[原著]

血管迷走神経反応による転倒の要因の解析と対策

埼玉県赤十字血液センター
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Analysis of factors which cause donors to collapse due to vasovagal reaction and prevention measures

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抄　録

血管迷走神経反応(VVR)は献血者の副作用として一番多く，献血者の約1%に起こる。VVRに伴う転倒は外傷に繋がり，その予防は献血者の安全を守る上で重要である。

埼玉県赤十字血液センターで2003年度から2005年度の3年間に起こったVVRに伴う転倒者16人について性別，年齢，献血種別について解析を行った。その結果，10歳代と60歳代に高い。成分献血では血漿献血者だけに転倒を認めた。全国統計でも同様の傾向がみられる。これらの群に注意をはらって，転倒を防ぐように努める必要がある。

10歳代の男性の全血献血者に特に転倒者が多かった。そこで，VVRの頻度が高い初回の献血者が集中する高校生の集団献血では，献血場所のすぐそばに椅子を用意して座らせ，30分以上の休憩と水分摂取を行うことによって転倒者が減少した。

Abstract

Among adverse events related to blood donation, vasovagal reaction (VVR) occurs most frequently and its incidence is around 1% of donors. Collapse related to VVR sometimes causes trauma to donors. It is important to prevent falls related to VVR for donor safety.

In order to decrease the incidence of falls linked to VVR, we analyzed the related factors in 16 donors who donated blood at Saitama Red Cross Blood Center between April 2003 and March 2006.

As a result, the risk factors of collapse are between 16 and 19 years of age and between 60 and 69 years of age, undergoing whole blood donation and plasmapheresis. The similar tendency was observed by the analysis of the nation wide study. We should, therefore, pay particular attention to these donors.

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In order to prevent male high school students from collapsing, we prepared a refreshment table next to the donation area and let them sit for at least 30 minutes. These procedures resulted in the decrease in the number of collapsing donors.

Key words: collapse of blood donors, vasovagal reaction, blood donation

はじめに

献血後の副作用は献血者の約1%に起こることが知られている[1]。その主なものは血管迷走神経反応(vasovagal reaction，VVR)，神経損傷と皮下出血である。VVRは全副作用のうち約75%を占める。VVRは転倒の原因となり，重篤な副作用に繋がる可能性がある。全国で年間約540万人の献血者がいるが，そのうちVVRによる転倒は100～150人の献血者に起こり，大きな問題と考える[2)-4)]。転倒事故を少なくするためにはVVRの発生率を下げる努力と転倒の直接的な予防策を立てる必要があると考える。

全血献血でVVRを起こしやすい人々は，①初回，②低体重，③若年，④白人，⑤若年初回の献血者では女性と報告されている[5)-7)]。一方，成分献血では①循環血液量の少ない人，②中高年の女性，③サイクル数の多い人等が上げられる[8)]。埼玉県赤十字血液センターの予備的な調査でも同様の傾向がみられ，中高年の女性の成分献血では1時間以上にVVRが持続する例が多い。

これらのVVRのハイリスクの献血者に2004年5月から①少なくとも30分以上休憩をとること，②水分を摂取することを勧めるパンフレットを渡している[9)]。その結果，VVRを起こす献血者は有意に減少したが，それによる転倒者の数は大きな変動を示さなかった。

そこで，VVRによる転倒者を減らす目的で2003年度から2005年度の3年間に埼玉県赤十字血液センターで発生したVVRに伴う転倒例16人についてその要因を解析し，その対策について検討したので報告する。

方　法

検討した献血者は2003年4月から2006年3月までの3年間に埼玉県赤十字血液センターに来訪した献血者722,768人(男性442,449人，女性280,319人，全血献血479,898人，成分献血242,870人)である（表1，表2)。それらの献血者のうち転倒した例は16人である（表3)。それらについて，性別，年齢，献血種別などについて検討した。

初回の若い男女の全血献血ではVVRが多いとされる。その献血者に転倒事故が起こる可能性が高い。とくにその中でも10歳代と20歳代の初回の男性を多く含む高校生献血あるいは専門学校生の集団献血では，転倒事故が起こりやすいと考えられる。埼玉県赤十字血液センターでは，そのような集団献血では多くの場合バスにおいて採血する。その場合に，図1に示すように，接遇の部屋をバスから離れたところに設営するのではなく，バスのすぐそばにテントで仮の接遇の場を造り，そこ

表1　2003年度から2005年度の献血種別による献血者数

献血種別	2003年度		2004年度		2005年度		合　計		総合計
	男	女	男	女	男	女	男	女	
200mL	14,248	36,428	13,751	37,329	12,522	37,517	40,521	111,274	151,795
400mL	84,593	24,897	85,229	23,197	85,992	24,195	255,814	72,289	328,103
血小板	19,678	7,966	20,743	8,169	21,647	7,879	62,068	24,014	86,082
血　漿	31,051	26,597	29,414	25,441	23,581	20,704	84,046	72,742	156,788
計	149,570	95,888	149,137	94,136	143,742	90,295	442,449	280,319	722,768

200mL：200mL献血　400mL：400mL献血　血小板：血小板献血　血漿：血漿献血

表2　2003年度から2005年度の年代別の献血者数

年代	2003年度		2004年度		2005年度		合計		総合計
	男	女	男	女	男	女	男	女	
10歳代	14,106	13,109	14,026	13,529	12,682	12,371	40,814	39,009	79,823
20歳代	31,227	26,761	30,167	25,541	28,279	24,045	89,673	76,347	166,020
30歳代	42,020	22,118	42,179	22,086	40,445	21,398	124,644	65,602	190,246
40歳代	30,753	13,477	31,277	13,636	31,224	13,847	93,254	40,960	134,214
50歳代	22,782	14,491	22,773	13,377	22,481	12,940	68,036	40,808	108,844
60歳代	8,682	5,932	8,715	5,967	8,631	5,694	26,028	17,593	43,621
計	149,570	95,888	149,137	94,136	143,742	90,295	442,449	280,319	722,768

表3　転倒者の年齢，性，献血種別および献血回数

年齢	性別	献血種別	献血回数
10歳代	男	200mL	初回
10歳代	男	200mL	2回目
10歳代	男	400mL	初回
10歳代	男	400mL	2回目
10歳代	男	400mL	2回目
10歳代	男	血漿	2回目
20歳代	男	400mL	3回目
20歳代	女	血漿	4回目
20歳代	女	200mL	3回目
20歳代	男	400mL	初回
30歳代	男	血漿	2回目
30歳代	男	400mL	13回目
30歳代	男	400mL	9回目
60歳代	女	400mL	13回目
60歳代	男	400mL	初回
60歳代	女	血漿	50回目

200mL：200mL献血　400mL：400mL献血
血漿：血漿献血

表4　献血者の性別と転倒者数および転倒率

	転倒者数	献血者数	転倒率
男性	12	442,449	0.0027%
女性	4	280,319	0.0014%

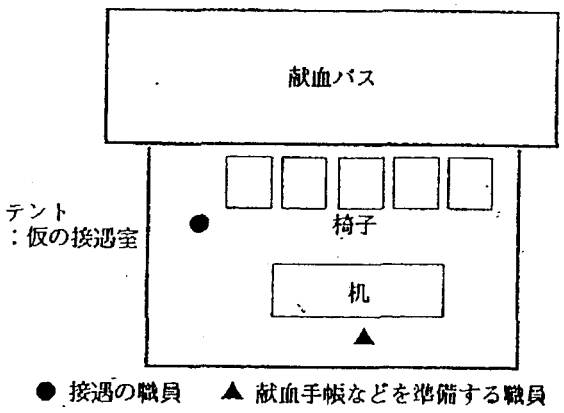

図1　高校生の集団献血の設営法

に1台のバスあたり約5脚の椅子を置き，さらに専門の職員を1人配置し，椅子に座ることと水分摂取を勧め，約30分後に献血手帳を渡すようにした。それによって，転倒事故が減少するか否かを検討した。

結　果

埼玉県赤十字血液センターにおいて，2003年度から2005年度の3年間にVVRに伴う転倒者は16人であった（表3）。その頻度は0.002%である。16人全員が治療のために医療機関を受診しているが，受診回数は1回受診が7人と多く，2回受診が3人，3回受診が2人，4回受診が1人，6回受診が1人，18回受診が1人，入院を要した献血者が1人であった。

転倒者と性別との関係をみると表4に示すように女性より男性に転倒率が有意ではないが高い傾向にある。このことはVVRが女性に多いことと対照的である[2)-4),9)]。さらに，性別と献血の種類を組み合わせてみると男性における全血献血におい

て転倒率が高い傾向がみられる（表５，表６）。また，その男性の全血献血の転倒者10人のうち初回の献血者が４人，２回目の献血者が３人とそれらで大半を占める（表３）。女性では成分献血の方が全血献血より転倒率が有意ではないが高い傾向がある（表５，表６）。

献血種別と転倒率の関係を調べると血小板献血で転倒した献血者は１人もいないので転倒率は0%となるが，それ以外で一番転倒率の低いのが200mL献血である。その値を１として，他の献血種別の転倒率を調べると，400mL献血が1.35倍と一番高く，ついで血漿献血が1.30倍と高い（表７）。

一方，転倒者を年齢別に同様の検討をすると40歳代と50歳代には転倒者がいない（表８）。転倒者がいた年代で一番転倒率の低いのは30歳代で，その値を１とすると，10歳代と60歳代がほぼ同じ転倒率を示し，それぞれ4.7と4.3と高い。20歳代は次に転倒率が高く1.5倍となる。

10歳代男性の全血献血の献血者に転倒者が多かったが，その多くが男性の高校生か専門学校生の集団献血で起こっている。そこで，10歳代の初回の男性を多く含む男性の高校生献血あるいは専門学校生の集団献血の場合に，転倒者を減らす目的でバスのすぐそばにテントで仮の接遇の場を造り，そこに１台のバスあたり約５脚の椅子を置き，さらに専門の職員を１人配置し，椅子に座ることと水分摂取を勧め，約30分後に献血手帳を渡すようにした（図１）。その結果，表９に示すように，その方法を開始後の３カ月間には約5,000人の高校生ならびに専門学校生の献血を行ったが，１人も転倒することはなかった。それ以前の３カ月間には約1,000人の献血者がいたが２人転倒した。さらに，2004年度の同時期の３カ月間にやはり約5,000人の献血をしたが，２人の転倒者がいた。

表５　男性献血者の転倒者数と転倒率

男　性	転倒者数	献血者数	転倒率
全　血	10	296,335	0.0034%
成分献血	2	146,114	0.0014%

表６　女性献血者の転倒者数と転倒率

女　性	転倒者数	献血者数	転倒率
全　血	2	183,563	0.0011%
成分献血	2	96,756	0.0021%

表７　献血種別と転倒者数および転倒率

献血種別	転倒者数	献血者数	転倒率	比　率
200mL	3	151,795	0.0020%	1
400mL	9	328,103	0.0027%	1.35
血　漿	4	156,788	0.0026%	1.30
血小板	0	86,082	0.0000%	0

200mL：200mL献血　400mL：400mL献血
血漿：血漿献血　血小板：血小板献血

表８　献血者の年代と転倒者数および転倒率

年　代	転倒者数	献血者数	転倒者率	比率
10歳代	6	79,823	0.0075%	4.7
20歳代	4	166,020	0.0024%	1.5
30歳代	3	190,246	0.0016%	1
40歳代	0	134,214	0.0000%	0
50歳代	0	108,844	0.0000%	0
60歳代	3	43,621	0.0069%	4.3

表９　高校生および専門学校生の集団献血における献血者数および転倒者数

1. 椅子をバスのそばに置く前の３カ月間（2005年７月27日－2005年10月26日）
   献血者数　1,142人　　転倒者数　２人
2. 椅子を置いてからの３カ月間（2005年10月27日～2005年１月23日）
   献血者数　4,988人　　転倒者数　０人
3. 前年同時期の３カ月間（2004年10月27日～2005年１月23日）
   献血者数　5,125人　　転倒者数　２人

考　察

転倒・転落は病院における医療でも医療事故の一つとして問題とされている。それを防ぐために，患者のリスクを分析し，それを点数化し，対策を検討する試みもなされている[10]。一方，献血者におけるVVRに伴う転倒はその頻度も少なく，その解析は十分行われてはいない。今回埼玉県赤十字血液センターにおいて2003年度から2005年度の3年間においてVVRに伴う転倒例の解析を行いその要因を調べた。

3年間の転倒者は16人で，献血者総数722,768人で除するとその頻度は0.002%である。埼玉県赤十字血液センターにおいて5秒以上の失神を伴う重症のVVRを起こした献血者の率は男性で0.03%で，女性で0.06%である。転倒率が0.002%であることは重症VVRを起こした献血者の約1/30～1/15に転倒が起こることを示している[9]。この転倒率は2003年度，2004年度，2005年度上半期の全国の統計の結果がいずれも約0.002%であることとも一致している[2)-4)]。米国においては，失神を起こしたVVRの頻度が0.09%であり，その14%が転倒するとのことであり，この値は埼玉県赤十字血液センターおよびわが国の全国統計の値とほぼ同じである[11]。

性別と転倒との関係を見ると，転倒者は男性に多い傾向がある。とくに埼玉県赤十字血液センターでは男性の全血献血での転倒者が多いのでその対策が必要であると考えた。しかし，全国統計では女性の転倒率の方が男性のそれより高い[2)-4)]。その理由は明らかでない。埼玉県赤十字血液センターにおける転倒者16人のうち10歳代の全血の献血者が一番多いことから10歳代の男性を多く含む高校生の集団献血で起こっている可能性があり，その解析と対策が今後必要であると考えた。

年齢と転倒率との関係を見ると，10歳代と60歳代が転倒のリスクが高いという結果であった。また逆に40歳代と50歳代は転倒のリスクが低いという結果であった。

一つのセンターの結果では転倒者の数も少なく，地域的な偏りもあることも考えられる。そこで，2003年度の日本赤十字社の全国統計をみるとやはり40歳代と50歳代は転倒率は0人ではないが他の年代より著しく低く，一番低い40歳代の転倒率を1とすると，10歳代が6.3，60歳代が3.6と高く，我々の結果と傾向は類似している。ただし，20歳代の転倒率が40歳代の3.7倍と我々の結果より高い値を示している[2)]。この傾向は，2004年度，2005年度の結果もほぼ同様である[3),4)]。

我々の結果から10歳代の男性の場合は初回の全血献血が転倒のリスクが高いと思われ（表3），それは男性の高校生あるいは専門学校生の集団献血の場で起こっている可能性が高い。

我々はVVRを防ぐためにVVRのハイリスクと考えられる①全血献血の初回の男女と，②中高年の成分献血の女性に対し，①30分間の休憩と②水分摂取を勧めるパンフレットを渡した[9]。それによって男女とも軽症のVVRの頻度は減少した。しかし，重症のVVRは女性の400mL献血と血漿献血で著明に減少したが，男性では，いずれの献血種別でも減少しなかった。とくに，200mL献血を行った献血者に重症のVVRの頻度が高かったが，それらの献血者にパンフレットを渡してもその減少がみられなかった[9]。200mL献血を行う男性は，高校生あるいは専門学校生の集団献血が多いことから，このパンフレットを渡す方策は男性の高校生あるいは専門学校生の集団献血では有効でないと考えられた。そこで，方法で述べたようなバスの周辺への椅子の設置，職員の配置，30分たってから献血手帳を渡す方策を考えた。その結果，表9に示すように転倒者を減少させるのに有用と考えられた。今後，さらに継続して，その効果をみていきたいと考える。

