Regular blood donation may help in the management of hypertension: an observational study on 292 blood donors

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BACKGROUND: Hypertension is one of the leading global risks for cardiovascular events worldwide. There is preliminary evidence that regular blood donation may be beneficial.

STUDY DESIGN AND METHODS: Unselected blood donors were included in this observational study. Blood pressure (BP) was measured before and after blood donation, with participants donating between one and four occasions in a 1-year study period.

RESULTS: In this study, 292 donors were enrolled. At baseline, 146 had elevated BP (>140/90 mmHg). In hypertensives, after four blood donations, systolic and diastolic blood pressure (SBP and DBP, respectively) decreased from a mean of 155.9 ± 13.0 to 143.7 ± 15.0 mmHg and from 91.4 ± 9.2 to 84.5 ± 9.3 mmHg, respectively (each p < 0.001). There was a clear dose effect with decreasing BP by the increasing number of blood donations. After at least four blood donations, donors with Stage II hypertensive baseline values (≥160 mmHg SBP and/or ≥100 mmHg DBP) were found to have the most marked reduction in BP, with 17.1 mmHg (95% confidence interval [CI], –23.2 to –11.0; p < 0.0001) and 11.7 mmHg (95% CI, –17.1 to –6.1; p = 0.0006) for SBP and DBP, respectively. The decrease in BP was not significantly associated with changes of blood count or variables of iron metabolism.

CONCLUSIONS: Regular blood donation is associated with pronounced decreases of BP in hypertensives. This beneficial effect of blood donation may open a new door regarding community health care and cost reduction in the treatment of hypertension.

Hypertension is a highly evident global public health issue. Despite improved public awareness and therapy, its control remains rather unsatisfactory.1 Recent data demonstrate that more than one-third of adults are affected, with many patients requiring two or more antihypertensive drugs to achieve acceptable blood pressure (BP) levels.1-4 By reducing systolic blood pressure (SBP) by 10 mmHg or diastolic blood pressure (DBP) by 5 mmHg, this would result in 40 and 30% reductions in the risk of death due to strokes and ischemic heart diseases, respectively.3

ABBREVIATIONS: BMI = body mass index; BP = blood pressure; DBP = diastolic blood pressure; LDL = low-density lipoprotein; SBP = systolic blood pressure.

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A possible association of a reduction in cardiovascular events with blood donation has been postulated in several epidemiologic studies. The mechanism by which blood donation may improve the outcome in cardiovascular disease is largely unclear. To date, hypotheses that have been put forward include the inhibition of lipid oxidation due to iron and/or ferritin reduction and a decrease in the concentration of low-density lipoprotein (LDL) cholesterol. The question of whether regular blood donation may also have an impact on increased BP has not yet been adequately addressed. In this study, we aimed to evaluate the effects of repeated regular blood donation within a period of approximately 12 months in subjects with normal and elevated BP. We hypothesized that regular blood donation leads to a reduction in BP. Furthermore, we assessed several potential factors that were hypothesized to play a role in the putative BP-reducing effect.

MATERIALS AND METHODS

Study design and participants
Participants for this observational cohort study were recruited via the Blood Transfusion Service of the Institute for Transfusion Medicine at the Charité University Medicine Berlin, Germany, between February 2012 and March 2014. This study was approved by the institutional review board and informed consent was obtained from all participants. This study is registered at ClinicalTrials.gov (NCT01553409).

Based on the results of smaller interventional studies on phlebotomy, we estimated that a minimum of 50 hypertensive subjects were required to detect a significant effect of blood donation on SBP. Given a prevalence of 35% to 40% of hypertension in the adult German population and an anticipated incremental loss to follow-up in the natural setting of a blood donation center, we aimed to include 100 patients with elevated BP at baseline and at least 280 subjects in total.

Participants were aged between 18 and 65 years and recruited via the blood transfusion service and additionally by press advertisements. All participants were required to have either no previous history of blood donation or no donation within the preceding 12 months, and were to fulfill the standard criteria of the blood transfusion service. Elevated BP was defined by a systolic value of at least 140 or a diastolic value of at least 90 mmHg. Participants with a BP of at least 160 SBP and/or at least 100 mmHg were further classified as Stage II hypertensives.

All subjects were free to decide on the repetition of blood donation or a longer time interval than 3 months. However, participants were encouraged to donate on a regular basis. At each phlebotomy, whole blood (approx. 480 mL) was removed in accordance with standard procedures (Haemonetics MCS+, Braintree, MA).

To control for a potential bias due to lifestyle changes during the study period, we asked all subjects to keep their lifestyle and nutritional habits unchanged. Furthermore, we assessed weight at each visit as an indicator of lifestyle change and included body mass index (BMI) in the multivariate analysis.

