IRON BALANCE IN REPEAT BLOOD DONORS - THE ROLE OF HEPCIDIN

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Background

Blood donation (D, 450ml) results in iron loss of ca 250 mg/D. Regular D leads to increased erythropoiesis that requires additional supply of iron from body iron stores and enteral iron absorption. These adaptations are thought to be mediated by hepcidin, the chief controller of body iron supply and storage. To examine the effects of sequential D on body iron and serum hepcidin, we prospectively studied iron and hematological parameters in newly recruited blood donors (BD). Here we present initial data from 54 BDs who have donated the maximum possible of 4 times within a year since study entry, according to the prescription by the Swiss Red Cross. The study protocol will investigate 204 BDs (102 males, 102 females) which will be monitored for one year of consecutive D applying the shortest possible interdonation intervall.

Methods

Since August 1st, 2007, newly recruited BDs (male(m):female(f) = 1:1), entered into the study after written consent and have agreed to make at least four sequential Ds (450 ml each) with a minimal interdonation interval of ≥10 weeks. In a venous sample collected before each donation, measurements are made of hemoglobin (Hb, g/L), reticulocyte hemoglobin content (CHr, pg), serum ferritin (SF, µg/L), soluble transferrin receptor (mg/L), C-reactive protein (CRP, mg/L), alaninaminotransferase (ALAT, U/L).
The majority of the donors (42 of 54 = 78%) were also tested for serum hepcidin[1](SH, ng/ml) and serum erythropoietin (EPO, mIU/ml) at consecutive donations.

Results

Table 1
Donor Characteristics

	male	female	over all
Number	34	20	54
Age at first donation (years)	37.6 (18.0-65.7)	33.2 (22.0-58.3)	36.0 (18.0-65.7)
Average donation interval (months)	3.2 (2.4-4.4)	3.4 (2.9-4.5)	3.3 (2.4-4.5)
Body weight at first donation (kilograms)	81 (66-102)	63.5 (52-82)	75 (52-102)

Numbers are given as median and range

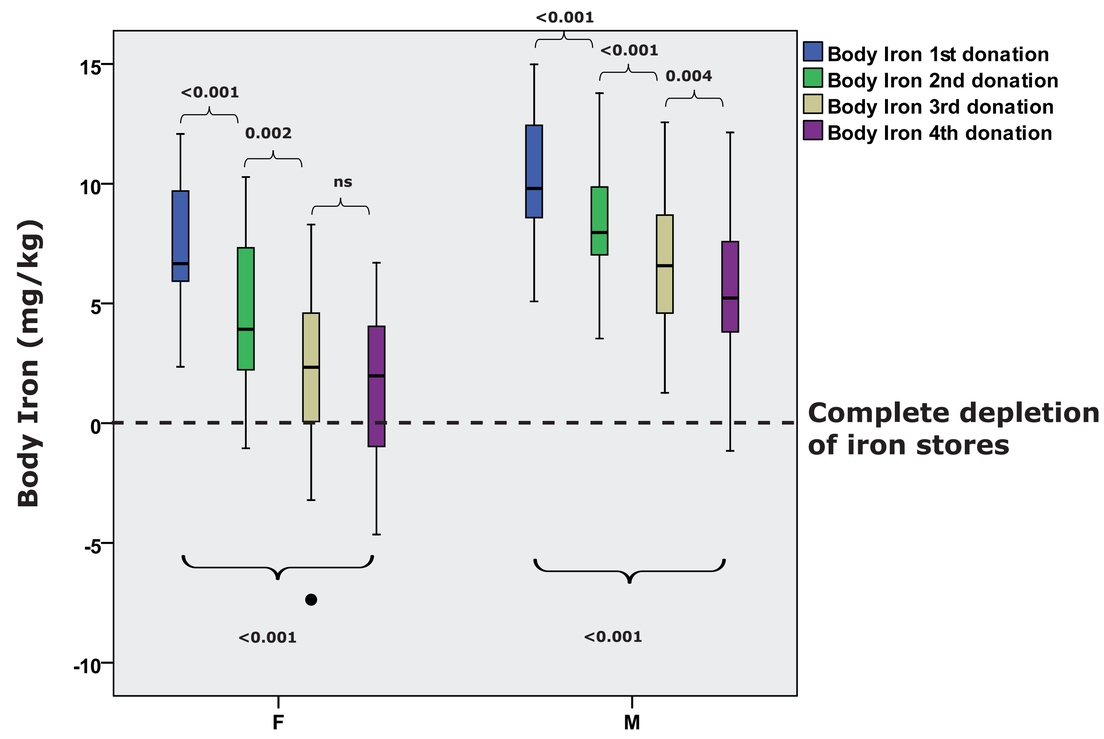
The reasons for this relative loss of female donors (first donation 102m:102f; last donation 34m:20f; relative ratio m:f at first donation 1.0, at last donation 1.7) has not yet been studied in detail but will be followed thoroughly in the final analysis. Up to now important reasons for leaving the study are: fainting after donation or feeling dizzy the next day; pregnancy, and iron replacement therapy initiated by the general practitioner. Females were more often affected by this dropout-reasons.