埼玉県赤十字血液センターにおいては10歳代の転倒者の割合は全転倒者の約40%であるが，2003年度の全国の統計を見ても10歳代の転倒者は約20人で全転倒者約100人の約20%を占めている。いずれにしても全国で10歳代の転倒者が多いが，これらの献血者に対し，我々の行った方策が全国で試され，有用であれば年間20～40人の転倒者が救われることになる。なお，全国の統計では20歳代の転倒率が60歳代と同程度に高く，10歳代と20歳代を合わせると全転倒者の40%を占めるので，20歳代の転倒者の要因を解析し，その転倒の対策を講じる必要があろう。

埼玉県赤十字血液センターのデータからは60歳代の転倒率が10歳代と同程度に高い結果であった。このように60歳代の転倒率が高いことは全国の統計からも明らかである[2)-4)]。VVRの頻度は60歳代で必ずしも高くないが，転倒率は高い。60歳代の転倒者に性差あるいは献血種別に差があるか等を検討する必要がある。当センターにおいて60歳代で転倒したのは全血献血と血漿献血で，血小板献血の献血者はいない。とくに，入院が必要であった献血者は64歳の女性で，血漿献血のリピーターであり，60歳代の血漿献血のリピーターの女性はとくに注意が必要であると考える。いずれにしても60歳代の献血者に対しては座るまで，看護師が付き添い，座らせ，必要な飲み物を取ってあげるなどの配慮が必要であろう。

成分献血では，転倒者は男女それぞれ2名ずつであるが，それらはすべて血漿献血のリピーターである。血小板献血は埼玉県赤十字血液センターでは初回の献血者には行っていないが，再来の血小板献血者でも転倒した献血者は1人もいない。血漿献血をした献血者では400mLの献血者と同程度の転倒率を認めている。転倒した献血者はいずれもリピーターであり，リピーターといえども十分な配慮をする必要がある。全国の統計でも血漿献血の方が血小板献血より転倒率は約4倍高い[2)]。VVRの頻度は血小板献血と血漿献血のそれと大きな違いはないが，転倒率でこのような差が起こる理由が何によるものか問題である。血小板献血と血漿献血の差異を調べてみると，血漿献血の方が献血者の条件がやや悪い。つまり，年齢制限については血小板献血は54歳以下であるが，血漿献血は69歳以下である。ヘモグロビン濃度は血小板献血では12g/dL以上であるが，血漿献血では女性では11.5g/dL以上である。また，ほぼ同程度の採液量であるが，それにかかる時間が血漿献血の方が血小板献血より短いことが多い。このようなことが，血漿献血の方が血小板献血より転倒率が高くなる要因である可能性がある。英国における年齢制限は血小板献血と血漿献血に差がなく，いずれも65歳以下である。ヘモグロビン濃度も血小板献血と血漿献血でその条件に差がなく，男性で13g/dL以上で，女性では12.5g/dL以上である[12)]。つまり，英国では，血小板献血と血漿献血の献血者の選択基準を同じにしている[12)]。また，成分献血は過去2年以内に全血献血を行い，大きな副作用のなかった献血者を受け入れている。さらに，成分献血の初回の献血者の年齢は60歳以下である。このような英国の基準の根拠は明らかでないが，わが国の基準を国際的な基準と比較し検討し直す必要があろう。

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[原著]

成分献血における血管迷走神経反応—性別，年齢，体重および献血回数の影響

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Vasovagal reactions in apheresis donors: the effects of sex, age, body weight and donation status

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抄　録

献血に関連して起こる副作用のうち血管迷走神経反応(VVR)の頻度が一番高く，全献血者の0.76%に起こる。成分献血者におけるVVRのリスク要因を明らかにするために，2004年6月から2005年4月までの11カ月間に埼玉県赤十字血液センターを訪れた成分献血者76,658人について，そのVVR発生率を性別，年齢，体重，献血回数との関係において検討し，同時期に訪れた全血献血者のそれと比較した。

その結果，女性の成分献血におけるVVR発生率は女性の全血献血および男性の全血献血と成分献血のVVR発生率より有意に高かった。初回の成分献血におけるVVR発生率は男性で4.7%，女性で7.4%であった。その頻度は，再来の成分献血のそれが男性で0.4%，女性で2.0%であるのに比べて著しく高く，初回の400mL献血のVVR発生率が男女それぞれ2.2%と2.6%であるが，これらよりも有意に高かった。初回の成分献血の是非について検討する必要があると考える。

Abstract

Among adverse events related to blood donation, the incidence of vasovagal reaction (VVR) occurs most frequently, involving around 0.76% of donors.

In order to clarify the risk factors of VVR in apheresis donors, we studied the incidence of VVR in 76,658 apheresis donors who visited Saitama Red Cross Blood Center for 11 months from June 2004 to April 2005 in relation to sex, age, body weight and donation status comparing with that of whole blood donors who visited our center during the same period.

As a result, the incidence of VVR in female apheresis donors was higher than that of female whole blood donors and that of male whole blood donors and

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apheresis donors. The incidence of VVR in male and female first-time apheresis donors is 4.7% and 7.4%, respectively. This incidence was significantly higher than that of male and female repeat apheresis donors, which is 0.4% and 2.0%, respectively, and was also significantly higher than that of male and female first-time 400mL whole blood donors, which is 2.2% and 2.6%, respectively. It is necessary to reconsider the enrollment of first-time donors for apheresis.

Key words: risk factors of vasovagal reactions, apheresis

はじめに

献血後の副作用は献血者の約1%に起こることが知られている[1]。その主なものは血管迷走神経反応(vasovagal reactions, VVR)，神経損傷と皮下出血である。VVRは全副作用のうち72%を占めると報告されている[1]。VVRは転倒の原因となり，重篤な副作用に繋がる可能性がある。VVRによる転倒は全国では年間100～150人の献血者に起こり，大きな問題と考える[2)~4)]。転倒事故を少なくするためにはVVR発生率を下げる努力と転倒の直接的な予防策を立てる必要がある。

全血献血でVVRを起こしやすい要因は，①初回，②低体重，③若年，④白人，⑤若年の初回献血では女性と報告されている[5)~10)]。一方，成分献血では①中高年の女性，②循環血液量の少ない人　③サイクル数の多い人がVVRを起こしやすいとされている[10),11)]。またMcLeodらは多数の血液センターのデータを集めた結果，初回の成分献血者もVVRを起こしやすいと報告している[12)]。

我々は成分献血者におけるVVRのリスク要因を明らかにする目的で，献血者の性別，年齢，体重および献血回数とVVR発生率との関係を検討した。

方　法

成分献血におけるVVRのリスク要因を明らかにするために，以下の検討を行った。

対象は2004年6月から2005年4月までの11ヶ月間に埼玉赤十字血液センターに来訪した献血者223,795人(男性136,901人，女性86,894人，成分献血76,658人，全血献血147,137人)であった（表1，表2，表3)。そのうち成分献血者について性別，年齢，体重，献血回数，献血種別とVVR発生率との関係について調査した。また，全血献血者について同様に調査し，成分献血と比較した。なお，埼玉県赤十字血液センターでは初回献血者に対して，原則として血小板献血は行っていないので，初回の成分献血者の結果は血漿献血者の結果である。

成分献血はほとんどの場合，献血ルームで行っている。全血採血は献血ルームと移動採血車で行っている。今回は全血献血におけるVVR発生率を献血ルームと移動採血車に分けては検討しなかった。

VVRの診断は，日本赤十字社の標準作業手順書に準拠した（表4)[13)]。標準作業手順書では表4に示すようにVVRを重症と軽症に分けているが，今回はその両者を併せた数を調査した。なお，献血場所から離れてから遅発性のVVRが起こるとされているが，今回は遅発性のVVRの調査は行わなかった[14),15)]。

表1　埼玉県赤十字血液センターにおける献血者数とVVR発生率(2004年6月～2005年4月)

性　別	男	女	計
献血者数	136,901	86,894	223,795
VVR発生数	696	1,086	1,782
VVR発生率	0.5%	1.2%	0.8%
初回献血者数	15,599	12,792	28,391
VVR発生数	319	260	579
VVR発生率	2.0%	2.0%	2.0%
再来献血者数	121,302	74,102	195,404
VVR発生数	376	826	1,202
VVR発生率	0.3%	1.1%	0.6%

VVR発生率＝(VVR発生数÷献血者数)×100

成分献血に用いた採血機器の主なものは，CCS（ヘモネティクスジャパン株式会社，東京），TERUSYS（テルモ株式会社，東京）あるいはTERUSYS S（テルモ株式会社，東京）である。今回は採血機種とVVR発生率との関係は検討しなかった。

表2　埼玉県赤十字血液センターにおける全血献血者数とVVR発生率（2004年6月～2005年4月）

採血種類	200mL献血			400mL献血			総　計		
性別	男	女	小計	男	女	小計	男	女	計
献血者数	12,678	34,372	47,050	78,456	21,631	100,087	91,134	56,003	147,137
VVR発生数	96	205	301	407	206	613	503	411	914
VVR発生率	0.8%	0.6%	0.6%	0.5%	1.0%	0.6%	0.6%	0.7%	0.6%
初回献血者数	5,230	8,880	14,110	9,713	3,118	12,831	14,943	11,998	26,941
VVR発生数	76	120	196	212	81	293	288	201	489
VVR発生率	1.5%	1.4%	1.4%	2.2%	2.6%	2.3%	1.9%	1.7%	1.8%
再来献血者数	7,448	25,492	32,940	68,743	18,513	87,256	76,191	44,005	120,196
VVR発生数	20	85	105	194	125	319	214	210	424
VVR発生率	0.3%	0.3%	0.3%	0.3%	0.7%	0.4%	0.3%	0.5%	0.4%

VVR発生率＝（VVR発生数÷献血者数）×100

表3　埼玉県赤十字血液センターにおける成分献血者数とVVR発生率（2004年6月～2005年4月）

採血種類	血小板献血			血漿献血			総　計		
性別	男	女	小計	男	女	小計	男	女	計
献血者数	19,360	7,618	26,978	26,407	23,273	49,680	45,767	30,891	76,658
VVR発生数	69	180	249	124	495	619	193	675	868
VVR発生率	0.4%	2.4%	0.9%	0.5%	2.1%	1.2%	0.4%	2.2%	1.1%
初回献血者数	3	0	3	653	794	1,447	656	794	1,450
VVR発生数	1	0	1	30	59	89	31	59	90
VVR発生率	33.3%	0.0%	33.3%	4.6%	7.4%	6.2%	4.7%	7.4%	6.2%
再来献血者数	19,357	7,618	26,975	25,754	22,479	48,233	45,111	30,097	75,208
VVR発生数	68	180	248	94	436	530	162	616	778
VVR発生率	0.4%	2.4%	0.9%	0.4%	1.9%	1.1%	0.4%	2.0%	1.0%

VVR発生率＝（VVR発生数÷献血者数）×100

表4　VVRの重症度分類[12]

分類	症　状	血圧（max，mmHg）採血前→測定最低値	脈拍数（/分）採血前→測定最低値	呼吸数（/分）
軽症	気分不良，顔面蒼白，あくび，冷汗，悪心，嘔吐，意識喪失（5秒以内），四肢皮膚の冷汗	120以上→80以上 119以下→70以上	60以上→40以上 59以下→30以上	10以上
重症	軽度の症状に加え，意識喪失（5秒以上），痙攣，尿失禁，脱糞	120以上→79以下 119以下→69以下	60以上→39以下 59以下→29以下	9以下

結　果

1．性別とVVR発生率との関係

男性ではVVR発生率は献血種別に関係なく，1%未満であった（表1，表2，表3，図1）。女性では全血献血におけるVVR発生率が1%以下であるが，400mL献血では女性が男性より有意に高かった。女性における成分献血では全体で2.2%，血小板献血で2.4%，血漿献血で2.1%と男性のそれより有意に高く，また，女性の全血献血のそれよりも有意に高かった。なお，女性の血小板献血と血漿献血の間にVVR発生率に有意差があるとはいえなかった。

献血回数を初回と再来に分けて，VVR発生率を検討した。400mL献血における初回者のVVR発生率は，男性で2.2%，女性で2.6%と再来者（男性0.3%，女性0.7%）より有意に高かった（表2，図2）。成分献血の初回者では男性で4.7%，女性で7.4%と，成分献血の再来者（男性0.4%，女性2.0%）や400mL献血の初回者に比べて有意に高かった（表3，図3）。ただし，埼玉県赤十字血液センターにおいては前述のように初回の成分献血者は血漿献血者だけである。また，初回の成分献血（血漿献血）ではVVR発生率は女性が男性より有意に高かった。再来の成分献血におけるVVR発生

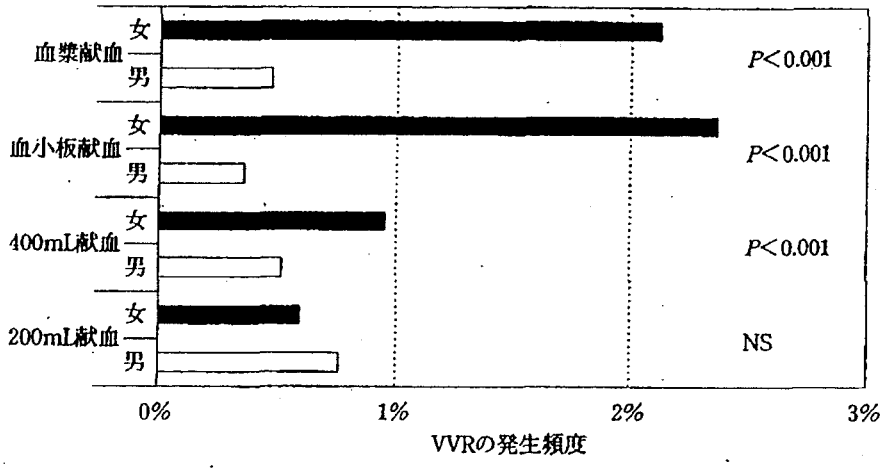

図1　性別ならびに献血種別ごとのVVR発生率

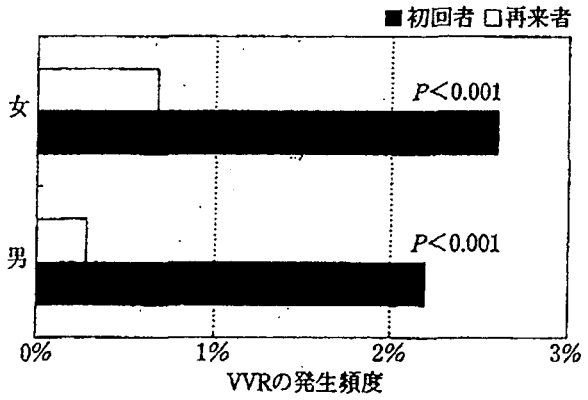

図2　400mL献血における献血回数とVVR発生率との関係

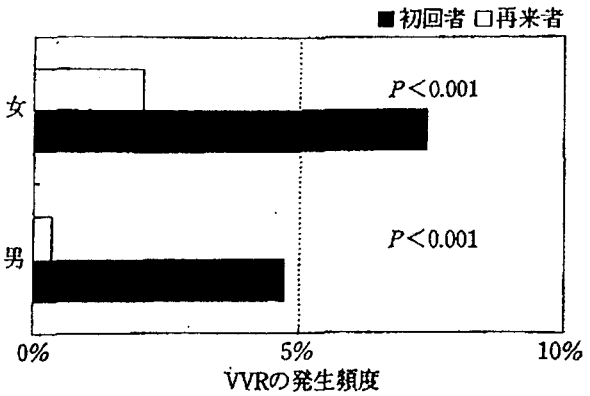

図3　成分献血における献血回数とVVR発生率との関係

率は血小板献血で1.1%，血漿献血で0.9%とほぼ同じ値であり（表３），いずれの場合もVVR発生率は女性が男性より有意に高かった。

2．年齢とVVR発生率との関係

400mL献血においては，いずれの年齢層においても男女とも初回献血者のVVR発生率が高かった（図４，図５）。また，男女とも若年層で高く，加齢と共に低下傾向を示した。