BP measurements
BP was measured following approximately 5 minutes of seated rest on the nondominant arm, using a mean value of four measurements before donation and three measurements after donation. If BP was observed to exceed the acceptable limits upon initial measurement, the donor was retested and was permitted to donate when one of the measurements fell within the limits. Measurements were performed automatically in 2-minute intervals (Dinamap Compact T, Johnson & Johnson Medical, Inc., New Brunswick, NJ).

Laboratory investigations
Blood counts using EDTA blood were measured at each donation using a hematology analyzer (Sysmex xs-800i, Sysmex, Kobe, Japan). Serum iron, ferritin, triglycerides, total cholesterol, and high-density lipoprotein and LDL cholesterol were measured by a clinical chemistry analyzer (COBAS 6000, Roche Diagnostics, Basel, Switzerland).

Interviews
Participants were interviewed by the study nurse before each follow-up donation to assess any adverse effects and changes in medical treatment and drug therapy. Weight was measured by a standard calibrated scale for each donation and the BMI calculated as weight (kilograms) divided by height (in meters) squared.

Statistical analysis
Statistical analyses for SBP and DBP comprised all data obtained from the blood donors. Missing data were not imputed or otherwise replaced. Mean values and standard deviations (SDs) were calculated for all assessed variables. SBP and DBP recordings were split for repeated measurement from T0 (baseline, first blood donation) to T3 (fourth blood donation) using pre- and postdonation values at each time point of measurement and sequential analysis of complete cases before blood donation. Univariate analyses were conducted on individual data at a 5% level of significance using Friedman's analysis of variance (ANOVA) for ranks.

To determine the influence of number of blood donations (time), group, and other fixed factors, a generalized linear mixed-effect model with random effects was...
applied for both SBP and DBP separately. To determine the influence of factors a sequential modeling strategy was used. In the first model, the sole effect of time was introduced as a fixed factor. In the second step, the group level was entered, followed by age and sex as sociodemographic variables in the third step and BMI as an indicator of a healthy lifestyle in the fourth step. In the next three steps, hemoglobin (Hb), hematocrit (Hct), and ferritin were introduced in the model as fixed factors. For each step of the modeling, Wald’s chi-square statistic, and log likelihoods were calculated as indicators for the model validity. Regression coefficients were calculated to determine whether a factor had a significant influence on the course of SBP and DBP. Finally, likelihood ratio tests were calculated to compare the models of each step with the previous one.

RESULTS

Interest in the study was high after an initial press release. More than 650 interested subjects were screened during their spontaneous visit at the blood donation center, via phone calls, or via e-mail correspondence. Approximately 55% of interested subjects did not meet the inclusion criteria and/or standard blood donation criteria. The most frequent exclusion criteria included residency in another state, very high BP (repeated measurements of SBP > 180 mmHg or DBP > 100 mmHg), hypertensive drug intake of more than two active substances, age (>65 years), last blood donation within the previous 12 months, and indicators of anemia. Finally, 292 participants were successfully included in the study with 146 donors having BP of less than 140/90 mmHg and 146 donors with BP of at least 140/90 mmHg at baseline (Fig. 1).

In the group with elevated BP, 146 donated at least once, 114 donated blood on at least two occasions, 81 thrice, and 39 on four occasions within the 1-year individual study period (Fig. 1). In the normotensive group, 146 donated at least once, 109 on at least two occasions, 66 at least thrice, and 34 on four occasions. The majority of blood donors with elevated BP had been previously diagnosed with hypertension. Of the 146 blood donors with elevated BP, Stage II hypertension was observed in 38 at the first donation. Thirty donors with Stage II hypertension donated blood on at least two occasions, 20 at least thrice, and 14 on four occasions.

BMI was observed to remain primarily unaltered in both cohorts, regardless of donor frequency (Table 1). Ferritin levels were observed to decline with each increasing donation in both the normotensive and the elevated BP cohorts (one-way ANOVA, each, p < 0.0001).

Immediate effect of phlebotomy on BP: pre- and post-BP measurements

Phlebotomy was observed to have an immediate effect on lowering BP in both cohorts, although the effect was constant with each subsequent donation and more predominant in the group with elevated BP (Table 2). At T0, the mean reduction in SBP was 3.3 mmHg in the control group and 7.1 mmHg in the group with elevated BP. An
immediate reduction in mean SBP of 4.8, 3.1, and 7.4 mmHg was observed for the subsequent donations (T1, T2, and T3, respectively) in the nonhypertensive cohort and of 7.8, 7.3, and 9.2 mmHg in the hypertensive cohort. DBP was observed to remain fairly constant in both groups immediately after donation, although a slight decrease was observed in the group with elevated BP (Table 2).

