The study was done in polycythemic patients in whom blood withdrawal at regular time intervals is part of the standard treatment.

Methods

Subjects

We studied 22 patients (16 men and 6 women; mean±SD age, 61.5±10.0 years) with a primary polycythemia who were followed in the hematologic outpatient clinic of the Maggiore Hospital (Milan, Italy). The patients were free from any major cardiovascular or noncardiovascular disease other than polycythemia and had been without any drug treatment during the 2 months preceding the study. Each patient gave informed consent to the procedure. The protocol of the study was approved by the ethics committee of the institutions involved.

Measurements

In all patients, blood samples were obtained from an antecubital vein and used for hematocrit, hemoglobin, blood viscosity, PRA, and

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plasma endothelin-1 determinations. Hematocrit and hemoglobin were measured with standard techniques. Blood viscosity (expressed in cP) was determined with a rotational viscosimeter (Bohlin CS-10; Bohlin Rheology AB) at 37°C using shear rates of 380 and 1 s⁻¹. These rates were selected because they are conventionally taken as reflecting the velocity gradients of blood flow in the arteriolar and venular bed, respectively.²³–²⁷ PRA was measured with a standard radioimmunoassay technique to ensure that the hemodilution procedure (see below) had not caused a reduction in circulating blood volume, which would have stimulated renin secretion.²⁸ This also was ensured through measurements of RA diameter with M- and B-mode echocardiography.²⁹ Plasma endothelin-1 was measured with radioimmunoassay after extraction from plasma with C18 Sep-Pak Cartridges (Millipore), as described in detail elsewhere.¹⁹ The cross-reactivity of the rabbit antibody against human endothelin-1 was 7% for both endothelin-2 and endothelin-3 and 0% for non–endothelin-related peptides. The intra-assay and interassay coefficients of variation were 7% and 10%, respectively.

BP was measured in two different ways (1) with a sphygmomanometer, with the subject in the sitting position, using the first and fifth Korotkoff sounds to determine SBP and DBP values, respectively, and (2) with noninvasive ABP monitoring with a SpaceLab device⁵⁰ that was programmed to obtain BP readings every 15 minutes. Each ABP recording started in the late morning and ended 24 hours later to ensure collection of BP data for a full 24-hour period. During the monitoring period, the subjects were sent home, instructed to attend to their usual activities, and asked to come back to the outpatient clinic for the device removal. All patients were instructed to undergo their usual activities during the monitoring period but to stop any ongoing exercise and to extend the arm during automatic BP measurements. They also were instructed to fill out a diary to determine whether unusual events and sleep disturbances occurred.

Protocol and Data Analysis

After the 2 months of no drug treatment, clinic BP, ABP, and laboratory and echocardiographic data were collected for a first time. The patients were subjected to isovolumic hemodilution through withdrawal of 400 to 700 mL of blood (depending on the basal hematocrit level) and simultaneous infusion of an equivalent amount of saline with the addition of 4% albumin. At 7 to 10 days after the isovolumic hemodilution, clinic BP, ABP, and laboratory and echocardiographic data were collected again, according to the same procedure and sequence used in the prehemodilution condition.

In each patient, the clinic BP values were obtained by averaging three sphygomanometric measurements collected at 5-minute intervals. ABP values were averaged for each hour and for the entire 24-hour period. The standard deviation of all 24-hour values was taken as a measure of BP variability.¹⁹ Mean values were calculated for the entire group of patients. Comparisons of values before and after isovolumic hemodilution were made with Wilcoxon’s nonparametric test. The Mann–Whitney nonparametric test also was used to compare data in the normotensive and hypertensive subgroups (see “Results”). A value of P<.05 was taken as the level of statistical significance. Unless otherwise indicated, values are ±SEM.

Results

Fig 1 shows that in our patients, isovolumic hemodilution induced (1) a significant reduction in hematocrit and hemoglobin levels, (2) a significant reduction in blood viscosity at both low and high shear rates, and (3) no change in PRA or RA diameter. In addition, plasma endothelin-1 level did not change (2.5±0.2 and 2.4±0.2 pg/mL before and after hemodilution, respectively). As illustrated in Fig 2, clinic SBP and DBP values were significantly reduced after hemodilution; this also occurred with 24-hour average SBP and DBP. The reduction in ABP values was evident throughout the 24-hour period. In contrast, clinic HR, 24-hour average HR, and hourly HR values were superimposable before and after hemodilution.

Of the 22 patients, 10 were normotensive (mean±SD age, 61.3±2.7 years), and 12 had a clinic SBP or DBP of >140 or 90 mm Hg, respectively, thereby being classified as hypertensive (age, 61.6±4.7 years). As shown in the Table, isovolumic hemodilution reduced hematocrit significantly in both groups. Blood viscosity was reduced significantly only in the hypertensive group, in which the predilution value was slightly although not significantly greater than in the normotensive group. Hemodilution caused a noticeable reduction in clinic and 24-hour average BP in the hypertensive group, whereas the change was small and nonsignificant in the normotensive group. HR was unaffected by the procedure in either group. In the group as a whole, hemodilution did not cause any change in 24-hour BP standard deviations, which were 13.4 mm Hg (SBP) and 10.3 mm Hg (DBP) in the prehemodilution condition and 13.0 mm Hg (SBP) and

### Effect of Isovolumic Hemodilution in Normotensive and Hypertensive Subjects With Polycythemia

<table>
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<th>Hypertensives (n=12)</th>
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<td>P</td>
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*P<.05, †P<.01.
10.7 mm Hg (DBP) in the posthemodilution condition. The results were similar in the normotensive and hypertensive groups when considered separately.