成分献血においても各年齢ともまた男女とも初回献血者のVVR発生率が再来のそれより高かった（図６，図７）。また，男女とも各年齢における初回の成分献血者のVVR発生率は初回の全血献血者のそれより高かった。男性においては初回も再来もVVR発生率は若年層で高い傾向がみられた。女

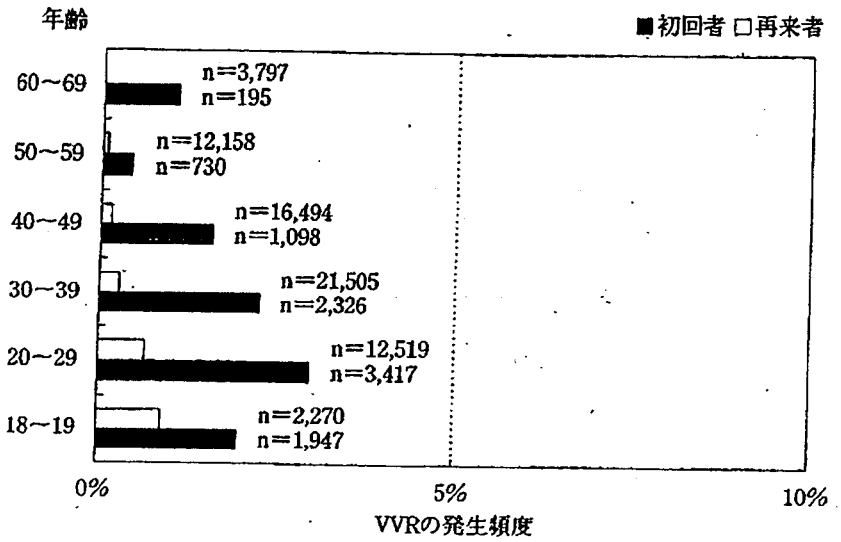

図４　男性の400mL献血におけるVVR発生率の献血回数と年齢との関係
n＝献血者数

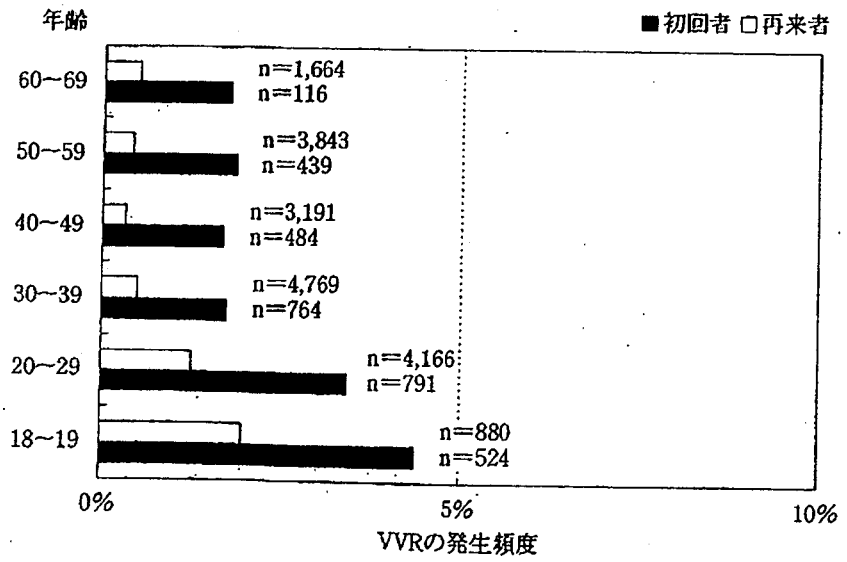

図５　女性の400mL献血におけるVVR発生率の献血回数と年齢との関係
n＝献血者数

性では，初回献血者のVVR発生率は非常に高く，すべての年齢層で5%を超えており，若年層でとくに高いという傾向はみられなかった。再来の成分献血の女性では，若年層にVVR発生率が高い傾向がみられた。

3．体重とVVR発生率との関係

（図8，図9，図10，図11）

400mL献血では，男女ともすべての体重において初回献血者が再来献血者よりVVR発生率が高かった（図8，図9）。さらに，男性では初回と再来の献血者いずれでも体重の少ない献血者にVVR発生率が高い傾向がみられた。一方，女性では初回および再来の献血者いずれでも体重とVVR発生率との関係は明らかでなかった。

成分献血では，すべての体重において，男女とも再来献血者より初回献血者でVVR発生率が高い

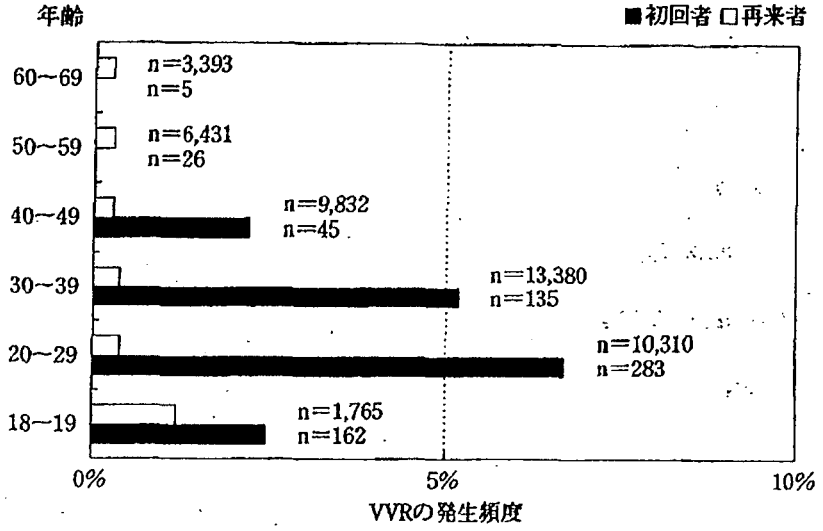

図6　男性の成分献血におけるVVR発生率の献血回数と年齢との関係
n＝献血者数

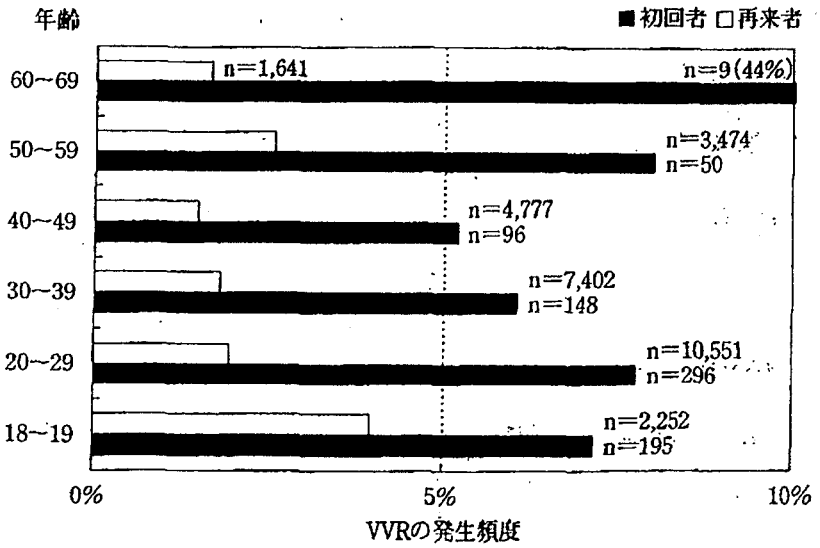

図7　女性の成分献血におけるVVR発生率の献血回数と年齢との関係
n＝献血者数

傾向がみられた（図10，図11）。また，男女ともほとんどの体重において初回の成分献血のVVR発生率は初回の全血献血のそれより高かった。初回献血者では男女ともVVR発生率と体重との間に一定の関係はみられなかった。再来の成分献血では，男性では体重が少ない献血者にVVR発生率がやや高い傾向があるが，女性ではその傾向は明らかでなかった。

考　察

Tomitaらは，全血献血におけるVVR発生率は男性で0.83%，女性で1.25%であり，成分献血では

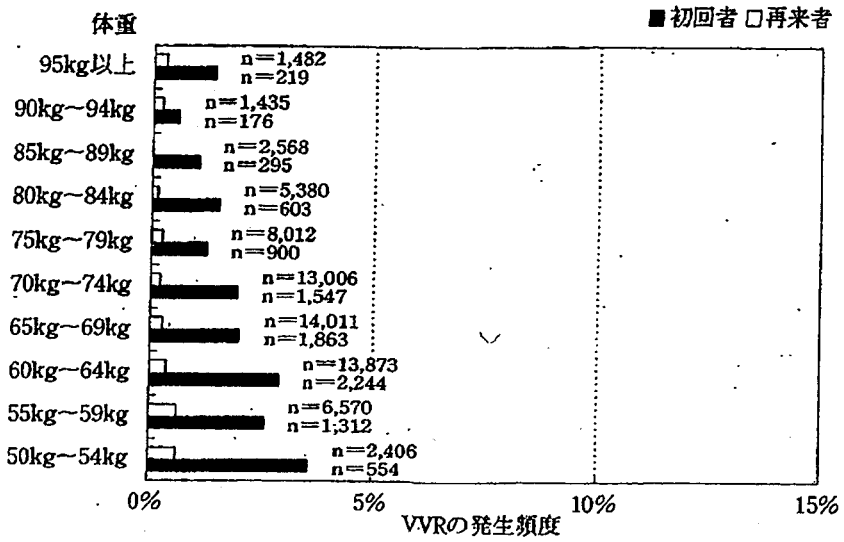

図8　男性の400mL献血におけるVVR発生率の献血回数と体重との関係
n＝献血者数

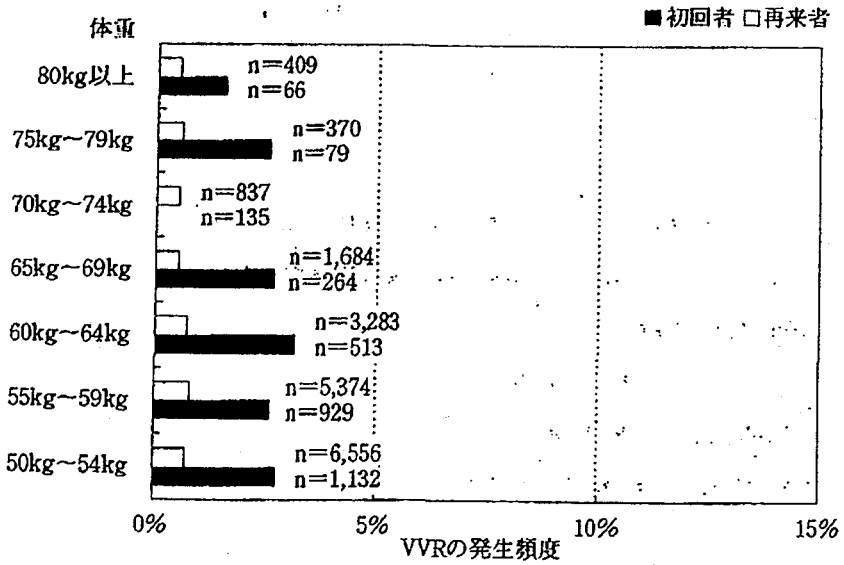

図9　女性の400mL献血におけるVVR発生率の献血回数と体重との関係
n＝献血者数

男性で0.99%，女性で4.19%という結果から女性の成分献血にVVR発生率が高いことを報告した。さらにVVRの要因を解析し，成分献血においては，①45歳以上の女性，②サイクル数の多い人，③循環血液量の少ない人にVVR発生率が高いと報告している。大坂らも成分献血では女性が男性よりVVR発生率が高いと報告している。その頻度は男性における血漿献血で1.2%，血小板献血で1.3%，女性における血漿献血で3.5%，血小板献血で4.7%であり，Tomitaらの報告に近い値である。Tomitaらの報告に対し，雑誌「Transfusion」の編集者は，成分献血では全血献血に比べて，献血に

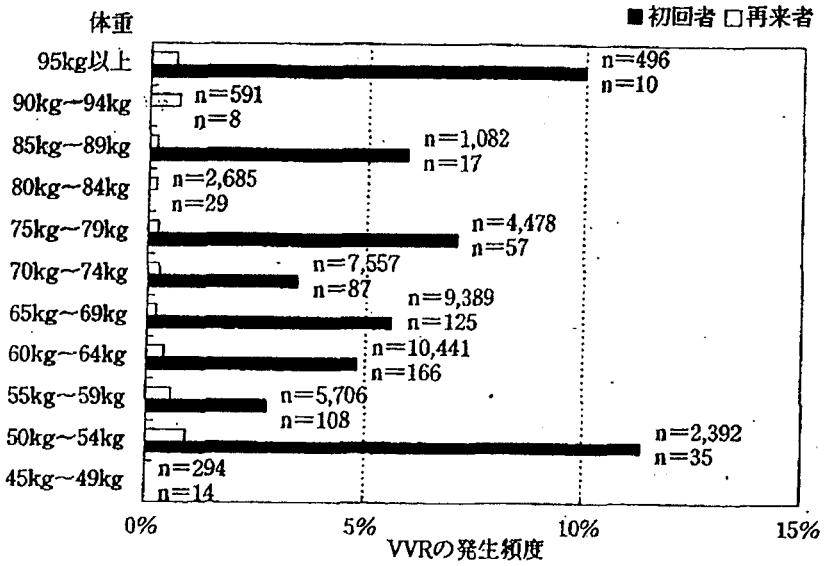

図10　男性の成分献血におけるVVR発生率の献血回数と体重との関係
n＝献血者数

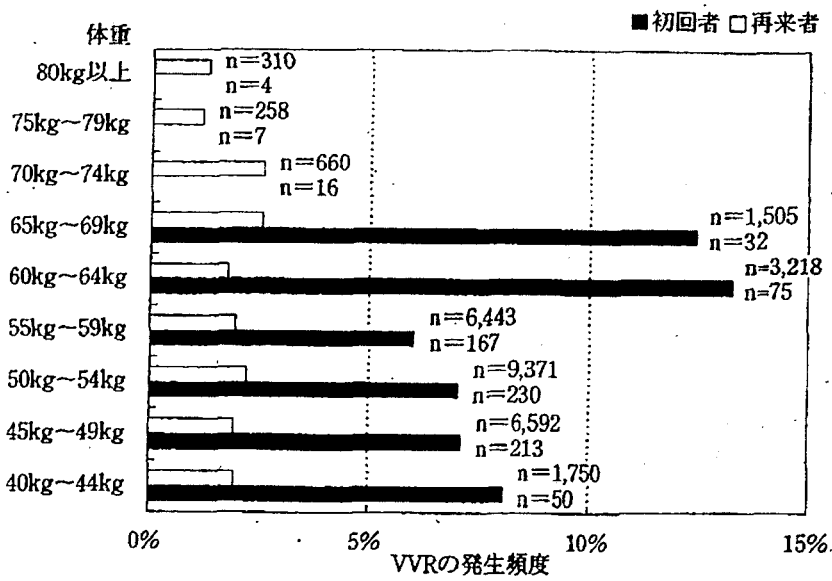

図11　女性の成分献血におけるVVR発生率の献血回数と体重との関係
n＝献血者数

要する時間が長いので，循環血液のバランスを回復するのに有利であり，成分採血装置の進歩により体外循環血液量も減少しているので，成分献血におけるVVR発生率は0.5%未満で低いと述べている[10,17]。