**BP decreases with regular blood donations**

A significant association between regular blood donation and BP was observed in the hypertensive group (Table 3). Donors were subcategorized into those that donated on two, three, or four occasions. Subjects with elevated BP who donated on two occasions (n = 114) demonstrated a mean reduction of 5.9 for SBP (95% confidence interval [CI], −9.2 to 2.6; p < 0.001). More regular donations were found to result in a more pronounced reduction in both SBP and DBP. Subjects with elevated BP donating thrice demonstrated a net mean decrease of SBP of 10 mmHg (95% CI, −15.4 to 4.65; p < 0.001) and of DBP of 3.4 (95% CI, −6.3 to 0.5; p = 0.025). The largest BP-reducing effect was found in the group of regular donors who donated four times (n = 37), where a mean decrease in SBP of 12.2 mmHg (95% CI, −18.7 to 5.7; p < 0.001) and in DBP by 6.9 mmHg (95% CI, −11.2 to 2.6; p < 0.001) were observed.

In the group of normotensive subjects, a slight but nonsignificant decrease in SBP and DBP was observed with increasing numbers of donations (Table 3). A significant effect was only observed upon the second blood donation with a mean reduction of 1.5 mmHg in DBP (95% CI, 0.7; p = 0.001). More regular donations demonstrated a pronounced mean decrease in SBP of 5.7 mmHg (95% CI, −9.1 to −2.3; p < 0.001) and a nonsignificant decrease in DBP of 0.7 mmHg (95% CI, 0.01 to 1.4; p = 0.07).
Pronounced BP reduction observed in Stage II hypertension

We further analyzed the antihypertensive effect of blood donation according to the stage of hypertension at baseline. Here, we found the most pronounced effect in Stage II hypertension. There was an incremental mean decrease of predonation SBP from 164.2 ± 8.3 to 155.4 ± 12.3 mmHg to 151.4 ± 11.9 and to 147.1 ± 13.0 mmHg after four donations resulting in a net difference of −17.1 mmHg (95% CI, −23.2 to −11.0; p < 0.0001) after four blood donations. DBP decreased, respectively, from 95.3 ± 8.9 to 91.4 ± 9.9, 87.1 ± 9.8, and 83.6 ± 8.5 resulting in a net difference of −11.7 mmHg (95% CI, −17.1 to −6.1; p = 0.0006) after four blood donations.

Multivariate analysis

Results of the multilevel analysis are demonstrated in Table S1 (available as supporting information in the online version of this paper). The effect of time (Model 1) as well as the addition of group (hypertensive vs. nonhypertensive, Model 2), sex, and age (Model 3) resulted in significant effects for both SBP and DBP. The addition of BMI as a lifestyle surrogate (Model 4), however, did not result in a significant explanation of variance. In regard to laboratory values, only the addition of Hb into the mixed model (Hb, Model 5) was found to have an impact on DBP but not on SBP. Both Hct and ferritin levels did not significantly impact the timely course of BP (Models 6 and 7).

Variations of drug therapy during the course of the study

During the course of the study, 11 subjects with elevated BP (11/146, 7.53%) reduced the dosage of hypertensive drug therapy, with an additional five (5/146, 5.17%) discontinuing drug therapy. Another subject discontinued the use of combined antihypertensive treatment (ramipril, amlodipine) and commenced therapy with candesartan. Six subjects with elevated BP increased drug dosage (6/146, 4.11%). A marked decrease in BP was observed in subsequent donations in only one of the six patients after the increase in dosage. Of the 38 Stage II hypertensive blood donors, 25 (65.8%) were under antihypertensive treatment. During the course of the study, two (8%) donors changed their antihypertensive medication, two (8%) reduced the dosage, one (4%) commenced antihypertensive drug treatment during the course of the study (second donation), and one donor (4%) reduced dosage followed by discontinuation for several months and then recommencement of drug therapy. The remaining Stage II hypertensive donors either did not alter their dosage (19/25) or remained untreated (13/38). Thus, the variance in drug therapy within the 1-year period was modest and more frequently characterized by reduced dosage of antihypertensive medication.

Safety

There were no serious adverse events for the study participants during or after blood donation. Of the 292 participants, 27 (9.2%) received oral iron supplementation therapy due to inadequate Hb levels (<12.5 g/dL for females, <13.5 g/dL for males). Seventeen of the 27 (63%) donors subsequently donated after iron intake.

DISCUSSION

In this study, two independent public health concerns of worldwide significance were addressed: hypertension as a global risk factor for ischemic disease and blood donation with its current situation of blood shortage. Although during the past decade, every effort has been made to resolve at least some of the major problems surrounding these
issues, the incidence of hypertension continues to increase and blood shortage cannot be currently compensated, despite restrictive transfusion practices. There is an increasing demand for blood and blood products that exceeds the current supply. Furthermore, an increasing aging population has been suggested to result in a future increase in demand. Interestingly, in a number of individual institutions worldwide, implementation of patient blood management programs has resulted in a reduction in blood use.

