How Much Can We Ask of An Apheresis Donor?

ASFA 2017
Francis S. Morrison Memorial Lectureship

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Francis S. Morrison, MD
Accomplished Scholar & Clinical Investigator

- Research trainee in Hematology, Blood Research Laboratory, NEMC, Boston (Dameshek)
- Research Medical Officer, LCDR, USN, Naval Blood Research Laboratory, Chelsea, MA
- Medical Research Council Experimental Haematology Research Unit, St. Mary's Hospital, London

**ORIGINAL ARTICLE**

Post-Transfusion Purpura

Lieutenant Commander Francis S. Morrison, (MC), USN, and P. L. Mollison, M.D.


- Professor of Medicine, U of Mississippi Medical Center
- SWOG trials of leukemia, benign and malignant hematology, red cell and platelet collection & storage
Francis S. Morrison, MD

- A “character” - a bear of a man with a commanding baritone voice, a courtly Southern bearing
- Twinkling sense of humor
- Long-time member of the ASFA Board of Directors
- President of ASFA 1991
- Down-to-earth, common sense approach to problems
- Great organizational skills, a strong sense of dignity and purpose, which he brought to ASFA
How Much Can We Ask of an Apheresis Donor?

Cytapheresis Donors - 24 times yearly

- Serial plateletpheresis donors
- Serial leukapheresis donors
- Serial granulocytapheresis in steroid/cytokine-stimulated donors
- Large volume leukapheresis in MNC or PBSC donors
Potential Long Term Risks of Serial Cytapheresis

Cell removal
• Effects on blood cell counts

Citrate administration
• Effects on calcium homeostasis and bone mineralization

Dexamethasone administration
• Effects on cataract formation
NIH: Two Retrospective “Data Mining” Studies

• Analyzed effect of long-term plateletpheresis on donor platelet counts over 4 yr period
  *Lazarus et al., Transfusion 2001*

• Analyzed effect of long-term leukapheresis on donor lymphocyte counts over 7 yr period
  *Kolf et al., Transfusion 2004*
Serial Plateletpheresis Donation

- 779 repeat donors → 8,333 cytapheresis procedures
- Frequency: maximum 12 donations/year
- Volume processed: 4-5 liters /procedure
- 10U (1.8 components) collected/procedure
- Instruments: Fenwal Amicus and CS-3000
- Deferral policies:
  - < 150,000 on one visit: defer x 2 months
  - < 150,000 on 2 visits in 12 mos: defer x 6 months
  - < 100,000: medical review

Lazarus et al. Transfusion 2001
Non-Transient Decreases in Platelet Counts in Serial Plateletpheresis Donors

- Mean decrease between 1st and last PC correlated with cumulative number of donations (p<0.0001)
Neither Sex nor Age of Donor Affected Platelet Count Difference
Frequent plateletpheresis does not clinically significantly decrease platelet counts in donors

Katz et al. Transfusion 2006 (MVRBC)

24-carat donors: 60 donors underwent plateletpheresis 24 x in 1 yr

Pre-apheresis PC known prior to donation.

1.7 components per procedure

12% of donors provided 55% of PLTs
Serial Lymphapheresis Donation

- IRB approved protocol: collect MNC for research use; 1500 procedures/yr
- Frequency: every 21 days
- Volume processed: 2-10 liters/procedure
- Instrument: Fenwal (Amicus or CS-3000 Plus)
- Safety: defer donors for 2 mos if pre-ALC < 0.8 x 10^9/L
- Database: 4,950 donations in 404 donors (6.8L/proc)
  - Mean WBC content 8.4 x 10^9
  - Mean lymph content 5.7 x 10^9 (71%)

Kolf et al. Transfusion 2004
Change from Initial Lymphocyte Counts

Analysis of co-variance for 4 ordered donation groups

Delta from First to Last Lymphocyte Count

- 9.7%
- 24.6%
- 37.3%
- 50.2%
Mean Pre-apheresis Lymphocyte Counts by Donation Number