われわれの検討では，成分献血において血小板献血および血漿献血で女性の方が男性よりVVR発生率が有意に高かった。この点はTomitaらあるいは大坂らの報告と一致する（図1）[10,11]。つまり，女性であることが成分献血におけるリスク要因と考えられる。しかし，われわれの検討では女性の成分献血におけるVVR発生率は2.2%であり，Tomitaらの報告や大坂らの報告より低かった。Tomitaらは女性では中高年層でVVR発生率が高いと報告しているが，われわれの検討では再来の成分献血者では逆に若年層で高い傾向がみられた。また，Tomitaらは循環血液量が少ない女性でVVR発生率が高いと報告しているが，われわれの検討では再来献血者では循環血液量が少ないと考えられる低体重の献血者でとくにVVR発生率が高いことはなかった。Tomitaらの報告とわれわれの結果との差が何によるかが問題である。

今回のわれわれの検討で一番顕著な所見は，男女とも初回のVVR発生率が非常に高いことであった。つまり，初回の成分献血のVVR発生率が，男性で4.7%，女性で7.4%であり，再来の成分献血より有意に高く，さらに初回の400mL献血のそれよりも有意に高かった。Tomitaらはとくに初回者と再来者を分けたデータを示していないので，彼らの検討例にどの程度の初回献血者が含まれているのか，またそれが結果にどの程度影響しているのかが明らかでない。Tomitaらは45歳以上の女性の成分献血にVVR発生率が高いのは初回献血者が多いためではなく，多くは再来献血者であると述べているが，やはりVVR発生率を初回と再来に分けたデータは示されていない。大坂らの報告においても，初回および再来の成分献血のVVR発生率は示されていない。

McLeodらは米国の17の血液センターにおける成分献血の副作用を集めて報告した[12]。各センターにおける献血者数は171人～2,519人と比較的少なく，総数は19,566人であった。その成分献血の80%を血小板献血が占め，7%が血漿献血，3%が顆粒球献血であった。彼らは副作用を静脈穿刺性(venipuncture)と非静脈穿刺性(nonvenipuncture)に分け，静脈穿刺性の副作用は神経損傷と血腫としている。一方，非静脈穿刺性の副作用にVVRとクエン酸中毒を含んでいる。非静脈穿刺性の副作用発生率は初回献血者が2.92%で，これは再来献血者が0.77%であるのに比べて有意に高いと報告している。また，採血機種によって副作用発生率が異なり，初回献血者ではHaemonetics(Haemonetics社)で5.08%と非常に高く，ついでSpectra(Gambro社)で3.04%，CS3000(Baxter社)では0.84%である。このHaemoneticsによる初回献血者の非静脈穿刺性の副作用発生率はわれわれの初回献血者のVVR発生率と同程度に高い。一方，再来献血者ではこれらの機種ごとのVVR発生率がそれぞれ0.80%，0.85%，0.64%とほぼ同じ値である。われわれの再来の成分献血者におけるVVR発生率が血小板献血で0.9%，血漿献血で1.1%であるが，これはMcLeodらの報告とほぼ一致する。McLeodは採血機器の違いによる初回献血者のVVR発生率の差異は，多数のセンターのデータを集めているので，センターの違いが大きく影響していると述べている。つまり，各センターで成分献血の初回としている献血者が以前に全血献血をしているかどうかを調査していないので，この点が影響している可能性を示唆している。成分採血機器には循環方式と間歇方式があり，現在のSpectraは2針法の循環方式であるが，McLeodらの報告した時のSpectraは単針法で採血するので間歇方式と思われる。Haemoneticsは現在も単針法の間歇方式で，体外循環血液量が305mLであるが，現在のSpectraとCS3000は2針法の循環方式でそれぞれ260mLと250mLとやや少ない。Haemoneticsではこの体外循環血液量が間歇的に体外に出るのに比べて，CS3000では献血者の循環血液量が減少することはない。今回われわれは採血機種とVVR発生率との関係を検討していない。しかし，われわれが用いた採血機器はすべて間歇方式であるので，McLeodらの報告したHaemoneticsと同じく循環血液量の減少が間歇的に起こるため，そのことが初回献血者にVVRが高頻度に起こったことと関係している

可能性がある。なお，Tomitaらの用いた採血機種はいずれもHaemonetics社のMCS-3PあるいはCCSであるので間歇方式であると思われる。今後，成分献血におけるVVR発生率を論ずるときに採血機種の差も調べる必要があると考える。

成分献血におけるVVR発生率と年齢との関係を見ると，いずれの年齢においても男女とも初回献血者のVVR発生率が再来献血者のそれより高く，また初回の全血献血のそれよりも高かった。とくに，60歳以上の女性で初回献血者9人のうち4人(44%)がVVRを起こしており，60歳代で献血が初めての女性に成分献血を適用することについて，至急検討する必要があると考える。Tomitaらは45歳以上の女性の成分献血にVVRが多いと報告しているが，われわれの検討では再来献血に限るとそのような傾向はみられなかった。むしろ，全血献血にみられるように加齢に伴って減少する傾向がみられ，その頻度は全年齢とも5%未満であり，初回の成分献血者のように非常に高いということはなかった。

成分献血におけるVVR発生率と体重の関係を見るとすべての体重において，初回献血者のVVR発生率は再来の成分献血や初回の全血献血のそれより高かった。また，その頻度もほとんどの体重で5%を超えており，初回献血者への成分献血の適用を再検討する必要があると考える。再来の男性では低体重の献血者でVVR発生率が高い傾向があるが，その頻度は全体重において1%以下であり，400mL献血のそれとほぼ同じ値である。現在のわが国の体重と採血量に関する基準では，成分献血者の安全性は十分確保されていると考えられる。Tomitaらの報告では，循環血液量の少ない女性でVVR発生率が4%を超えている。われわれは循環血液量を調べていないが，その算出値の大きな要素となる体重について調査した。その結果，再来の女性ではVVR発生率が低体重で非常に高いということはなかった。初回献血者では，すべての体重でVVR発生率が5%以上と非常に高いので，初回献血者の割合が多くなることの方がVVR発生数に大きな影響があるのではないかと考えられる。

われわれは初回の成分献血でVVR発生率が非常に高いことを認めたが，このことは献血者の安全上問題である。それとともに，一度VVRを起こした献血者はその後に献血をすることが少ないという報告もあり[8),18)]，血液の安定供給という点でも問題であると考える。英国の基準では，過去2年以内に全血献血を行い副作用のなかった人に成分献血を適用している[19)]。わが国でもそのようなことを考慮する必要があるのではないかと考える。また，採血機種によってVVR発生率に差があるかどうかも今後に残された問題である。

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Vasovagal reactions in apheresis donors

Tadao Tomita, Miyuki Takayanagi, Kimie Kiwada, Akemi Mieda, Chiyoko Takahashi, and Tadayoshi Hata

BACKGROUND: The incidence rate of vasovagal reactions (VVRs) in apheresis is known to be higher in women than in men donors. VVRs in women apheresis donors were therefore analyzed to find out possible factors for their high incidence.

STUDY DESIGN AND METHODS: VVR incidence was compared between whole blood (WB) and apheresis donation in relation mainly to age and circulatory blood volume (CBV). In addition, blood pressure and pulse rate were measured during apheresis.

RESULTS: In WB donors, the VVR incidence was 0.83 and 1.25 percent, while in apheresis donors it was 0.99 and 4.17 percent in men and women, respectively. The VVR incidence decreased with age in WB donors, but age dependence was very weak in apheresis donors. In elderly women, the incidence increased with repeating cycle of apheresis. There were three different patterns of pulse fluctuation during apheresis, that is, stable (type A), increased rate during blood withdrawal (type B), and irregular pattern (type C). Elderly women donors and donors who suffered from VVRs mostly showed type B fluctuation. There was no particular fluctuation in blood pressure in relation to apheresis cycles.

CONCLUSION: The VVR incidence rate was particularly high in women apheresis donors over 45 years old and increased with repeating cycles of apheresis. Smaller CBV, high sensitivity of low-pressure baroreceptors, and citrate effects on cardiovascular reflex might be major factors involved in the high incidence of VVRs.

ABBREVIATIONS: CBV = circulatory blood volume; VVR(s) = vasovagal reaction(s); WB = whole blood.

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Blood donors occasionally have adverse reactions such as weakness, pallor, nausea, sweating, and fainting during or after blood withdrawal.[1,2] These symptoms are generally called vasovagal reactions (VVRs). The rate of incidence of VVRs has been analyzed mainly on the whole blood (WB) donors and reported to be higher in younger donors and at the first time of donation.[2-4] The contribution of other factors such as body weight and blood pressure is less clear. It has been reported for Japanese donors that there is no clear sex difference of VVR incidence in WB donors (1.70% in men, 1.85% in women), but that the rate of VVRs in apheresis is significantly higher in women (4.04%) than men donors (1.24%).[4] Failure of proper circulatory compensation by the autonomic nervous system may be an important factor responsible for the VVRs, but the mechanisms underlying these reactions are still mostly unclear. In the present study, therefore, the VVR incidence was demographically analyzed mainly on the apheresis donors in our blood center. In addition to this, blood pressure and pulse rate were measured to determine if characteristic alterations occurred during apheresis.

MATERIALS AND METHODS

The data accumulated from the voluntary blood donors were analyzed for the incidence of VVRs in the population of WB donors (a total of 20,025 men and 8,164 women during a 1-year period in 2000; including 200 and 400 mL phlebotomy) and in apheresis donors (14,523 men and 6,722 women; combined plasma [68.1%] and platelet collection [21.9%]), during the 3-year period 1999 to 2001. The equipment used for apheresis was either a multicomponent system (MCS 3P) or a component collecting system (Haemonetics, Tokyo, Japan). There was little functional difference between these machines. VVRs were judged from donor's symptoms described in the introduction by experienced nurses. VVRs were mostly relatively minor and syncopal episodes only occurred in a few percent of VVR donors. The VVR incidence rate was calculated for each age or for the circulatory blood volume (CBV) at a 100-mL step and averaged at each range indicated in the figures. Numerical values are expressed

as means ± SD. The data approximated most closely to normal distributions when examined with the Kolmogorov-Simirnov test. Significance of the difference was tested by with two-tailed, unpaired t-tests and the level of significance was set at $p < 0.05$.

The CBV (in mL) was estimated by following equations proposed by Ogawa et al.[5] for Japanese people:

$$CBV = 168H^3 + 50W + 444 \text{ for men}$$

$$CBV = 250H^3 + 63W - 662 \text{ for women}$$

where H is height (m) and W is weight (kg).

Blood pressure and pulse rate were measured automatically every 1 minute during apheresis in 42 men (19-67 years old) and 72 women (18-69 years old) with a automatic blood pressure monitor (Paramatec, PS-230). The reliability of the pulse rate measurement was confirmed by the simultaneous electrocardiograph measurements in three donors. All procedures were fully explained beforehand and carried out on donors who agreed to participate in the study.

RESULTS

In Fig. 1, the incidence of VVRs that occurred in WB and apheresis donation was compared between men and women donors of different ages. The incidence rate of VVRs associated with WB donation decreased with advancing age both in men and in women. In contrast, there was no such a clear tendency in VVRs in apheresis and the VVR incidence rate in apheresis was much higher in women than men, particularly in elderly donors. The mean incidence of VVRs of WB donors was 0.83 percent in men and 1.25 percent in women, while that of apheresis donors was 0.99 percent in men and 4.17 percent in women. These incidence rates were similar to those previously reported.[4]

The relationship between the VVR incidence and age in apheresis donors differed depending on the apheresis cycle (Fig. 2). In men donors, the incidence of VVRs that occurred during the first and second cycles decreased with age and was similar to the WB donation shown in Fig. 1, but it was independent of age at the third-fourth cycles. In women donors, the incidence also decreased with age at the first cycle, but it was independent of age at the second cycle and increased slightly with advancing age at the third to fourth cycles. There was a clear tendency for VVRs to occur at a later stage of apheresis with advancing age.

VVRs are known to occur more frequently in first-time donors than in repeated donors.[2-4,6] However, in women apheresis donors, there was no significant difference in the number of previous donations between healthy and VVR donors. Nearly all of the women apheresis donors over 45 years old who suffered from VVRs donated repeatedly (mean, 24.8 times) and VVRs were detected in only one first-time donor (1 of 45).

The high rate of VVRs in women donors in apheresis could partly be related to the fact that the CBV is significantly less (approx., 20%) in women than in men donors (Table 1). The mean CBV of the donors who suffered from VVRs was also slightly less (approx., 4%) than that of the control donors and the differences were significant ($p < 0.01$) both for men and for women donors.

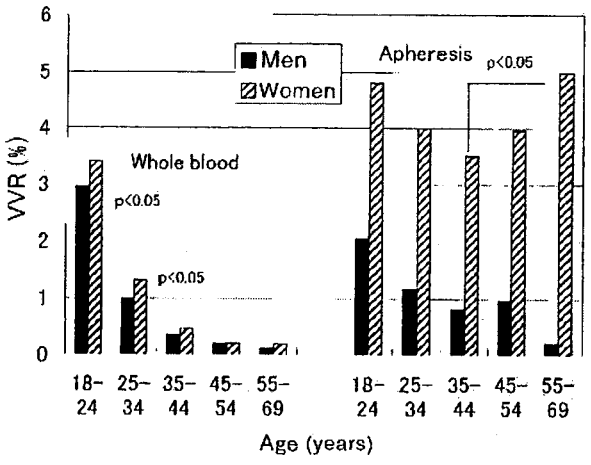

Fig. 1. VVR incidence rate in relation to age in WB and apheresis donors. Note that in men donors the incidence decreased with advancing ages both in WB and in apheresis donation, but that in women donors there was a large difference between WB and apheresis donation. The difference was significant ($p < 0.05$) between the younger three ranges of WB donors and men apheresis donors and also between 35- and 44- and 55- to 69-year-old women apheresis donors.