Upon reflection of these circumstances, the results obtained in this study are rather encouraging. We found that regular blood donation results in a significant and lasting decrease in SBP and DBP in hypertensive subjects, most profoundly in Stage II hypertension and was well tolerated. An immediate BP-reducing effect was observed after each blood donation, becoming more pronounced with each additional donation. Although BP did not significantly change in normotensive individuals, a prophylactic effect cannot be ruled out in these cases when analyzing larger cohorts. Indeed, our observation is supported by several preliminary reports that have explored the effect of therapeutic phlebotomy on hypertension. In a previous small uncontrolled study, repeated phlebotomy has been observed to decrease BP with increasing duration, and after a period of 4 to 6 weeks, a renewed increase in BP was observed. Furthermore, in patients with posttransplant hypertension associated with erythrocytosis, treatment via phlebotomy resulted in a significant reduction in SBP and DBP 2 and 6 weeks postbleeding. Interestingly, frequent and long-term blood donors were found to use less antihypertensive drugs than casual donors, and the risk of arteriosclerotic cardiovascular events was less common in the frequent donor group. Finally, we recently investigated the effect of phlebotomy on patients with metabolic syndrome in a first smaller randomized clinical study. Phlebotomy with 350 to 400 mL at baseline and after a period of 4 weeks resulted in a pronounced reduction of SBP (16 mmHg) and DBP (11 mmHg) in comparison to controls. However, the study by Ascherio and colleagues failed to support the hypothesis that reduced body iron stores lowers the risk of coronary heart disease in male blood donors.

The aforementioned reports and the results presented in this study do, in fact, point to a new method that may help in the management of hypertension. This opportunity is meaningful in several aspects including the potential prevention of hypertension and cardiovascular events, reduction, or discontinuation of drugs used in the treatment of hypertension and related cost and, of note, the long-term compensation of a global blood shortage that could thereby be achieved simultaneously. This is not only important for the health care of patients, but also for blood donors. Transfusion safety is dependent on altruistically motivated blood donors and blood donations should not be made as a therapeutic intervention. We do not believe that the notice of health benefits of donating blood violate the nature of altruism. In contrast, donors can be integrated into the community health system, motivated by this aspect, and contribute to save public health costs. A similar situation is reflected by hereditary hemochromatosis. In some countries, these “patients” are qualified as voluntary blood donors without a labeling requirement.

The question of how blood donation impacts BP still remains speculative. We observed a stepwise decrease in ferritin, but no significant changes in blood count variables were found. Unlike the findings in our previously randomized trial, ferritin reduction by phlebotomy (blood donation) was not associated with the decreases in BP in the multivariate analysis in this study. Here, we found a slight association between the reduction of DBP and the variation of Hb. However, this finding does not seem to provide an adequate explanation for the beneficial effects of blood donation. Further studies should investigate the role of changes in blood viscosity and shifts in old versus young red blood cells, which have both been documented after blood donation.

Furthermore, regular blood loss or donation is associated with a reduction of whole blood viscosity, Hct, and fibrinogen, which are also significant identified risk factors in the development or prognosis of cardiovascular diseases. In addition, blood donation may also reduce oxidative stress and inflammation. Whatever the mechanisms may be, the fact that blood donation improves and may be helpful in the prevention of hypertension and/or cardiovascular events highlights new options in this field, as well as in transfusion medicine. As this study is an initial observational study and provides preliminary results, further studies are required to assess the long-term effects of regular blood donation in hypertensive patients. Hypertension is a complex multifactorial disorder; thus, the association between regular phlebotomy and BP needs to be determined by large, blinded studies. Future studies are planned to investigate the effect of long-term (i.e., >12 months) regular blood donation in hypertensive and nonhypertensive blood donors.

Interpretation of the results of this study should be made in light of particular limitations. First, this is an uncontrolled, observational study with its bias of included nonspecific effects; second, the loss to follow-up; and third, we could not include ambulatory 24-hour BP measurements not to disturb the regular blood donation setting. Finally, we cannot exclude bias through white coat hypertension; however, we attempted to provide a relaxed and friendly study setting for all the participants in this study. Our participants reported that they were quite comfortable within the study settings and had adapted to the blood donation conditions, which we believe resulted in
the absence of relevant white coat hypertension at least from the second donation onward.

In conclusion, regular blood donation is associated with a clinically relevant and incremental reduction in BP in donors with elevated BP, particularly with Stage II hypertension. Repeated blood donation may be a simple supportive option in hypertension and may help in compensating the demand for blood products in global health care. Based on the results of our study, at least patients with Stage II hypertension benefit from blood donation. These patients may be further stimulated to donate blood based on the good tolerance of blood donation.

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CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher’s website:

Table S1. Multivariate analysis using a mixed model approach.