

# The effect of plasmapheresis on blood pressure in voluntary plasma donors

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## Vox Sanguinis

**Background and Objectives** Donor plasmapheresis involves the removal of a weight-adjusted volume of plasma and the return of cellular components to the donor. Although plasma volume generally returns to normal, some residual effect on vital signs may be possible. This analysis was performed to determine the possible effects of plasmapheresis on blood pressure.

**Materials and Methods** A 16-week study was conducted to evaluate the effects of plasma donations on cholesterol levels in healthy donors. From this study, the vital signs obtained prior to donation were analysed using statistical and dynamic analytical predictive models.

**Results** Preliminary analyses revealed a change in systolic and diastolic blood pressure from the corresponding baseline values (Pearson Coefficient  $-0.44$  and  $-0.47$ , respectively). Statistical models predicted a marked decrease in systolic and diastolic blood pressure following multiple donations in donors with baseline pressure in the Stage 2 hypertension range with less pronounced decreases predicted in Stage 1 donors. Little or no change in blood pressure was predicted in donors with baseline normal blood pressure or prehypertension. Dynamic models including time between donations supported these results and predicted a recovery period of about 14 days without donation in donors with Stage 2 baseline levels.

**Conclusions** Results suggest that systolic and diastolic blood pressure may be decreased following plasmapheresis used for plasma donations at intervals of  $<14$  days in donors with high baseline blood pressure levels.

**Key words:** blood pressure, plasma donation, plasma donor, plasmapheresis.

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## Introduction

Automated plasmapheresis is routinely used to obtain human plasma to segregate and purify proteins such as clotting factors, albumin and immunoglobulins for medical use [1, 2]. In the United States, the volume of plasma withdrawn at each donation is weight-dependent, according to applicable US guidelines, with donors weighing 110–149 pounds, 150–174 pounds and  $\geq 175$  pounds permitted to donate 625, 750 and 800 ml, respectively

(excluding anticoagulant) [3]. In the United States, individuals can donate twice in any 7-day period with an annual maximum of 104 donations [4]. Following plasmapheresis, plasma volume is thought to replenish within a relatively short period of time.

Along with extensive testing [5], donors are questioned regarding their recent medical history and medications and are monitored for haematocrit, protein, blood pressure (BP), heart rate and temperature prior to each donation. Donors with values outside an acceptable range are temporarily deferred, and multiple out of range values may result in permanent deferral. Donors who undergo plasmapheresis under these standardized conditions experience a low incidence of adverse events [6–10]. However,

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multiple donations can affect the protein content of plasma since experienced donors generally have lower levels of immunoglobulins, albumin and total serum protein [11–13], and a decrease in cholesterol has been reported in donors with high baseline cholesterol levels [5].

Numerous factors, including cardiac output, peripheral resistance, blood vessel elasticity and blood volume, can affect BP. When there is a short-term decrease in blood volume following plasmapheresis, a temporary BP drop may result although, over a longer period, compensation by homeostatic mechanisms returns volume and BP to normal levels. The volume of plasma removed during plasmapheresis (625–800 ml) is expected to result in only minimal physiological changes due to hypovolaemia [14]. However, the effect of plasmapheresis on BP has rarely been reported, and studies generally involve assessments of immediate BP changes [15, 16]. In a recent study evaluating the effect of plasmapheresis on cholesterol levels in healthy donors [5], BP data were collected prior to each donation. The objective of this analysis is to evaluate the possible effects of plasma donation on BP in the donor population.

## Materials and methods

### Study design

Participants in the prospective, longitudinal cohort trial were 18–69 years old and from nine US donation centers. They were new donors or previous donors who had not donated for at least 6 months [5]. Donors met all industry standards for plasma donation, including all standard BP requirements for donor participation. A diagnosis of hypertension was acceptable for donation as was the use of antihypertensive medications, except beta-blockers. Donors who took part in the study signed a separate consent for study participation. Participants were asked to donate at least once weekly for 16 weeks, and two donations in any 7-day period were permitted.

### Donation procedure

Following check-in, donors sat to wait their turn for requalification, including vital signs. Donors who met all criteria for donation were seated in the donation area and prepared for plasmapheresis. The donation was obtained using a single venipuncture; no saline volume replacement was employed. Following routine procedures, sodium citrate was used during automated plasmapheresis to prevent cell clotting. Donors remained seated for approximately 5 min following donation to allow for volume change adjustment.

### Vital signs measurements

Blood pressure was measured prior to donation using electronic vital signs measurement systems from Welch Allyn (Skaneateles Falls, NY, USA) or IVAC (San Diego, CA, USA). Machines were calibrated daily and are routinely inspected at 6-month intervals to insure accurate data collection.