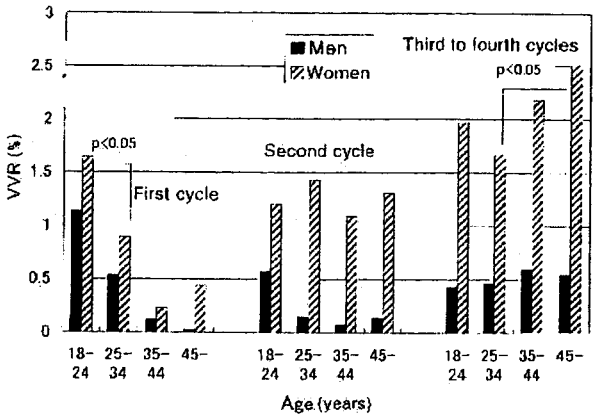

Fig. 2. The relationship between VVR incidence and age at different stages of apheresis. In younger donors, VVRs incidence did not differ much at different cycles of apheresis. In contrast, older donors tended to experience VVRs at a later stage of apheresis. A significant difference was indicated by the p value of less than 0.05. The difference between 18- and 24- and 25- to 34-year-old men donors at the second cycle was also significant ($p < 0.05$).

TABLE 1. CBV (mL) in WB and apheresis donors*

	Control	VVR donors
WB		
Men	4617.5 ± 536.4 (n = 1582)	4417.7 ± 496.8 (n = 168)
Women	3681.3 ± 520.2 (n = 668)	3475.5 ± 447.6 (n = 102)
Apheresis		
Men	4587.8 ± 505.0 (n = 1592)	4431.9 ± 431.5 (n = 144)
Women	3719.1 ± 546.7 (n = 734)	3584.7 ± 425.7 (n = 280)

* The values of control WB and apheresis donors were based on the data for 1- and 4-month periods, respectively. The differences of blood volume between control and VVR donors were statistically significant ($p < 0.01$) for WB and apheresis donors of both sexes.

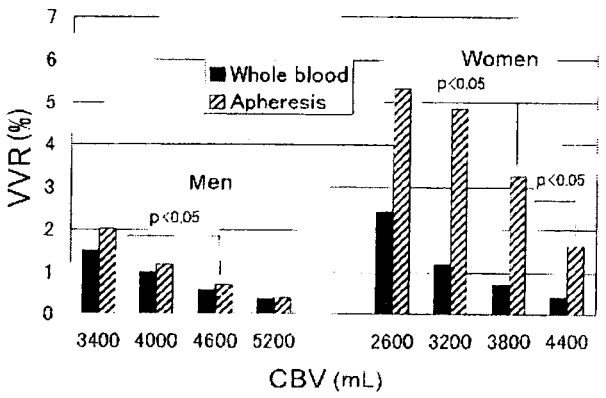

Fig. 3. VVR incidence in relation to CBV in WB and apheresis donation. The CBV was calculated by the equations described in the method. The significance of the difference is indicated by $p < 0.05$.

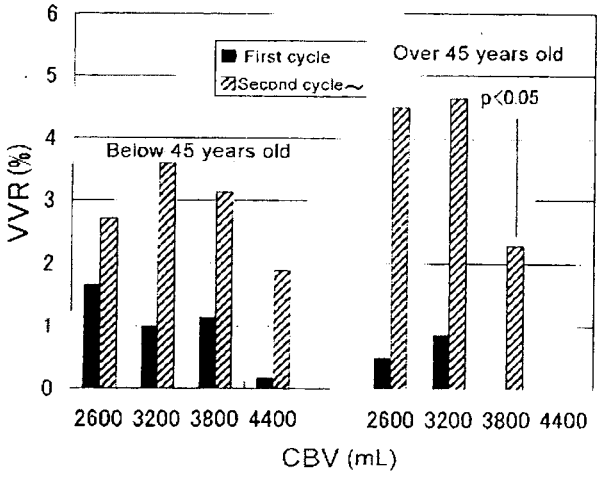

Fig. 4. VVR incidence in relation to CBV before (first cycle) and after the end of first cycle of apheresis (second cycle) in women donors below and over 45 years old. Note the higher incidence with smaller CBV and also after the first cycle of apheresis.

The relationship between the CBV and VVR incidence was compared in WB and apheresis donation (Fig. 3). In men, there was a tendency for the incidence of VVRs to decrease with larger CBV both in WB and in apheresis donors. In women apheresis donors, the CBV dependency was weaker in apheresis compared with WB donors.

CBV dependency of the VVR incidence was greater in older than young women donors. The incidence rate of women donors over 45 years old was 4.8, 2.8, and 0 percent with CBV of 2600 to 3700, 3800 to 4300, and greater than 4400 mL, respectively. In contrast, in the donors below 45 years old, it was 5.1, 3.6, and 1.9 percent, respectively. In men donors, such a clear difference was not detected.

The relationship between CBV and VVR incidence during the first and the second to fourth cycles of apheresis differed between women donors younger and older than 45 years old, as shown in Fig. 4. Below 45 years of age, approximately 25 percent of VVRs occurred at the first cycle relatively independent of the CBV, whereas over 45 years of age, only 10 percent of VVRs were observed at the first cycle. In women over 45 years old, the VVR incidence was much less in the donors having CBVs greater than 3800 mL.

VVR incidence during apheresis in women donors over 45 years old was relatively high (see Fig. 1), particularly at the later stage of apheresis (see Figs. 2 and 4). To investigate the possible mechanisms underlying these factors, blood pressure and pulse rate were measured during apheresis in 72 women (19-36 years old, n = 53; 40-69 years old, n = 19) and 42 men donors (19-27 years old, n = 27; 44-67 years old, n = 15).

Typical examples of blood pressure and pulse rate recorded during apheresis are shown in Figs. 5A and 5B, by averaging values obtained from five donors. Systolic blood pressure gradually decreased by about 15 mmHg in 10 to 15 minutes after starting apheresis and then became more or less steady. Diastolic pressure also decreased with time at the beginning but its degree was less than systolic pressure. Irregular fluctuations were often observed in diastolic pressure. No clear change was observed in relation to blood withdrawal and return both in systolic and in diastolic pressure. A particular pattern of blood pressure could not be used for prediction of VVR occurrence.

In contrast to blood pressure, blood withdrawal affected the pulse rate. Three different patterns of changed pulse rate were found during apheresis. One pattern was a reasonably stable rate throughout apheresis (type A), as shown in Fig. 5A. The second showed an increase in pulse rate during withdrawal and its recovery during return of

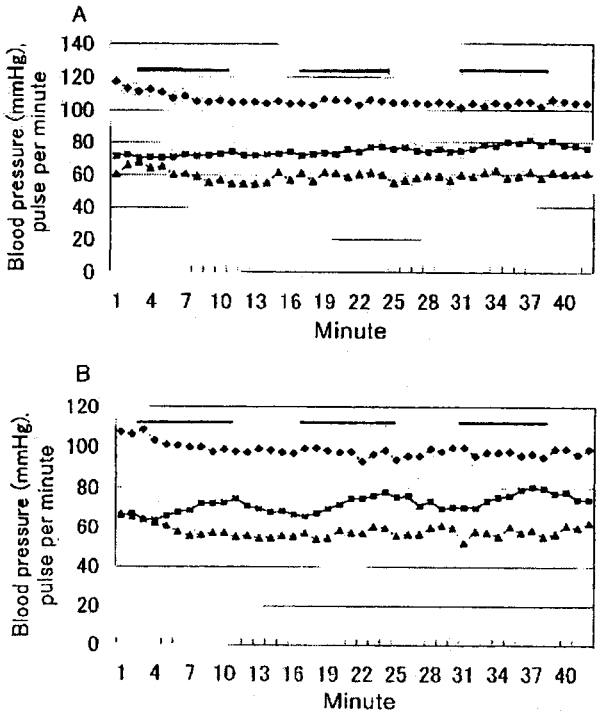

Fig. 5. Blood pressure and pulse rate measured every 1 minute during apheresis, averaging from five women donors whose pulse rate was stable (A) and increased (B) during blood withdrawal. (♦) Systolic and (▲) diastolic blood pressure; (■) pulse rate.

TABLE 2. CBV (mL) in donors showing stable pulse (type A) and fluctuating pulse rate (type B) during apheresis and in VVR donors*

Men	
Type A	4657.3 ± 284.3 (n = 20)
Type B	4347.1 ± 391.7 (n = 19)
VVR	4160.8 ± 458.6 (n = 2)
Women	
Type A	3819.1 ± 387.0 (n = 21)
Type B	3550.9 ± 341.1 (n = 41)
VVR	3535.6 ± 248.6 (n = 6)

* The differences of blood volume between type A and type B donors were statistically significant ($p < 0.05$) for both men and women donors. There was no difference in blood volume between VVR donors and type B donors.

blood (type B), as shown in Fig. 5B. The third was an irregular fluctuation without any clear relationship to blood withdrawal (type C, not shown). Types A, B, and C were shown in 31, 60, and 9 percent of women donors and 49, 46, and 5 percent of men donors, respectively. Women donors over 40 years old mostly (15 of 19) showed the type B fluctuating pattern, and there were only two each of donors showing types A and C, respectively. In contrast, in men donors over 40 years old, 40 percent were type B (6 of 15) and 60 percent were type A.

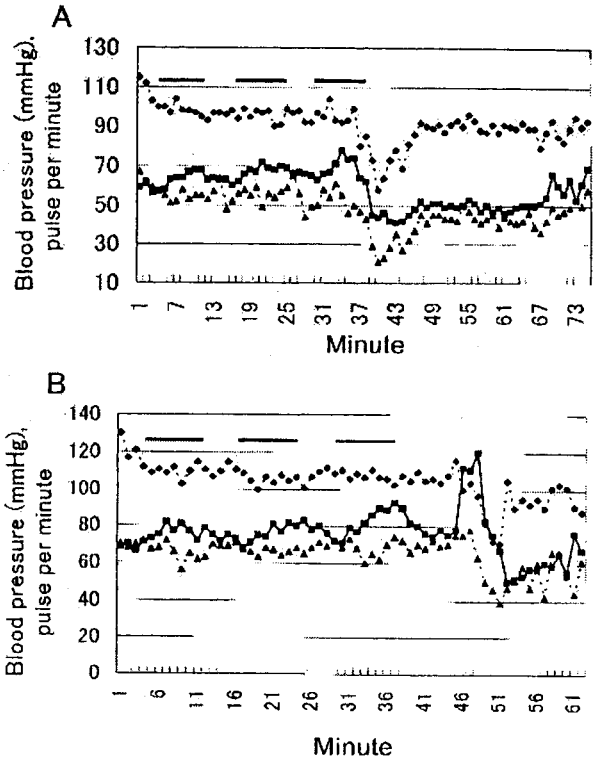

Fig. 6. (A) Blood pressure and pulse rate in a women donor (43 years old) who suffered from VVRs during the third cycle of blood withdrawal. VVRs were accompanied by tachycardia and lowered blood pressure, and then tachycardia was followed by prolonged bradycardia. The donor was laid down flat until recovery. (B) Another example of VVRs (a 20-year-old woman donor). VVRs occurred when she started to leave the bed and were accompanied by bradycardia and hypotension following transient tachycardia. Both donors showed an increase in pulse rate during blood withdrawal (indicated by horizontal bars). (♦) Systolic and (▲) diastolic blood pressure; (■) pulse rate.

The mean CBV of the donors showing pulse rate fluctuations (type B) was less (about 7%) than those showing stable pulse rate (type A) both for men and for women donors (Table 2), and their differences were significant ($p < 0.05$).

The pulse rate data on VVRs were obtained from six women (20-43 years old) and two men donors (23 and 44 years old). They all showed the pulse rate fluctuations of the type B before the appearance of VVRs, as shown in two examples illustrated in Figs. 6A and 6B. The donors shown in Fig. 6 were kept in bed horizontally until they recovered, without medication. Typical VVRs were accompanied by marked bradycardia and periods of hypotension of various durations. The mean CBV of donors

who suffered from VVRs was similar to that of donors showing pulse fluctuations of type B both for men and for women (see Table 2).

DISCUSSION

The incidence of VVRs decreased with advancing age in the population of WB donors, both men and women donors, as previously reported.[2-4,6] A similar relationship was observed in men apheresis donors. However, no such a tendency was found in women apheresis donors. The VVR incidence of women apheresis donors was rather independent of age or even higher over 45 years old (see Fig. 1). This was not due to a high proportion of first-time donors in older women, because most donors over 45 years old were repeated donors.

The CBV was significantly (approx., 20%) less in women and it was also about 4 percent less ($p < 0.05$) in VVR donors than in healthy control donors. The VVR incidence tended to be higher with smaller CBV (see Figs. 3 and 4). It is possible in old donors that the actual CBV is less than that estimated solely from the height and weight determinations[7] and that the peripheral blood pool is small.[8] This may explain the larger effects of blood withdrawal in older donors. If stronger hypovolemia was a major factor in VVR incidence, it seems difficult to explain the difference in VVR incidence between WB and apheresis donors (see Figs. 1 and 3). Some other factors such as autonomic malfunction and hypocalcemia are more likely to be involved in higher VVR incidence in women, particularly older, apheresis donors.

A tachycardia was often observed during blood withdrawal without an associated change in arterial pressure. The ratio of the donors who showed such pulse rate fluctuations (type B) was higher in women than men and this difference was larger over 40 years of age. Furthermore, the VVR donors all showed type B fluctuations. Donors having smaller CBV have a tendency to produce tachycardia during apheresis (see Table 2). The increase in pulse rate usually became more marked with increasing cycles of blood withdrawal. This may have been due to an increased hypovolemia, because the extracorporeal blood volume increases with number of apheresis cycles. Tachycardia, without any significant changes in arterial blood pressure, has also been reported in response to a decreased venous return caused by lower-body negative pressure in humans[9,10] or by hemorrhage of up to 10 mL per kg blood in conscious dogs.[11] These responses are likely to be mediated by cardiopulmonary (low-pressure) baroreceptors, the sensitivity of which to hemorrhage is shown to be higher than those of carotid sinus (high-pressure) baroreceptors in dogs.[12] The mechanism causing the tachycardia during blood withdrawal is likely to be involved in triggering the patterns of VVRs by the circulatory control center.

In the apheresis, it is possible that the sensitivity of baroreceptor-mediated reflex is increased by a decrease in plasma Ca^{2+} concentration that is known to be caused by the supply of citrate during blood return.[12,13] This is probably one of the factors involved in the high VVR incidence in older women apheresis donors, whose VVR incidence is increased by repeating blood withdrawal and return. Not only the effects of blood withdrawal, but also the effects of citrate on the reflex mediated by cardiopulmonary baroreceptors would be stronger in the smaller CBV of old women donors. These factors may explain a high VVR incidence of elderly women donors and at later stage of apheresis.

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Guidance for Industry and FDA Review Staff

Collection of Platelets by Automated Methods

Additional copies of this guidance are available from the Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/cber/guidelines.htm.