Lymphocyte Count (10^3/μL)

Donation Number

Mean Pre-apheresis Lymphocyte Counts by Donation Number

- R = 0.9721
- p < 0.0001

Lymphocyte Counts:
- Pre-apheresis: 1.87 ± 0.92

Donation Numbers: 0, 1, 2, 3, 4, 5, 6, 7, 8
Lymphocyte Yield per Liter Processed

R = 0.8695
p < 0.0001
Changes in WBCs, Grans, Monos, Lymphs

- **WBCs**: R=0.098, p=0.387
- **Granulocytes**: R=0.525, p<0.001
- **Monocytes**: R=0.564, p<0.001
- **Lymphocytes**: R=0.972, p<0.001

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**Donation Number**

**PRE-COUNT (x10^9/L)**
Summary

- Serial plateletpheresis and leukapheresis procedures in healthy donors are associated with sustained and significant decreases in circulating platelet and lymphocyte counts.
- The cumulative number of donations correlates with decreases in counts.
- There is no evidence that these decreases have clinical significance for the donor, particularly if rigorous ongoing review and prudent donor deferral policies are established and followed.
- Prospective monitoring system must be in place with well-defined deferral criteria to ensure donor safety.
Evaluation of Citrate Effects in Long-Term Apheresis Donors

**Citrate Effects: Acute**
- Decreases ionized calcium
- Compensatory increase in PTH
- Mobilization of Ca from bone, ↑ GI uptake, ↑ renal reuptake
- Net body loss of Ca due to obligate post-apheresis calciuria

*Bolan et al, Transfusion 2003*
Bone Density in Apheresis Donors – Lab Results

Mean PTH (anabolic and catabolic)

Mean Vitamin D 1,25 (anabolic)

Mean C-Telopeptide (breakdown)

Mean Osteocalcin (re-modelling)
Citrate Effects and Bone Density

• Chronic high PTH $\rightarrow$ osteopenia
• Intermittent, bolus PTH $\rightarrow$ bone remodeling, increased bone density
• Dettke et al, 2003:
  “Apheresis donors with more cumulative life-time donations had more marked decreases in bone density than donors with fewer donations”
Impact of Frequent Apheresis on Bone Mineral Density Cross Sectional Study

• **NIH plateletpheresis donors (n=45)**
  - >50 donations over past 10 years
    - Maximum of 12 donations yearly

• **NIH research leukapheresis donors (n=44)**
  - >50 donations over past 10 years
    - Every 3 wks, maximum 17 donations yearly

• **NIH whole blood donor controls (n=85)**
  - Matched by gender, race, weight

• **ARC plateletpheresis donors (n=20)**
  - > 100 donations over past 10 years
    - Maximum of 24 donations yearly
Bone Density (DEXA) Z-Scores – AP Spine

Z score - # SDs above/below a reference database of individuals of same age, gender, race.

<table>
<thead>
<tr>
<th></th>
<th>APL</th>
<th>ARC</th>
<th>LEUK</th>
<th>WB</th>
</tr>
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<tbody>
<tr>
<td>N</td>
<td>50</td>
<td>20</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>54</td>
<td>58</td>
<td>48</td>
<td>50</td>
</tr>
<tr>
<td>Donations</td>
<td>112</td>
<td>198</td>
<td>107</td>
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</table>
Bone Mineral Density in Apheresis Donors

Femoral Neck

Distal 1/3 Radius

Bolan et al. Transfusion 2005
Special Demands we make in Granulocytapheresis Donors

To maximize circulating granulocyte counts and granulocyte yields, donors are given:

- Hydroxyethyl starch
- Steroids (dexamethasone)
- Filgrastim (rhG-CSF)
Granulocytapheresis Yields vs Marrow Production