The time between donor check-in and vital signs assessment was not tracked, and no minimum rest period was required. However, donors were expected to have been at the site at least 15 min before BP measurements were obtained due to routine donor centre procedures.

### Donor deferrals due to vital signs

Study participants who did not meet all donation criteria were temporarily deferred and could donate following expiration of the deferral period if donation criteria were met. The BP limits used (SBP 90–180 mmHg and DBP 50–100 mmHg) were based on those commonly employed in the blood and plasma industry and are based on previously published guidelines in the United States and Europe [17, 18] although BP is no longer a donation screening criteria for many countries. If BP was outside the acceptable limits on initial testing, the donor could be retested up to two times with a 15-min resting period required between tests. Donors who failed to qualify following retesting received a 1-day deferral and educational material on the abnormal test.

### Statistical analysis

Participants were assigned to one of four baseline BP groups according to the classification of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure of the NHLBI [19]: normal (SBP < 120 mmHg and DBP < 80 mmHg); prehypertensive (SBP 120–139 mmHg or DBP 80–89 mmHg); Stage 1 hypertension (SBP 140–159 mmHg or DBP 90–99 mmHg); Stage 2 hypertension (SBP  $\geq$ 160 mmHg or DBP  $\geq$ 100 mmHg).

Initially, exploratory analyses were used to evaluate the effect of different variables on BP. Graphical plots of baseline BP and change from baseline BP, with their correlation coefficient, were created for each of the possible explanatory baseline variables (days since first observation, time since last donation, donation count, and an estimate of the rate of donations) and the end-points of interest: change in systolic blood pressure (SBP) and diastolic blood pressure (DBP).

Statistical models were used to quantify the effect of donation after adjusting for the potential effect of baseline SBP and DBP. The donor's baseline BP category

was treated as a categorical variable and included in the models by default to remedy potential regression to the mean effects [20]. The statistical models consisted of generalized additive models that tested linear and nonlinear effects of donation counts in addition to testing the potential interactions between explanatory variables.

Since the statistical model does not consider the possible effect of time between donations, a dynamic indirect-response model was tested [21]. These models assume that there is an endogenous homeostatic process which helps maintain the stability of the end-point, in this case BP. The effects of explanatory variables (donation and pattern of donations across time) were then determined using analyses which allowed them to accumulate or wear down according to the donation frequency and time between donations. The potential delay between the donation event and BP change was also tested by including a delay compartment. The dynamic model used baseline values as a covariate to adjust for a potential regression to the mean effect. Refer to Supplemental Information for details.

Graphical analyses and the general linear models were performed using R, version 2.15.3 (2013; R Foundation for Statistical Computing, Vienna, Austria). The package rms was used to fit the models and conduct the statistical tests. Dynamic models were fitted using the PHOENIX<sup>®</sup> NLME<sup>™</sup> version 1.2 [Certara LP (Pharsight), St. Louis, MO, USA] with the Lindstrom-Bates first-order conditional estimation method (FOCE-L-B).

## Results

Overall, 666 donors were studied (407 males and 259 females). Two donors with data for only one donation were included as part of the baseline (intercept fit) calculation. Baseline BP was normal in 29.8% of donors and prehypertensive in 44.9% (Table 1).

**Table 1** Baseline blood pressure categories

Category <sup>a</sup>	Criteria		n (%)
	SBP (mmHg)	DBP (mmHg)	
Normal	<120	and <80	197 (29.8)
Prehypertension	120–139	or 80–89	299 (44.9)
Stage 1 hypertension	140–159	or 90–99	147 (22.1)
Stage 2 hypertension	≥160	or ≥100	23 (3.5)

SBP, systolic blood pressure; DBP, diastolic blood pressure.