For questions on the content of this guidance, contact the Division of Blood Applications, Office of Blood Research and Review at 301-827-3524.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
December 2007

Contains Nonbinding Recommendations

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Guidance for Industry and FDA Review Staff

Collection of Platelets by Automated Methods

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance provides you, blood establishments, and FDA staff with revised recommendations for the collection of Platelets by automated methods (plateletpheresis). This guidance is intended to help you ensure donor safety and the safety, purity, and potency of Platelets collected by an automated blood cell separator device. For the purpose of this document, Platelets collected by automated methods and resuspended in plasma will be referred to by the product name "Platelets, Pheresis." We consider the recommendations in this guidance document to provide appropriate criteria for a biologics license application or supplement for manufacturing Platelets, Pheresis, and provide guidance on preparing a manufacturing supplement for Platelets, Pheresis under Title 21 Code of Federal Regulations 601.12
(21 CFR 601.12).

This guidance applies only to the following Platelets, Pheresis components:

- Platelets, Pheresis (single, double, and triple collections);
- Platelets, Pheresis Leukocytes Reduced (single, double, and triple collections); and
- Platelets, Pheresis or Platelets, Pheresis Leukocytes Reduced collected concurrently with Plasma, Red Blood Cells (RBCs), and/or Source Plasma.[1]

This guidance replaces FDA's "Revised Guideline for the Collection of Platelets, Pheresis" dated October 1988. Also, this guidance finalizes the draft guidance, "Guidance for Industry and FDA Review Staff: Collection of Platelets by Automated Methods" dated September 2005.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited.

[1] This guidance does not apply to plateletpheresis components collected concurrently during apheresis granulocyte collection procedures or plasma reduced apheresis platelets, which are not currently licensed products, or to platelets prepared from plasmapheresis as described in 21 CFR 640.22(b).

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The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

If you have any questions about the effect of any portion of this guidance on a regulatory requirement, contact the Center for Biologics Evaluation and Research (CBER), Office of Blood Research and Review, Division of Blood Applications, at 301-827-3524.

II. DISCUSSION

A. Background

Plateletpheresis is the routine collection of platelets using an automated blood cell separator device, which results in the product Platelets, Pheresis manufactured from a high yield of platelets from a single donor. Transfusion of Platelets, Pheresis is effective for treating patients with platelet related insufficiencies, while limiting the recipient's exposure to platelets from multiple donors. In recent years, many improvements have been made in automated blood cell separator device technology, platelet storage stability, and blood cell counting methods, including:

- collection process efficiency;
- storage container characteristics; and
- accuracy of methods for determining a donor's pre-donation platelet count and component yields.

Automated blood cell separator devices are now capable of various plateletpheresis collection procedures including but not limited to the following:

- collection of double and triple platelet components obtained during a single procedure;
- use of in-process leukocyte reduction (Ref. 1);
- collection of concurrent plasma components (Ref. 2); and
- collection of concurrent RBC components (Ref. 3).

This document includes the following recommendations:

- Published research indicates that there is poor recovery of viable platelets stored at a pH of less than 6.2 (Refs. 4 and 5). Therefore, your process validation and quality control (QC) testing for Platelets, Pheresis should assure a pH at or above 6.2, to rule out a pH less than 6.2 on the date the product is issued or on the date the product expires (outdates). Note that we recommend that you adopt a stricter pH standard than that currently specified in 21 CFR 640.25(b)(2).
- You should include additional deferral criteria for donors of Platelets, Pheresis who have taken certain medications (see section III.A.) (Refs. 6, 7, and 8).

- To protect the safety of the donor, seven days should elapse after collection of a double or triple Platelets, Pheresis before the donor is eligible to donate Platelets, Pheresis again. In addition, first-time donors without a pre-donation platelet count should not undergo collection of a triple Platelets, Pheresis.
- Because of similarities between plateletpheresis and Source Plasma donation, you should follow the donor weight provisions for Source Plasma donors under 21 CFR 640.63(c)(6) (see Section III.A.).
- QC testing, as prescribed in 21 CFR 640.25(b)(1) through (3) requires that, each month, four units prepared from different donors be tested at the end of the storage period for platelet count, pH of not less than 6.0 when measured at the storage temperature of the unit, and volume. In addition, 21 CFR 211.160(b) requires that laboratory controls include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity.

We also note that bacterial contamination of blood components and associated transfusion risks is a continuing problem (Refs. 9 and 10). Bacterial contamination testing is a necessary part of process validation and quality assurance monitoring for Platelets, Pheresis.

B. Definitions

For purposes of the terms used in this guidance, the following definitions apply:

Actual platelet yield – The total platelet yield in the component, calculated by multiplying the platelet count of the sample times the volume of the component (platelet count x component volume = actual platelet yield).

Apheresis – Automated blood collection in which a device continuously or intermittently removes a small volume of whole blood, separates the components, collects certain components, and returns to the donor the uncollected remainder.

Automated blood cell separator – A device that uses a centrifugal or filtration separation principle to automatically withdraw whole blood from a donor, separate the whole blood into blood components, and return to the donor the remainder of the whole blood and blood components. The automated blood cell separator device is intended for routine collection of blood and blood components for transfusion or further manufacturing use.

Bacterial contamination testing – Testing conducted to determine whether a product contains viable contaminating bacteria.

Component – A part of a single donor's blood, such as platelets, separated from whole blood by physical or mechanical means. For Platelets, Pheresis, a component is a

transfusable product that may result from a single collection (resulting in one component), a double collection (resulting in two Platelets, Pheresis components), or a triple collection (resulting in three Platelets, Pheresis components).

Concurrent component – When a blood component, such as Platelets, is being collected during an apheresis procedure, a concurrent component is a different blood component (i.e., Plasma, RBCs) collected at the same time.

Dedicated donation – Platelets, Pheresis donated for a specific recipient.

Devices cleared or approved – Describes a device that has been cleared or approved by FDA pursuant to a 510(k) Premarket Notification (cleared device) or Premarket Approval Application (approved device). (See Title 21, United States Code, section 360c; Federal Food, Drug, and Cosmetic Act (FDCA), section 515 – Premarket Approval; and, FDCA, section 510(k)).

Donation frequency – Interval between a donor's collection procedures.

Process validation – Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics.

Qualification – A part of process validation that establishes confidence that a manufacturing device is capable of operating consistently (equipment installation qualification) and can be performed effectively and reproducibly (process performance qualification), and that the finished product meets all of the release requirements for functionality and safety (product performance qualification).

Residual White Blood Cell (WBC) count – The number of WBCs remaining in a Leukocytes Reduced component, calculated by multiplying the WBC count from a sample of the component times the volume of the component. In this document:

- references to residual WBC count testing apply when the Platelets, Pheresis will be labeled as Leukocytes Reduced.
- references to percent platelet retention apply to leukocyte reduction by filtration, provided there is access to a pre-filtration sample.

Rolling 12-month period – Continual assessment of a donor over a 12-month period. This is not a set 12-month period (i.e., calendar year).

Target platelet yield – The intended platelet yield programmed into an automated blood cell separator device, which may be based on the donor's platelet count and other factors.

Tolerance values – Minimum and maximum values (i.e., container volume; platelet concentration) described by the manufacturer as being acceptable. These values may also be described as specifications.

Weight/volume conversion – The total weight of the component minus the tare weight of the empty container divided by the specific gravity of the component equals volume of the component.

III. DONOR SELECTION AND MANAGEMENT

A. Donor Selection

Under 21 CFR 640.21(c), plateletpheresis donors must meet donor suitability criteria described in the biologics license application or supplement. These typically conform to donor suitability requirements (21 CFR 640.3) and recommendations applicable to donors of Whole Blood. In addition, we recommend:

- donor weight of at least 110 pounds (currently required for Source Plasma donors under 21 CFR 640.63(c)(6))
- Prior to the first donation, collect a sample for a platelet count.
- If you cannot test a sample for a platelet count prior to the first donation (for example, because the donor presents at a mobile collection site), you should collect a pre-donation sample and evaluate the donor's platelet count after the first collection.

You should not collect Platelets, Pheresis from donors who have ingested platelet inhibitory drugs recently enough to adversely affect platelet function in the product, or the safety of the donor. These recommendations include, but may not be limited to:

- Aspirin (ASA)/ASA-containing drugs/Feldene – two full medication free days prior to donation (Refs. 6 and 7)
- Plavix (Clopidogrel) and Ticlid (Ticlopidine) – 14 full medication free days prior to donation (Ref. 8).

When the drugs listed in this section are taken for a specific medical condition, donors should not discontinue taking drugs prescribed or recommended by their physicians in order to be eligible[2] to donate Platelets, Pheresis. However, we do not necessarily recommend deferral of such donors for all blood products, if the donors are in good health, and establishments may make eligibility determinations for donations of other products.

[2] We are using the terms "eligible" and "eligibility" in this guidance to refer to the donor suitability requirements described in 21 CFR 640.3 and 640.21(c).

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B. Donor Management

1. Platelet Count

- You should collect a pre-donation sample from the donor for a platelet count. The device operator should enter that platelet count, or the one obtained immediately following initiation of the collection procedure, to more accurately set the target platelet yield parameters for each collection of Platelets, Pheresis. These steps should be consistent with the automated blood cell separator device manufacturer's directions for use.

- For any collection facility that cannot test a pre-donation sample for a platelet count (for example, a mobile collection site), you may use an average of previous historic platelet counts (as specified by the device manufacturer), or a default platelet count (either as recommended by the automated blood cell separator device manufacturer, or determined by using blood center specific values), to set the target platelet yield. You should not collect a triple Platelets, Pheresis from first-time donors who do not have a pre-donation platelet count available either prior to or immediately following initiation of the collection procedure. Concurrent components may be drawn if the donor meets eligibility requirements for those components.

- You should defer from donation donors whose platelet counts are less than 150,000 platelets/uL until a subsequent pre-donation platelet count indicates that the donor's platelet count is at least 150,000 platelets/uL.

2. Donation Frequency

To protect the safety of the donor:

- a donor should undergo no more than 24 Platelet, Pheresis collections in a rolling 12-month period.
- the interval between each collection of Platelets, Pheresis should be at least two days with no more than two procedures in a seven-day period.
- the interval between collection of a double or triple Platelets, Pheresis and any subsequent collection of Platelets, Pheresis should be at least seven days.
- the automated blood cell separator device should be set with a post-donation platelet count target of no less than 100,000 platelets/uL.

3. RBC Loss Prior to a Collection of Platelets, Pheresis

To protect the donor from significant RBC loss, we recommend that:

- you not allow a donor who has donated a unit of Whole Blood, a single unit of Red Blood Cells by apheresis, or a single unit of Red Blood Cells by apheresis concurrent with Platelets, Pheresis or Plasma in the previous 8

weeks to donate Platelets, Pheresis, unless the extracorporeal red blood cell volume during the Platelets, Pheresis collection is expected to be less than 100 mL (Ref 3).

- you not perform any collection procedure on a donor who has donated two units of Red Blood Cells by apheresis within the previous 16 weeks (Ref. 3).

4. Total Plasma Volume Loss Per Collection Procedure

The total plasma volume (excluding anticoagulant) of all blood components retained per collection of Platelets, Pheresis should not exceed:

- 500 mL (600 mL for donors weighing 175 lbs or greater), or
- the volume described in the labeling for the automated blood cell separator device (this volume may be more or less than the 500 mL or 600 mL volume stated in the above bullet).

IV. INFORMATION PROVIDED TO THE DONOR

Under 21 CFR 640.22(c), the collection procedure must be as described in the biologics license application or supplement. As part of the collection procedure, Platelets, Pheresis donors should receive information about the collection procedure and its associated risks. You should provide Platelets, Pheresis donors with the same information that is provided to a Whole Blood donor[3], plus the following information specific to the platelet collection:

- a description of the procedure for collection of Platelets, Pheresis and its associated risks.
- information about potential side effects of the procedure including possible effects as a result of solutions and/or treatment to reduce side effects such as treatment with a calcium replacement. Examples of side effects include anticoagulant effects (tingling and/or nausea), hypovolemia (decreased blood volume), fainting, and any other side effect as described by the automated blood cell separator device manufacturer.
- information indicating that there are limitations to the number and types of components that can be donated per year.

V. COMPONENT COLLECTION

Improvements in collection of Platelets, Pheresis have enabled blood establishments to obtain from a single collection procedure one, two, or three Platelets, Pheresis component(s) (and concurrent collection of Plasma, Source Plasma and/or RBC components).

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[3] Refer to FDA regulations and guidance developed by FDA on this topic and available on the FDA website. http://www.fda.gov/cber/blood/bldpubs.htm

Under 21 CFR 640.22(c), the collection procedure must be as described in the biologics license application or supplement. In addition, the phlebotomy must be performed by a single uninterrupted venipuncture with minimal damage to, and minimal manipulation of, the donor's tissue (21 CFR 640.22(d)). A sterile connecting device may be used as described in the manufacturer's directions for the apheresis collection set. The automated blood cell separator device must perform in the manner for which it was designed (21 CFR 606.60(a)). Accordingly, your collection procedures should be consistent with the Operator's Manual, directions for use, and/or manufacturer's specifications. Specifications identified by the manufacturer may include, but not be limited to, the donor's platelet count, weight, height or hematocrit; the minimum/maximum volume of the storage container; platelet concentration per uL in the storage container, or actual platelet yield. In addition, supplies and reagents must be used in a manner consistent with instructions provided by the manufacturer (21 CFR 606.65(e)).

VI. VALIDATION OF THE COLLECTION PROCESS

The Current Good Manufacturing Practice (CGMP) regulations described in 21 CFR Parts 210 and 211 contain the minimum requirements for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing or holding of a drug to assure that the drug meets the requirements of the FDCA as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess (21 CFR 210.1(a)). These CGMP regulations also apply to Whole Blood and blood components (21 CFR 210.2(a), 211.1(b)) and supplement the CGMP regulations for blood and blood components contained in 21 CFR Part 606. As an element of CGMP, process validation "establishes documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics" (Ref. 11).[4] We recommend that establishing documentation of process validation include, but not be limited to, validation protocol development, installation qualification, process operator performance qualification, and product performance component qualification (Ref. 11).

Each device intended for the routine collection of Platelets, Pheresis must be cleared or approved by FDA for this purpose (see 21 CFR 864.9245). You should conduct validation of the collection process using each type of device used in your establishment prior to implementing routine collections.

In addition, your validation efforts should include the following manufacturing steps:

- cell counting
- pH measurement: we recommend that a pH meter or gas analyzer be routinely used rather than pH (nitrazine) paper.
- component weighing

[4] The requirement for process control is set forth in general terms in 21 CFR 211.100.

- sterile connecting method (Ref. 12)
- storage
- shipping

A. Equipment Installation Qualification

21 CFR 606.60(a) requires that equipment be observed, standardized and calibrated on a regularly scheduled basis as prescribed in the Standard Operating Procedures Manual and must perform in the manner for which it was designed. Upon initial installation, the automated blood cell separator device should be qualified as described in the Operator's Manual or manufacturer's directions for use.