<table>
<thead>
<tr>
<th>Donor Preparation</th>
<th>Yield (x 10^9)</th>
</tr>
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<tbody>
<tr>
<td>No donor preparation</td>
<td>3 - 5</td>
</tr>
<tr>
<td>Hydroxyethyl starch</td>
<td>5 - 9</td>
</tr>
<tr>
<td>Starch + steroid</td>
<td>10 - 20</td>
</tr>
<tr>
<td>Starch + steroid + GCSF</td>
<td>60 - 80</td>
</tr>
<tr>
<td>Daily turnover (steady state)</td>
<td>100</td>
</tr>
<tr>
<td>Daily turnover (stress)</td>
<td>350</td>
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Posterior Subcapsular Cataract

- Rare form of age-related cataract (4.5%)
- Central location, in visual axis
- Symptomatic even if small, cause glare, near vision sx
- Major risk factors: age, sun-exposure, & steroids
Cross-sectional Study

• **100 granulocyte donors**: donated grans $\geq 4$ x in prior 20 yrs
  – Dexamethasone 8 mg PO 12 hr prior
  – GCSF 480 mcg SC 12-16 hrs prior
  – Hydroxyethyl starch 30 gm IV

• **100 platelet donor controls**: matched for age, sex, cum # cytapheresis donations, $\leq 3$ lifetime gran donations

• **Standardized Clinical (CEE) & Photo Grading**
  – Single experienced ophthalmologist
  – U Wisconsin Reading Center (retroillumination lens photos)

• **No exclusion for prior cataract surgery**
Granulocyte donors n=100

Platelet donors (n=100)

ICCE =

14 eyes of 10 donors

5 eyes of 4 donors
Results: Summary

After adjusting for age, odds ratio of PSC in granulocyte donors relative to platelet donors

2.82
95% CI: 0.83-9.61
p = 0.07

Clayton et al. Transfusion 2011
Prevalence of PSC with Increasing Number of Granulocyte Donations

Per donor analysis

<table>
<thead>
<tr>
<th># Gran Don.</th>
<th>0-3</th>
<th>4-9</th>
<th>10-19</th>
<th>≥ 20</th>
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<tbody>
<tr>
<td>OR</td>
<td>1.0</td>
<td>2.25</td>
<td>2.53</td>
<td>3.60</td>
</tr>
<tr>
<td>p</td>
<td>-</td>
<td>0.30</td>
<td>0.21</td>
<td>0.11</td>
</tr>
<tr>
<td>Percent of Donors with PSC</td>
<td>4%</td>
<td>8.6%</td>
<td>9.5%</td>
<td>13%</td>
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P for trend: 0.06
## Power Analysis

### Ability to Detect a Difference in Cataract Frequency with Given Number of Subjects

<table>
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<tr>
<th>No. donors per group</th>
<th>100</th>
<th>200</th>
<th>300</th>
<th>400</th>
<th>500</th>
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<tbody>
<tr>
<td>Power*</td>
<td>28%</td>
<td>58%</td>
<td>78%</td>
<td>89%</td>
<td>95%</td>
</tr>
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</table>

*Probability, with number of subjects, of detecting a difference in PSC prevalence of 10% in granulocyte and 4% in platelet donors (in 2-sided test of 2-sample proportion tests).*
How Much Can We Ask of a PBSC Donor?

Randomized Prospective Study of PBSC Collection: Single 25 L vs Two Consecutive 15 L Procedures

- In order to collect an adequate CD34 cell dose for transplant (2 - 5 x 10^{10} CD34/kg), often need to process large volumes of blood: 3-6 blood volumes (15-30 L) total. Split into 2 consecutive procedures.