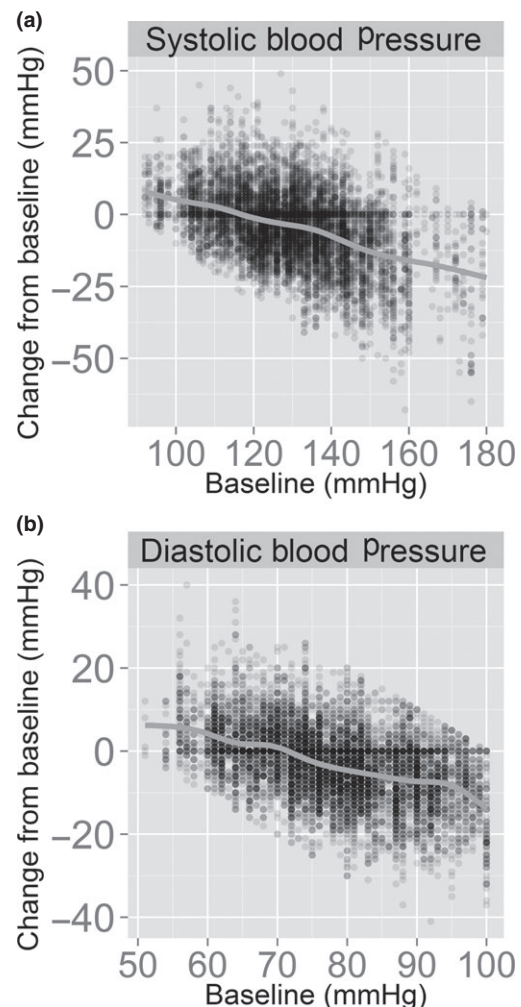
<sup>a</sup>Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure.

## Exploratory analysis

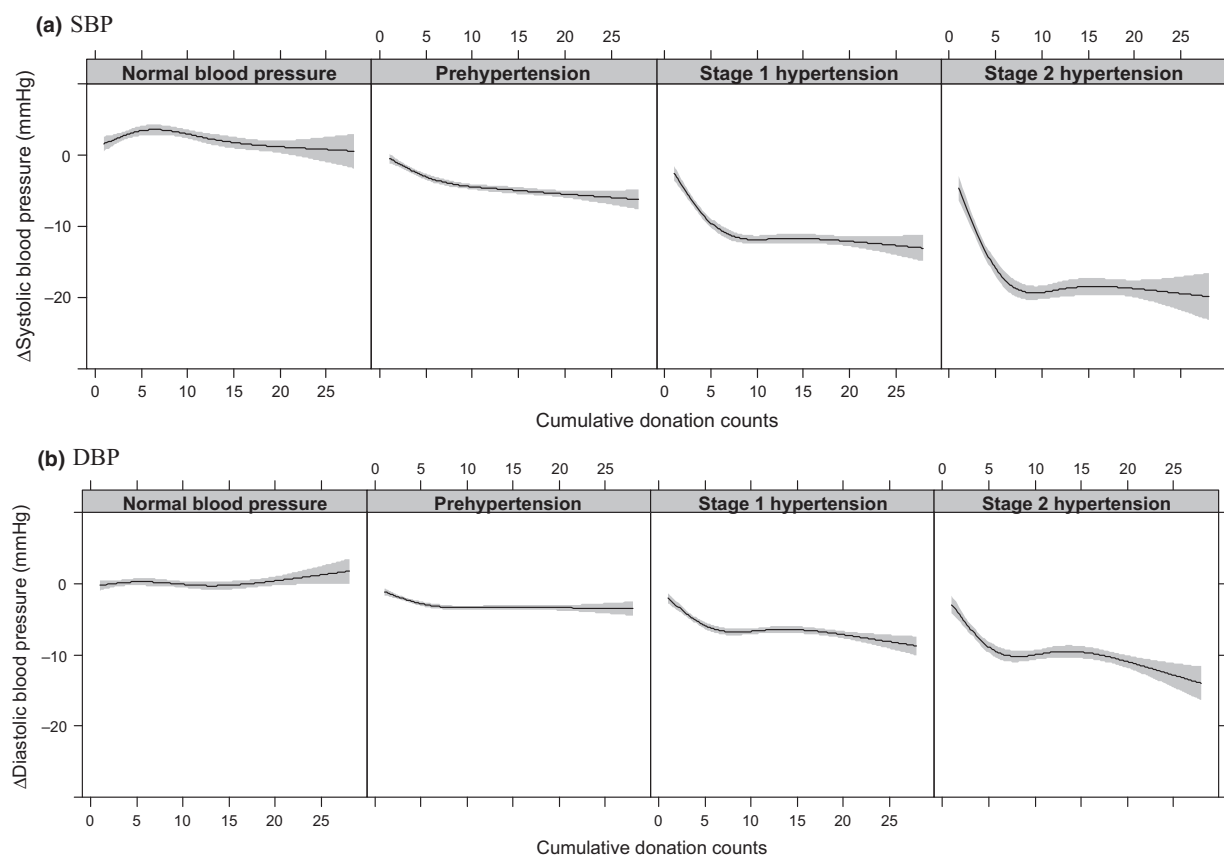
Plots of change in BP vs. baseline BP levels suggested that donors with higher baseline BP experienced greater BP decreases (Fig. 1). Moderate negative correlations (correlation coefficients  $-0.44$  and  $-0.47$ ) observed for SBP and DBP, respectively, supported these observations. Correlations between BP and days since first donation, time since last donation, and cumulative donation count were only weakly negative ( $-0.15$  to  $0.04$ ), suggesting that these variables had little impact on the change in BP.