B. Validation Protocol

An integral element of the performance and documentation of process validation is the development of a validation protocol. You should refer to FDA's "Guideline on General Principles of Process Validation" (Ref. 11) as an outline for developing your validation protocol. The validation protocol should include at least the following:

- a description of the equipment to be used
- minimum/maximum acceptable values for the Platelets, Pheresis collection and/or component as specified by the automated blood cell separator device manufacturer
  - total volume (after removal of samples for hematological testing and bacterial contamination testing), including per component (container) from double and triple collections
  - actual platelet yield
  - residual WBC count (if Leukocytes Reduced) for the collection and components (if multiple components are collected), and percent platelet retention when applicable
  - concurrent component volume (Plasma or RBC), if applicable
  - pH measurement
- manufacturer's specifications or recommendations for processing parameters (i.e., actual platelet yield and concentration, weight or volume collected)
- description of supplies used in the collection (e.g., collection/storage containers, anticoagulants, etc.)
- failure investigation criteria
- personnel training criteria
- standard operating procedures for performing each element of the collection process
- documentation of the validation protocol criteria (all of the above)

C. Process Performance Qualification (Operator)

Each person engaged in the collection of Platelets, Pheresis must have adequate education, training, or experience to assure competent use of the automated blood cell separator devices involved (21 CFR 211.25(a)). Establishments must maintain applicable proficiency test results (21 CFR 606.160(b)(5)(v)).

We recommend that personnel training include the successful, consecutive, performance under supervision of an appropriate number of procedures, as defined by your facility. These procedures should result in the collection of Platelets, Pheresis meeting relevant component specifications.

D. Product Performance Qualification for Component Collection Process

Various mechanical and biological factors may influence the plateletpheresis collection process (i.e., the optical qualities of a donor's plasma, the donor's platelet count and platelet size, vascular access, and procedure duration) (Ref. 14). The objective of collection performance qualification is to verify that the automated blood cell separator device performs according to the manufacturer's claims when used, and through appropriate testing establishes confidence that the finished product produced by the specified process meets all release requirements for functionality and safety (Ref. 11). All components collected during the validation process can be released for transfusion provided that they meet minimum specifications as defined by the manufacturer, are labeled appropriately, and are otherwise suitable.

Process performance qualification should include testing for the actual platelet yield, pH, and volume; residual WBC count and percent platelet retention (for Leukocytes Reduced components) (See Table 1). We recommend that you assess the following at each collection site:

- **actual platelet yield** (platelet count multiplied by the volume):
  - determine actual platelet yield at collection.
  - follow the platelet pre-donation count recommendations in section III.B.1., and set an appropriate target platelet yield as recommended by the automated blood cell separator device manufacturer to maximize the likelihood that each transfusable component contains $\geq 3.0 \times 10^{11}$ platelets and the target collection type (single, double, triple) is achieved.
- **pH** as a measurement of quality after storage:
  - determine pH on the date the product is issued or on the date the product expires (outdates).
  - each transfusable component should have a pH ≥ 6.2
- **percent platelet retention**
  - perform when the automated blood cell separator device or filtration method is first put into use at an establishment and/or as recommended by the automated blood cell separator device manufacturer.
  - if leukocytes are reduced by filtration and there is access to both a pre-filtration and post-filtration sample, calculate percent platelet retention using pre- and post-filtration volume and cell content.
- **residual WBC count**:
  - perform when the automated blood cell separator device or filtration method is first put into use at an establishment and/or as recommended by the automated blood cell separator device manufacturer.

- perform within 48 hours of collection or per the manufacturer's directions for the cell counting methodology used (Ref. 15).
- conduct testing on the collection (parent container) and on the individual components from double and triple collections

- **volume**:
  - determine the volume after removal of samples for testing (i.e., cell count, bacterial contamination testing).
  - fill each storage container consistent with the manufacturer's minimum/maximum specifications.
  - equilibrate storage containers for double or triple collections $\pm$ 10 mL, or per the manufacturer's directions if different.

You also should qualify devices and perform failure investigations as follows:

- **Devices**:
  - complete product performance qualification for apheresis devices from different manufacturers, and for each model.
  - obtain data from all automated blood cell separator devices at each site for initial product performance qualification. If additional devices of the same model are added at the facility after qualification, include qualification data in monthly QC only.
- **Failure investigation**: Conduct an investigation for all component qualification failures, and when appropriate, initiate corrective action and follow-up measures (see 21 CFR 211.192; 606.100(c)). We understand that some failures may occur due to conditions **not** resulting from a failure of the process (e.g., automated blood cell separator device failures, donor reactions). In addition, you should:
  - investigate as qualification failures residual WBC counts that exceed the following:
    - single collection: $\geq 5.0 \times 10^6$ (collection)
    - double collection: $\geq 8.0 \times 10^6$ (collection), **and** $\geq 5.0 \times 10^6$ (either or both components)
    - triple collection: $\geq 1.2 \times 10^7$ (collection), **and** $\geq 5.0 \times 10^6$ (one, two or all three components).

  - However, each transfusable component from a double or triple collection of Platelets, Pheresis may be labeled as Leukocytes Reduced provided the residual WBC count on the component is found to be $< 5.0 \times 10^6$. investigate collections that fail to meet the percent platelet retention, if performed. However, the component may be transfused if the actual platelet yield is determined subsequent to filtration, and the component is labeled appropriately.

Variation in the actual platelet count might be due to the platelet counter used and the type of platelet count used at the time of collection (pre-donation or historic average). However, you should select a statistically sound sample size, based on 95% confidence that 75% of components (platelet yield) will meet the recommended results (see Table 1). For pH and recommended residual WBC count, you should select a statistically

sound sample size, based on 95% confidence that 95% of components (pH) or collections (residual WBC count) will meet the recommended results. Using the binomial statistic for example, a minimum of 60 components/collections should be tested, with zero process failures (93 tested with one process failure, 124 tested with two process failures, etc.) to qualify the process. Determine the sample size selection before starting the qualification process. For example, if you test 60 samples and encounter a failure, you should not continue with the testing of an additional 33 components. If you select a sample size of 93 and encounter a failure during testing, you may continue to test but there should be no additional failures. Similarly, if you select a sample size of 124 and encounter two failures, you may continue to test, but there should be no additional failures.

Table 1. Product Performance Qualification Criteria for the Platelet Component Collection Process

Test	Recommended Results	Target[1]	Allowable Process Failures[2] to achieve recommended results for a set of N tests[3]		
Actual platelet yield of transfusable component	$\geq 3.0 \times 10^{11}$	95%/75% *	N=11 **	N=18 **	N=23 **
			0	1	2
pH	≥ 6.2	95% / 95% ***	N=60	N=93	N=124
			0	1	2
Percent component retention	≥ 85% component retention if performed ****	95%/95%	N=60	N=93	N=124
			0	1	2
Residual WBC count *****	Single collection: $< 5.0 \times 10^6$	95% / 95%	N= 60 collections	N=93 collections	N=124 collections
			0	1	2
	Double collection: Collection: $< 8.0 \times 10^6$ or Components: $< 5.0 \times 10^6$	95%/95%	N=60 collections	N=93 collections	N=124 collections
			0	1	2
	Triple collection: Collection: $< 1.2 \times 10^7$ or Components: $< 5.0 \times 10^6$	95%/95%	N=60 collections	N=93 collections	N=124 collections
			0	1	2

[1, 2] Process failures only; non-process failures should be excluded.

[3] Corrective actions for exceeding allowable process failures

- if you select a sample size of 11 and find one failure, 17 additional samples would need to be tested with no additional failures.
- if you select a sample size of 60 and find one failure, 91 additional samples would need to be tested with no additional failures. If you select a sample size of 93 and find two failures, 157 additional samples should be tested with no failures. If you select a sample size of 124 and find three failures, 127 additional samples should be tested with no failures.

* 95% confidence that greater than 75% of the components meet the standard.

** The sample size numbers can be used in a sampling plan that should be representative of products collected on each machine type in each facility.

*** 95% confidence that greater than 95% of the components meet the standard.

**** Or per the container/automated blood cell separator device manufacturer's specifications

***** The stratified recommended results should ensure that the individual transfusable units will be $< 5.0 \times 10^6$ even with a 25% error in equilibration of the volume for double and triple collections.

E. Re-Qualification/Re-Validation

- Exceeding the allowable **process** failures of the collection process qualification may indicate that the process is not in control. You must investigate and correct the source of this failure (see 21 CFR 211.192, 606.100(c)) and should repeat validation.

- The manufacturer may provide re-qualification requirements for the automated blood cell separator device to be followed.

VII. QUALITY ASSURANCE AND MONITORING

Quality assurance (QA) is the sum of activities planned and performed to provide confidence that all systems and system elements that influence the quality of the component are functioning as expected (Ref. 13). When this is demonstrated, the process is considered to be in a state of control. Whether a process is operating in a state of control is determined by analyzing the day-to-day process and the data for conformance with the manufacturer's specifications and for variability.

You must have a quality control (QC) unit that has the responsibility and authority to approve or reject all components, containers, closures, in-process materials, packaging material, labeling and drug products and the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated (21 CFR 211.22(a)). Thus, the QC unit's responsibilities include the review of production records, and the review of complaints involving the possible failure of a product to meet its specifications. (See, for example, 21 CFR 211.22, 211.192, 211.198, 606.100(c)). Please refer to FDA's "Guideline for Quality Assurance in Blood Establishments" (Ref. 13) for developing a QA and Monitoring program.

A. Standard Operating Procedures (SOPs) and Recordkeeping

1. Requirements for SOPs

- An automated blood cell separator device must "perform in the manner for which it was designed" (21 CFR 606.60(a)) during the collection or processing of apheresis components. Written SOPs must be maintained and must include all steps to be followed in the collection, processing, compatibility testing, storage, and distribution of blood and blood components (21 CFR 606.100(b)). Therefore, you must have written SOPs for each step in the collection of Platelets, Pheresis.

2. Additional Provisions Applicable to SOPs

- **Adverse reactions:** You must have a written SOP for investigating adverse donor and recipient reactions (21 CFR 606.100(b)(9)). In addition, you should have a written SOP for managing a cardiopulmonary emergency or

any other adverse reactions associated with donation, containing steps for contacting physicians, obtaining an emergency rescue squad response, and transporting the donor to the hospital.

- **Hematocrit**: If the final platelet collection contains more than 2 mL of packed RBCs, you should attach a sample of donor blood to the platelet storage container for compatibility testing to prevent the possibility of an adverse reaction during transfusion. In addition, you should hold the Platelets, Pheresis collection prior to distributing as Leukocytes Reduced until a residual WBC count of the transfusable component can be determined and found to be $< 5.0 \times 10^6$.

- **Component volume**: You should describe how to process components in the event the volume exceeds the automated blood cell separator device manufacturer's specifications. In addition, the volume in the storage containers from double or triple collections should be within ± 10 mL of each other or per the manufacturer's directions if different.

- **Samples for QC:** Containers for QC samples should be attached to the component/collection set using a sterile connecting device, to ensure the maintenance of the closed system.

- **Actual platelet yield**: The platelet yield from each collection of Platelets, Pheresis should be available to provide to the transfusion facility.

- **pH measurement**: Accurate pH measurement is time dependent, and samples should be tested within 1 hour of sampling, or as suggested by the manufacturer of the pH measurement system. We recommend that a pH meter or gas analyzer be routinely used rather than pH (nitrazine) paper. However, if you choose to determine pH measurements with nitrazine paper, the selected paper should read in increments of one-tenth units, or it may provide inaccurate measurements.

- **RBC loss**: You must have a written SOP for your collection procedure, including in-process precautions to measure accurately the quantity of blood removed from the donor (21 CFR 606.100(b)(5)). You should calculate the donor's RBC loss, which may include the residual RBCs remaining in the apheresis collection set after a collection of or discontinued collection of Platelets, Pheresis; the extracorporeal RBCs remaining in event of no RBC rinseback; the RBC loss from collection of tubes for testing; and/or collection of a concurrent RBC. You should record such RBC loss in the donor's record, in a manner that allows tracking of cumulative RBC loss over time.

- **Bacterial contamination testing**: You must maintain written SOPs and include all steps to be followed in the testing of blood and blood components (21 CFR 606.100(b)). Bacterial contamination testing should be performed using a culture based methodology, and using your established procedures.

- **QC failures**: You must thoroughly investigate any unexplained discrepancy or the failure of a batch to meet any of its specifications (21 CFR 211.192). You should define appropriate criteria for retesting of components, testing of additional components, final labeling, and disposition of components that fail to meet specifications.

- **Failure investigations**: (see 21 CFR 211.192; 606.100(c)) The criteria to assess in the performance of a thorough failure investigation (including the conclusions and followup) should include, but not be limited to: donor characteristics or specifications; operation and or performance of the collection device; adherence to SOPs; lot numbers of reagents or supplies; sample collection, handling, storage or shipping; operator performance, training or competency; and cell counting instrument performance including shifts or trends in controls.

- **Manufacturer's performance specifications**: You should state the acceptable tolerance specifications for the volumes, platelet concentration, and/or actual platelet yield for each storage container as described by the manufacturer. You should have a procedure addressing the handling of components that do not meet the manufacturer's performance specifications (e.g., use in research or further manufacture).

- **Labeling**:
  - The final component volume stated on the label should be determined after removal of samples for platelet count determination, QC, and/or bacterial contamination testing.
  - Platelets, Pheresis for transfusion should routinely contain $\geq 3.0 \times 10^{11}$ platelets. When special circumstances warrant their use, Platelets, Pheresis components containing less than 3.0×10^{11} platelets should be labeled with the actual platelet content.

- **Component Storage**:
  - If Platelets, Pheresis are stored at 20 to 24 °C, you must maintain a continuous gentle agitation throughout the storage period (21 CFR 640.25(a)). You should describe how temperature and agitation will be monitored, and the disposition of platelet components that are not stored properly.
  - You must follow the automated blood cell separator device manufacturer's directions for use (21 CFR 606.60(a)). If sterile connecting an additional container(s) is necessary, use a container(s)

designed to achieve and protect a sterile conduit. Because of differences in container specifications, you should use containers from the same manufacturer.

3. Recordkeeping

All recordkeeping requirements of 21 CFR Part 606, Current Good Manufacturing Practice for Blood and Blood Components, Subpart I (Records and Reports); Part 211, Current Good Manufacturing Practice for Finished Pharmaceuticals, Subpart J (Records and Reports); and applicable provisions of 21 CFR 640.20 through 640.27, must be met.

B. Donor Monitoring

1. Platelet Counts

If the platelet count is known, you should notify your Medical Director when a donor has a post collection platelet count less than 100,000/uL, and you should defer the donor until his/her platelet count has returned to at least 150,000/uL.

Transient decreases in platelet counts have been reported in donors undergoing multiple collections of Platelets, Pheresis (Ref. 16). You should periodically review a donor's records to monitor platelet counts.

2. Adverse Reactions in Donors

Records must be maintained of any reports of complaints of adverse reactions regarding each unit of blood or blood product arising as a result of blood collection or transfusion and a thorough investigation of each reported adverse reaction must be made (21 CFR 606.170(a)).