Table 2
Laboratory changes during repetitive blood donations

	male	
	Before 1st D	**Before 4rd D**
Number of BD investigated	34	34
Hemoglobin (g/dl)	15.4 (14.1 - 17.0)	15.0 (12.5 - 17.9)
CHr (pg)	33 (31 - 36)	32 (29 - 34)
CRP (mg/L)	4 (0 - 4)	0.7 (0 - 11)
ALAT (U/L)	28 (9 - 99)	18 (10 - 77)
Calculated iron loss* (mg)	0	810 (647 - 891)
Ferritin-Index**	1.29 (0.58 - 2.37)	1.90 (1.01 - 5.45)
Serum ferritin (ng/ml, geometric mean, range)	108 (24 - 317)	33 (9 - 188)
Soluble transferrin receptor (mg/l)°	2.7 (1.30 - 4.71)	2.8 (1.64 - 5.15)
Body iron (mg/kg)[2]	9.80 (5.08 - 14.98)	5.23 (-1.16 - 12.14)
EPO (mlU/ml)	7.00 (0.6 - 13.4)	7.50 (<LLOD - 27.3)
SH (ng/ml)	83.5 (30.2 - 200.2)	39 (<LLOD - 183)
	female	
	Before 1st D	**Before 4rd D**
Number of BD investigated	20	20
Hemoglobin (g/dl)	13.7 (12.5 - 15.1)	13.0 (11.6 - 14.2)
CHr (pg)	33 (31 - 35)	31.5 (26 - 33)
CRP (mg/L)	4 (4 - 8)	0.6 (0 - 6)
ALAT (U/L)	17 (13 - 41)	13 (5 - 26)
Calculated iron loss* (mg)	0	704 (500 - 796)
Ferritin-Index**	1.44 (0.65 - 3.12)	3.00 (1.26 - 9.71)
Serum ferritin (ng/ml, geometric mean, range)	50 (18 - 151)	11 (3 - 36)
Soluble transferrin receptor (mg/l)°	2.4 (1.14 - 3.91)	3.4 (1.58 - 4.77)
Body iron (mg/kg)[2]	6.66 (2.36 - 12.08)	1.97 (-4.65 - 6.70)
EPO (mIU/ml)	6.51 (3.6 - 12.4)	8.20 (3.6 - 14.8)
SH (ng/ml)	46.4 (<LLOD - 171)	16.8 (<LLOD - 141)