## Statistical model

Baseline SBP category, donation counts and an interaction term between these two effects were statistically significant ( $P < 0.0001$ ). Pronounced BP changes were predicted in donors with baseline measurements in the



**Fig. 1** Relationship between change from baseline and baseline values for systolic blood pressure (SBP) and diastolic blood pressure (DBP).



**Fig. 2** Effects of donations on changes from baseline systolic blood pressure (SBP) and diastolic blood pressure (DBP) by Blood Pressure Category. (a) SBP, (b) DBP.

Stage 1 and Stage 2 ranges, with change increasing as the number of donations increased (Fig. 2a). Donors with baselines in the Stage 2 hypertension range showed marked SBP decreases during the first 2–5 donations (mean change  $-4.00$  to  $-21.65$  mmHg), with similar but more modest changes ( $-3.01$  to  $-14.87$  mmHg) predicted for those with baseline Stage 1 hypertension. Almost no effect was predicted for donors with baseline normal BP (mean change  $+0.37$  to  $+3.21$  mmHg) or prehypertension (mean  $-0.30$  to  $-5.75$  mmHg).

Similarly, for DBP, baseline DBP category, donation counts and an interaction term were significant ( $P < 0.0001$ ). Model effects predicted for DBP are represented in Fig. 2b. The greatest predicted change in DBP (mean change  $2.13$  to  $-16.73$  mmHg) was in donors with baseline Stage 2 pressures. There was almost no change in donors with normal baseline BP (mean change  $-0.54$  to  $+0.35$  mmHg).

### Dynamic model

The effect of donations on mean predicted individual changes in SBP and DBP is summarized in Table 2.

Minimal decreases in SBP and DBP were predicted for donors with baseline normal BP, while marked decreases in SBP ( $-19.5$  mmHg) and DBP ( $-9.05$  mmHg) were predicted for donors with baseline BP in the Stage 2 range.

The predicted effect of donation interval in donors with normotensive and Stage 2 hypertensive baseline readings is presented in Fig. 3. Using a 5-day donation interval, SBP in Stage 2 donors decreased following the first two donations with SBP  $16$ – $17$  mmHg below baseline and a recovery of about  $4$ – $5$  mmHg between donations for subsequent donations. With a 14-day donation interval, there was a maximum SBP drop of  $11$ – $12$  mmHg and recovery to near baseline levels between donations. Donors with normotensive baseline measurements showed a SBP drop of  $3$ – $4$  mmHg with a recovery to baseline levels  $5$ – $6$  days postdonation. DBP modelling for baseline Stage 2 donors with 5-day donation intervals predicted a drop of about  $5$  mmHg after two donations and for all subsequent donations which recovered to within  $1$ – $2$  mmHg of baseline. With 7- and 14-day donation intervals, similar DBP drops and a return to baseline within 7 days were predicted.

**Table 2** Effect of plasma donations on mean predicted change in systolic blood pressure (SBP) and diastolic blood pressure (DBP) by baseline blood pressure (BP) category, dynamic model

Baseline BP category	Mean predicted change	
	SBP (mmHg)	DBP (mmHg)
Normal	-3.34	-2.62
Prehypertension	-6.46	-4.36
Stage 1 hypertension	-11.7	-6.51
Stage 2 hypertension	-19.5	-9.05

### Donor deferrals for blood pressure

Deferrals due to unacceptable BP were infrequent, with only 32 temporary deferrals required (10 in seven donors for SBP and 22 in 14 donors for DBP); no donor was permanently deferred due to BP excursions. BP deferrals occurred similarly in male and female donors (12 male; nine female) and were reported for donors in all baseline BP groups. There were three deferrals in two donors for low SBP (5–24 mmHg below acceptable levels). Twenty deferrals were for increased DBP while only two resulted from low DBP readings.