**Discussion**

In our polycythemic patients, a isovolumic hemodilution that reduced blood viscosity was accompanied by a significant reduction in BP. The reduction involved both systolic and diastolic values. It also involved both the BP values taken in the outpatient clinic and the BP values obtained under ambulatory conditions throughout the day and night. It thus can be concluded that this intervention has a BP-lowering effect and that this effect is also evident when daily-life BP is considered.

Several other points should be mentioned. First, the reduction in BP induced by hemodilution was small in normotensive polycythemic subjects but consistent and clear-cut (13.0 and 7.6 mm Hg for clinic SBP and DBP and 5.5 and 3.6 mm Hg for ambulatory SBP and DBP) in hypertensive polycythemic subjects. Several mechanisms may account for this difference. For example, the reduction in hematocrit was more consistent and greater in hypertensives than in normotensives, leading to a more consistent and somewhat greater reduction in blood viscosity in the former compared with the latter group. Furthermore, in hypertensives, the reduction in hematocrit and blood viscosity may have improved hemorheology to a greater degree because compared with normotensive control subjects, animals and humans with a high BP have a greater aggregability and a smaller deformability of red blood cells, respectively.

Finally, studies in normotensive animals have shown a reduction in blood viscosity to be...
accompanied by an increase in cardiac output, which compensates for the viscosity-dependent reduction in vascular resistance and prevents a fall in BP. This may occur to a lesser degree in hypertension, which is characterized by an impairment of cardiac reflex responses to alterations in vasomotor tone and possibly by a decrease in cardiac performance that follows a reduction in afterload. At any rate, it should be emphasized that the reduction in BP induced by hemodilution in our hypertensive subjects represents an effect greater than that seen with several nonpharmacological methods of lowering BP and is similar to that seen with antihypertensive drug therapy.

Second, the reduction in blood viscosity and hematocrit induced by hemodilution was not accompanied by any change in HR, which means that the presumable reduction in vascular resistance associated with this intervention did not trigger a reflex increase in neural cardiac drive, probably because of a resetting phenomenon analogous to the one seen when peripheral vascular resistance is reduced with antihypertensive drugs.

Third, because the study design did not include any sham hemodilution procedure, the possibility exists that the BP reductions were due to “placebo” or “time” effects. However, this might hold for clinic but not for 24-hour average BP, which is devoid of any substantial placebo or time effect when assessed over a several-week period. Fourth, because our study did not include blood volume measurements, the possibility exists that the BP-lowering effect was due to hypovolemia and to a reduction in cardiac output. However, in all patients, hemodilution was accomplished by substituting the amount of blood withdrawn with a rigidly equivalent amount.

![Figure 2](http://hyper.ahajournals.org/)

**Figure 2.** Effects of isovolumic hemodilution on clinic BP and HR, 24-hour average BP and HR, and 24-hour BP and HR profiles. Data are mean ± SEM for the entire group of 22 subjects. S indicates systolic; D, diastolic.
of 4% albumin-supplemented saline. Furthermore, the effects on BP were assessed 7 to 10 days after the hemodilution intervention (ie, at a time interval sufficiently long to allow any small initial reduction in blood volume to be corrected by the mechanisms involved in blood volume homeostasis).25 Finally, indirect evidence that circulating blood volume was not substantially affected was provided by the absence of hemodilution-induced changes in PRA and atrial diameter (ie, by sensitive markers of blood volume variations).26,29

Two limitations should be discussed, however. (1) Our study was restricted to the effect of hemodilution over a 7- to 10-day period, thereby failing to determine whether this procedure retains a BP-lowering effect throughout longer time intervals, and thus represents an effective therapeutic intervention against an elevated BP also when, in polycythemic patients, hemodilution is performed at longer time intervals. (2) Because the data were collected in polycythemia, it is difficult to extrapolate our results to the BP effects of viscosity changes in essential hypertension in which hemorheological abnormalities that possibly increase blood viscosity have been reported but the hematocrit is normal.9,24,53 Our present demonstration that hemodilution had clear-cut BP-lowering effect in hypertensive polycythemic patients makes this issue a relevant one to be addressed, however.

Finally, although in previous studies hemorrhage has been shown to increase plasma endothelin-1,18–22 in our patients hemodilution did not have any effect on the circulating level of this substance, with this being the case in both normotenive and hypertensive groups. We cannot exclude that this was due to the fact that measurements were obtained after 7 to 10 days of blood withdrawal, leading to an initial but temporary increase in plasma endothelin-1 that then subsided. We also cannot exclude that our stimulus did not have adequate power for an increase in endothelin-1 mainly takes place with a reduction in blood volume (which was prevented in our patients) and that changes in shear stress or other hemorheological variables play a lesser role.

References

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