- Use of resources: space, personnel, equipment, supplies

- Donor safety, comfort, convenience
CD34 Cell Yield Per Liter Processed as a Function of Preapheresis CD34 Cell Count (NIH data on NMDP donors)

- 80 kg patient
- Desired CD34 dose $6 \times 10^6$/kg $= 480 \times 10^6$
- Vol to be processed $= 480 \times 10^6 / 30 \times 10^6$/L $= 16$ L

$R^2 = 0.77$

Vasu et al, Blood 2008
Allogeneic PBSC Collections at NIH

• **Standard LVL**: 15 L processed on days 5, 6 of G-CSF
  - AC ratio 1:13 → citrate rate 1.2 mg/kg/min
  - WBFR 30 - 84 mL/min, duration **3.0 - 8.6 hrs**

• **Review of recent NIH experience**
  - Prophylactic IV CaCl$_2$ → citrate rate ↑ to 2.5 mg/kg/min
    ↑ WBFR to 75-85 ml/min, duration **3 - 3.3 hrs**
  - Day 6 pre-apheresis CD34 counts: 71% of day 5 (65 vs 91/μL)
  - Day 6 CD34 product yields: 80% of day 5 (402 vs 495 x10$^6$)

Would a larger procedure on day 5 safely provide similar yields?
CBC, CD34 Monitoring During LVL in Healthy Allogeneic Sibling Donors

25-L LVL Day 5

0 5 10 15 20 25 1hr post

15-L LVL Day 5

0 5 10 15 1hr post

15-L LVL Day 6

0 5 10 15 1hr post

Blood Bag 1 Bag 2
## Study Subjects and Apheresis Characteristics

WBFR 75-85 mL/hr, WB:AC ratio 13:1, IV CaCl₂ 0.6 mg per mL ACD-A

<table>
<thead>
<tr>
<th>Procedure</th>
<th>M/F</th>
<th>Wt kg</th>
<th>BV’s/LVL</th>
<th>Citrate mg/kg/min</th>
<th>Duration min</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>25L x 1</td>
<td>4/3</td>
<td>77</td>
<td>4.8</td>
<td>2.0</td>
<td>444</td>
<td>2/7**</td>
</tr>
<tr>
<td>15L x 2</td>
<td>5/2</td>
<td>85</td>
<td>2.7</td>
<td>1.8</td>
<td>638*</td>
<td>0/7</td>
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</table>

* Day 5 and 6 combined  
** Fatigue (n=1), nausea (n=1).

*Bolan et al, Brit J Hem 2003*
Peripheral Blood CD34 Counts During LVL

Bolan et al, Brit J Hem 2003
Cell Yields

Bolan et al, Brit J Hem 2003
Conclusions

• A single 25L LVL procedure on day 5 of G-CSF mobilization provided the same product yield as two 15L procedures on days 5 and 6.

• The 25L procedure required fewer donor venipunctures and G-CSF administrations, and less total apheresis time, laboratory tests, apheresis kits, clerical work and cell processing and cryopreservation procedures.

• Adverse reactions were more common with 25 rather than 15 L procedures (fatigue, nausea, fluid retention)
How Much Can We Ask of an Apheresis Donor?

• To donate their time and renewable hematopoietic resources
• To tolerate discomfort, inconvenience, and pain
• To engage in prospective clinical trials

As long as we:

• Establish robust systems to monitor clinical and lab data
• Establish and enforce evidence-based policies to prevent or minimize long & short term consequences
• Educate them on the meaning and impact of changes in clinical parameters or lab values that may result
# Acknowledgments

<table>
<thead>
<tr>
<th>Dept of Transfusion Medicine Nursing Staff</th>
<th>Dept of Transfusion Medicine Fellows</th>
<th>Dept of Transfusion Medicine Senior Staff</th>
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<td>Charles Bolan</td>
<td>Harvey Klein</td>
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<td>Bonnie Sink</td>
<td>Cathy Cantilena</td>
<td>Harvey Alter</td>
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<td>Janet Browning</td>
<td>Ellen Lazarus</td>
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<td>Hanh Khuu</td>
<td>Bob Wesley</td>
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<td>Phyllis Byrne</td>
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**NIH Collaborators**

- Bob Wesley
- Janine Clayton Smith
- Rick Childs
- Harry Malech