### Discussion

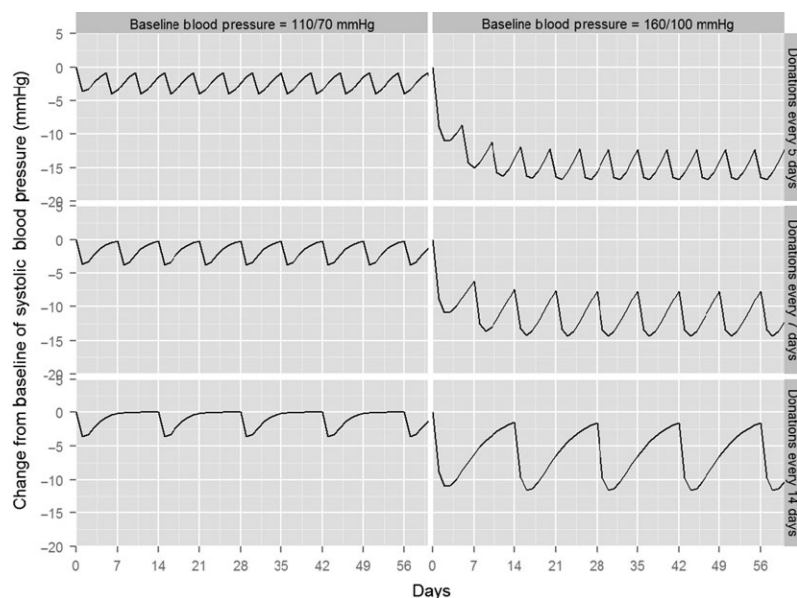
The results indicate that BP in donors with baseline Stage 1 or Stage 2 hypertensive levels may be affected following plasma donation at intervals of <14 days. When donations were less frequent (intervals of about 14 days), BP returned to near baseline levels suggesting that, to maintain the lowering effect, a donation interval of

<14 days is necessary. The models predict that, following the allowable plasma donation frequency in the United States or a plasma donation once weekly, would maintain the BP lowering effect. This effect was not seen following plasmapheresis in donors with normal baseline BP.

The BP decreases observed likely do not relate to the temporary drop in blood volume since postplasmapheresis volume returns to normal levels within a short period of time. The BP changes appear highly dependent on the donor's baseline BP category, and while the possibility of some regression to the mean effect cannot be excluded, the models were intended to minimize this possibility.

The mechanism governing this postdonation BP decrease may relate to the removal of one or more molecules affecting BP levels [22–26]. Studies have suggested that the use of therapeutic plasmapheresis in patients with refractory or severe malignant hypertension due to essential hypertension may reduce BP and that this reduction may relate to the removal of dialyzable molecules during plasmapheresis [22, 23]. The volume removed during therapeutic plasmapheresis, which can be 1.0–1.5 times a patient's total plasma volume, is much greater than the volume in a plasma donation although the frequency of therapeutic plasmapheresis is generally less than the maximum permitted plasma donation schedule. It is possible that a drop in mediators affecting BP regulation could result from multiple plasma donations following mechanisms similar to those observed during therapeutic plasmapheresis and that replacement of these factors was sufficiently slow with 5- to 7-day donation intervals to allow BP to remain lowered.

One limitation of the data is that BP was measured prior to the donation, and procedure-related changes likely



**Fig. 3** Effect of donation interval on predicted changes in systolic blood pressure (SBP) in baseline normotensive and Stage 2 hypertensive donors.



resulted from the previous donation which occurred, at a minimum, 48 h prior to the measurement. This supports the hypothesis of some prolonged effect of plasma donation on BP but does not provide additional information on intraprocedural or immediately post-procedural changes. Another limitation was the lack of a standardized rest period prior to obtaining vital signs data although the normal donor centre flow was sufficient to allow donors to achieve a reasonable stabilization prior to measurement. Although there were no longitudinal data between donations or after the cessation of donations, donation intervals varied widely with many donors having donation intervals of 14 days or more. While this did not permit a direct evaluation of return to baseline levels based on raw data, model-based predictions suggested that, as expected, any effect on BP levels was transient and did not persist more than a few weeks after the cessation of donations.

The relatively small number of donors with Stage 2 baseline BP may have some effect on the level and variability of change observed in this group. However, the mixed effects dynamic model is simultaneously fitted to all available data, allowing data from all individuals to contribute to the result. The model showed little to no change in donors with normal SBP or DBP which was in strong agreement with the observed results, supporting

the idea that the model is adequate and described a process that is physiologically possible.

This study suggests that plasma donation is well tolerated and may lower both SBP and DBP in donors with baseline BP in the Stage 1 and Stage 2 hypertension ranges. Although these drops appeared to persist with frequent donations (about 5–7 days), the effect appeared transient and BP likely returned to baseline levels soon after discontinuation of plasmapheresis. Further studies are needed to confirm these results and to determine whether this apparent decrease in BP might provide any clinical benefit for long-term donors with high baseline BP.

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