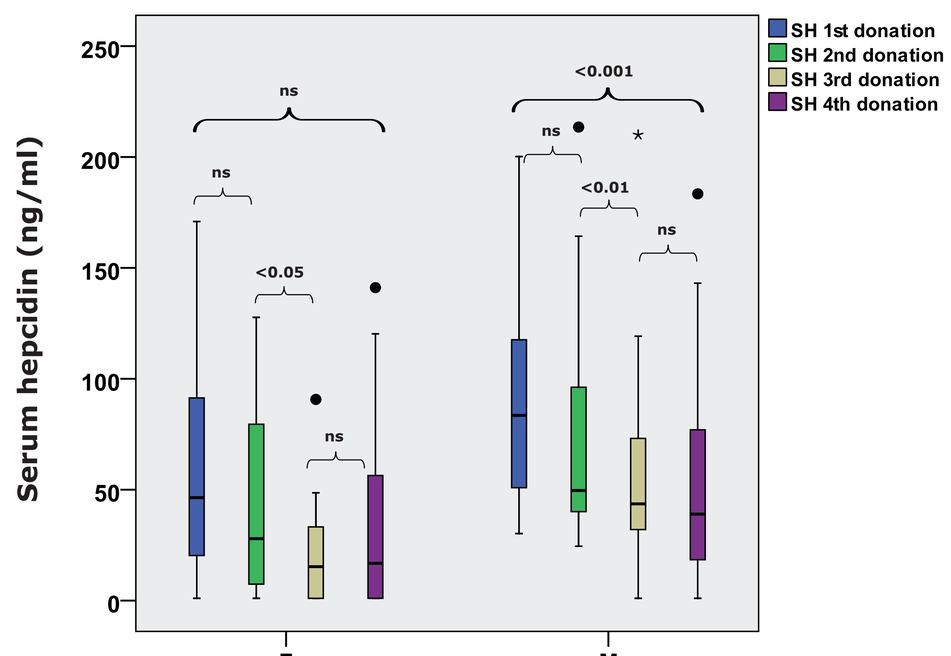
Numbers are given as median and range; except serum ferritin
* Iron loss in mg = Σ 1-3 (venous hemoglobin concentration x donation volume x 3.49)
** Ferritin-Index: (soluble Transferrin Receptor / log (Ferritin))
°sTfR normalized for Integra 400, Roche
<LLOD:Value smaller than lower limit of detection
Lower limit of detection for EPO: 0.6mlU/ml
Lower limit of detection for hepcidin: 5ng/ml

Figure 1:
Changes of Body Iron following repetitive Blood Donation



Body Iron was calculated with the formula described by Cook et. al. (Blood, 2003)[2]. Positive values of Body Iron represent presence of iron in storing tissue (liver, spleen, bone marrow), and negative values indicate empty iron stores (Skikne, Blood 1990). No donor had a negative value for body iron at first donation. At last donation 2/34 (5.9%) male donors and 8/20 (40%) female donors showed a negative iron balance reflected by empty iron stores.

Figure 2:
Changes of Serum Hepcidin following repetitive Blood Donation



Equally, hepcidin abated to undetectable level in 30% (6/20) of female donors and 11.8% (4/34) of male donors. Downregulation of hepcidin secretion may allow to mobilize stored body iron to be supplied to the stimulated erythropoiesis[3)], which compensates for blood loss by D. The amount of body iron and the extent of downregulation of hepcidin reflect the individual capacity to compensate for iron loss due to D.

At first donation all donors had sufficiently filled iron stores (see Figure 1). As these stores are smaller in females they have more often a negative body iron-value. The baseline values of hepcidin and of body iron at study entry were statistically lower in females than in males (p= 0.009, p = 0.001, respectively). While on donation, the smaller amplitude of hepcidin downregulation in female donors may prevent adequate intestinal iron absorption causing a more dramatic and clinically significant depletion of body iron.

Conclusions

1. Consecutive blood donations lead to depletion of body iron stores and a decrease of serum hepcidin concentration as a compensatory adaptation on iron loss by blood donation.
2. Due to smaller iron stores and lower hepcidin levels in women as compared to men, female donors are affected earlier and more severely by iron loss due to regular donation.
3. Measurement of serum hepcidin (initially and on follow-up) could help to identify blood donors who will maintain body iron stores despite regular blood donation.
4. Firm conclusions on the value of hepcidin measurement in blood donors may be taken, once the whole study is completed and data of deferred donors are co-evaluated.

[1)]Tomas Ganz et al; Immunoassay for human serum hepcidin; Blood 2008;112:4292 – 4297
[2)] Cook JD et al.; The quantitative assessment of body iron, Blood. 2003 May 1;101(9):3359-64
[3)] Nancy C. Andrews; Forging a field: the golden age of iron balance; Blood 2008; 112:219-230

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