3. Red Blood Cell Loss

- **Per collection**:
  - If the collection procedure needs to be discontinued for any reason before completion, and if the Operator's Manual allows, you should attempt to return RBCs to the donor.
  - Donor eligibility based on RBC loss (with or without RBC rinseback, and including all other types of donation) is described in Table 2.

Table 2: Recommendations for donor eligibility based on RBC loss per collection

Donor's Initial packed RBC loss	**Donor's Second packed RBC loss within 8 weeks**	**Eligibility**
Less than 200 mL	No donation or total from initial and second loss less than 200 mL	No deferral of donor for packed RBC loss; frequency of donation of Platelets, Pheresis as discussed in section III.B.2
Less than 200 mL	More than 200 mL but less than 300 mL total	Donor is not eligible to donate for 8 weeks from 2nd loss
More than 200 mL but less than 300 mL	NA	Donor is not eligible to donate for 8 weeks from initial loss
Less than 200 mL	Total loss from initial and second loss of more than 300 mL	Donor is not eligible to donate for 16 weeks from the 2nd loss
300 mL or more	NA	Donor is not eligible to donate for 16 weeks from initial loss.

- **Per 12 months:**
  Under 21 CFR 640.3(b), a person may not serve as a source of Whole Blood more than once in 8 weeks. In any such assessment, and in assessing a donor's RBC loss during the past rolling 12-month period, the RBC loss associated with the collection of Platelets, Pheresis, and including any other donation type (i.e., Whole Blood, RBC by apheresis), should also be considered.
- **Total plasma volume loss per 12 months:**
  The maximum volume (excluding anticoagulant) collected from a donor during a rolling 12-month period, and including any other donation type (i.e. Whole Blood, plasmapheresis) should not exceed:
  - 12 liters (12,000 mL) for donors weighing 110 – 175 lbs
  - 14.4 liters (14,400 mL) for donors weighing more than 175 lbs

  (Ref. 2).

C. Component Testing

1. Component Specification Check

- Actual platelet yield (volume x platelet count) must be determined after each collection (21 CFR 211.103).
- Weight/volume conversion is necessary to determine the volume of each collection. To convert weight to volume, divide the weight of the collection (the total weight minus the weight of the bag) by the specific gravity (1.03).

- Bacterial contamination testing: You should perform bacterial testing as specified by the storage container manufacturer (i.e., 7-day storage of Platelets, Pheresis, Leukocytes Reduced).

2. QC Monitoring

Under 21 CFR 211.160(b), laboratory controls must include the establishment of scientifically sound and appropriate specifications, standards, sampling plans and test procedures to assure that components and products conform to appropriate standards. One example of a scientifically sound statistical sampling and analytic plan is based on a binomial approach (see Table 1: Product Performance Qualification Criteria for the Platelet Component Collection Process). The sampling sizes described in Table 1 will confirm with 95% confidence a < 5% non-conformance rate for pH and residual WBC count, and < 25% non-conformance rate for actual platelet yield.

However, other statistical plans may also be appropriate, such as the use of scan statistics.

As part of your QC protocol you should:

- define a plan for non-selectively identifying collections to be tested. This should ensure testing of components collected on each individual automated blood cell separator device, each collection type, and each location.
- define sampling schemes for actual platelet yield (including volume determination) and pH, and residual WBC. We recognize that these sampling schemes may be mutually exclusive. However, the platelet yield of the collection (and designation of single, double or triple) should be made prior to performing the residual WBC count QC.
- test actual platelet yield (platelet count times the volume) and pH at the maximum allowable storage time for the container system used (or representing the dating period). Title 21 CFR 640.25(b) specifies that QC testing, including platelet count and measurement of actual plasma volume, be performed at the end of the storage period. We believe that such testing may be conducted "at issue" or within 12 hours after expiration. In addition, actual platelet yield and pH testing may be conducted on one storage container of a double or triple collection.
- include the residual WBC count (Ref. 1) for Leukocytes Reduced collections, if manufacturing leukocytes reduced products.
    - Perform the residual WBC count on the collection. For the purpose of labeling as Leukocytes Reduced (see 21 CFR 606.121(c)(1)), you may also perform a residual WBC count on the transfusable units for double and triple collections that fail the collection acceptance criteria listed (see below in this section).

  - Test for the residual WBC count within 48 hours after collection (Ref. 15), or per the manufacturer's directions for the cell counting methodology, to reduce aberrant results due to cellular deterioration and clumping.
  - Test for percent platelet retention, if leukocytes reduced by filtration.
- describe the criteria for investigation of failures during QC, including the factors to consider in categorizing a failure as process or non-process.
- have a method to document all calculations and test results.

We recommend that you consider the following QC results to be acceptable:

- pH $\geq$ 6.2. If one component from a double or triple collection is found to have a pH < 6.2, the corresponding component(s) from the collection should be retrieved and/or quarantined until they are tested and found to be acceptable.
- transfusable Platelets, Pheresis components $\geq 3.0 \times 10^{11}$ platelets.
- residual WBC count:
  - Single collection: $< 5.0 \times 10^6$ WBC
  - Double collection: $< 8.0 \times 10^6$ WBC
    Note: If $\geq 8.0 \times 10^6$, **but** each transfusable component is $< 5.0 \times 10^6$, this is not considered a collection failure.
  - Triple collection: $< 1.2 \times 10^7$
    Note: If $\geq 1.2 \times 10^7$, **but** each transfusable component is $< 5.0 \times 10^6$, this is not considered a collection failure.
- percent platelet retention should be $\geq$ 85% or per the manufacturer's specifications. Components with < 85% platelet retention may be distributed, but a failure investigation should be performed.
- negative for bacterial contamination testing, when performed.

D. Equipment/Supplies

Equipment must be observed, standardized, and calibrated on a regularly scheduled basis as prescribed in the Standard Operating Procedures Manual (21 CFR 606.60(a)). Such equipment includes, but may not be limited to, the automated blood cell separator device, cell counting instrument(s), pH meter, scales and sterile connector.

All supplies (including containers) and reagents must meet all of the requirements described in 21 CFR 606.65.

E. Operator Training

Operators must have adequate training, education and experience, or combination thereof, to assure competent performance of their assigned functions (21 CFR 606.20(b)). We recommend that assessment of operators include scheduled

competency assessment and proficiency testing. In addition, we recommend that you develop and document appropriate training on component preparation and/or machine maintenance as updated information becomes available (Ref. 12).

F. Quality Monitoring

You should assess the following:

- total component volume and equal distribution of volume in double and triple component collection containers. This assessment should include checking the performance of the scale; the use of the tare weight of the empty containers/tubing; and the weight/volume conversion.
- component bacterial contamination testing: Rates of bacterial contamination of plateletpheresis should be monitored, and bacterial contamination rates that exceed 1:3000 (Refs. 10 and 12) should be investigated.

VIII. PROCESSING AND TESTING

A. Processing

Platelets, Pheresis must be processed as described in 21 CFR 640, Subpart C – Platelets (21 CFR 640.20-640.27).

B. Communicable Disease Testing

Donations of Platelets, Pheresis must be tested for communicable diseases (21 CFR 610.40, 640.5(a) through (c), 640.23). Platelets, Pheresis may be released or shipped prior to completion of communicable disease testing in accordance with 21 CFR 610.40(g).

You must test donations of human blood and blood components from a donor whose donations are dedicated to and used solely by a single identified recipient except that, if the donor makes multiple donations for a single identified recipient, you may perform such testing only on the first donation in each 30-day period (21 CFR 610.40(c)(1)(i)).

C. Expiration Date

The dating period for Platelets, Pheresis collected using an FDA cleared or approved collection container under a closed or functionally closed system will be specified by the collection container manufacturer.

In accordance with such instructions and our recommendation, Platelets, Pheresis collected in an open system expire 24 hours from the termination of the procedure if the integrity of the hermetic seal is broken during processing.

If the integrity of the hermetic seal is broken after collection, the Platelets, Pheresis expire 4 hours from the time of the integrity violation, or at the original expiration date, whichever is earlier (21 CFR 606.122(l)(2)).

IX. LABELING

An instruction circular must be available for distribution if the product is intended for transfusion (21 CFR 606.122).

Your container labels must comply with 21 CFR 606.121 and 610.60.

In addition:

- The label should include the estimated amount of anticoagulant in the component container.
- Platelets, Pheresis components for transfusion, containing less than 3.0×10^{11} platelets per storage container, should be labeled with the actual platelet content.
- A component from a double or triple Platelets, Pheresis may accurately be labeled as Leukocytes Reduced when the residual WBC count of the collection is $\geq 8.0 \times 10^{6}$ (double) or $\geq 1.2 \times 10^{7}$ (triple) **IF** the transfusable component is tested and found to have a residual WBC count $< 5.0 \times 10^{6}$.
- Platelets, Pheresis may be labeled (i.e., tie-tag) with the residual WBC count if counted and found to contain $< 1.0 \times 10^{6}$.

X. REPORTING CHANGES TO AN APPROVED BIOLOGICS LICENSE APPLICATION (BLA)

Licensed establishments must report changes to their approved application(s) in accordance with 21 CFR 601.12. For assistance in reporting your changes see FDA's "Guidance for Industry: Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture." The information below is intended to assist you in determining which reporting mechanism is appropriate for a change to your approved BLA, as it applies to the manufacture of Platelets, Pheresis. You should prominently label each submission with the reporting category under which you are reporting your change, e.g., "Prior Approval Supplement;" "Supplement - Changes Being Effected in 30 Days;" "Supplement - Changes Being Effected;" or "Annual Report."

A. Prior Approval Supplement (PAS): Changes Requiring Supplement Submission and Approval Prior to Distribution of the Product Made Using the Change (Major Changes) (21 CFR 601.12(b))

Under 21 CFR 601.12(b), changes that have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product must be reported to FDA in a Prior Approval Supplement (PAS).

Under this standard, the following kinds of manufacturing changes would fall within this category, warranting submission of your request to implement the following changes to your approved BLA as a PAS:

- if you currently hold an unsuspended, unrevoked BLA to manufacture blood components other than Platelets, Pheresis, and you intend to manufacture and distribute Platelets, Pheresis under that license.
- if you are currently approved to manufacture Platelets, Pheresis at a specific facility, and you intend to manufacture Platelets, Pheresis at a different facility, not under an approved Comparability Protocol. To submit a request for a Comparability Protocol see below.
- if you are approved to manufacture Platelets, Pheresis, but intend to change your manufacturing process in a manner that presents a substantial potential for an adverse effect on the product. FDA believes that such manufacturing changes include: change in storage conditions; change in anticoagulant; leukocyte reduction; and collection of an additional or different product.
- if you intend to collect Platelets, Pheresis using an automated blood cell separator device new to the market or new to your establishment.
- if you are requesting approval for a Comparability Protocol. The Comparability Protocol described in 21 CFR 601.12(e) is a supplement that describes the specific tests and validation studies and acceptable limits to be achieved to demonstrate the lack of adverse effect for specified types of manufacturing changes on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product. A new Comparability Protocol, or a change to an existing one, requires approval from FDA prior to distribution of the product which, if approved, may justify a reduced reporting category for the particular change because the use of the protocol for that type of change reduces the potential risk of an adverse effect (21 CFR 601.12(e)).

  A Comparability Protocol is appropriate, but not required, if you wish to add multiple collection facilities under your direction and control, using the same process to manufacture Platelets, Pheresis. If you request approval for a Comparability Protocol, you should describe the procedures and processes that each new collection facility will implement to ensure conformance with the Comparability Protocol. You may identify one or more collection facilities for the purpose of validation and submission of the Comparability Protocol and supporting data to CBER for review. Approval of such a Comparability Protocol for future collection facilities justifies a reduced reporting category for the particular change because the use of the protocol for that type of change reduces the potential risk of an adverse effect.

  If you are using an approved Comparability Protocol, you should routinely review the procedures and specifications in the Comparability Protocol to assure that they remain current and consistent with the applicable application and current guidance. If modifications are required, you should contact FDA to discuss the change and to determine the appropriate reporting category.

- We consider the recommendations in this guidance document to provide appropriate criteria for a biologics license application or supplement for Platelets, Pheresis. You may use an alternative approach if such approach satisfies the requirements of the applicable statutes and regulations. Your alternative procedure(s) may be acceptable if you demonstrate that the resulting Platelets, Pheresis components meet applicable standards. We have determined that it may be adequate to determine the actual platelet yield at collection, and that re-determination of the actual platelet yield at issue or outdate is unlikely to provide additional relevant information. If you choose to discontinue determining the platelet count for QC testing as described under 21 CFR 640.25(b)(1), you must submit a request for an alternative procedure under 21 CFR 640.120.

You must not distribute in interstate commerce blood components made using a changed manufacturing process requiring a PAS until you have received our approval of your PAS (21 CFR 601.12(b)(3)).

B. Changes Being Effected in 30 Days (CBE-30) Supplement: Changes Requiring Supplement Submission at Least 30 Days Prior to Distribution of the Product Made Using the Change (21 CFR 601.12(c))

Under 21 CFR 601.12(c), changes that have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product must be reported to FDA in a Changes Being Effected in 30 days (CBE-30) supplement.

You must submit your request to implement manufacturing changes with a moderate potential for an adverse effect to your approved BLA as a CBE-30 supplement under 21 CFR 601.12(c). The manufacturing changes described below are examples of changes that we believe fall within this category:

- certain software and hardware upgrades provided by the manufacturer to your cleared or approved automated blood cell separator device
- addition of concurrent plasma collection
- implementation of a new collection facility under an approved Comparability Protocol

You may distribute your blood components made using the change requested in your CBE-30 supplement in interstate commerce 30 days after we receive your supplement, unless we notify you otherwise (21 CFR 601.12(c)(4)).

C. Submission Inclusion Documents

1. PAS: To comply with the requirements in 21 CFR 601.12(b)(3), the following must be included in the supplement:

- identification of the components involved (e.g., single plateletpheresis component, double plateletpheresis components, and/or triple plateletpheresis components) and manufacturing site(s) or area(s) affected, and a detailed description of the manufacturing change (including device collection technology and the collection protocol(s)) (21 CFR 601.12(b)(3)(i) through (iii)). We recommend that this information be documented in a cover letter and FDA Form 356h. To permit assessment of the manufacturing change we recommend including copies of the following SOPs:
  - collection
  - informed consent
  - labeling including labels
  - donor qualification, deferral and adverse event follow-up
  - a description of training (or an example of training documents)
  - component manufacturing
  - monitoring donor RBC and plasma loss
  - failure investigation
  - quality control including sampling scheme, sample handling, tracking and trending
  - equipment standardization/calibration
  - quarantine and disposition of unsuitable products

Additionally, we recommend that the following SOPs, if already approved for other blood collection activities and unrevised, would not need to be submitted:

- sample preparation
- component storage and shipping
- donor arm preparation

- product labeling for each component, if changed (21 CFR 601.12(f)). We recommend submitting a Form FDA 2567 including Circular (unless already on file at FDA)
- a reference list of relevant SOPs (21 CFR 601.12(b)(3)(vii))
- relevant validation protocols and data (21 CFR 601.12(b)(3)(vi)). We recommend a summary of the validation protocol, including failure investigations.
- a description of the methods used and studies performed to evaluate the effect of the change and the data derived from such studies (21 CFR 601.12(b)(3)(iv) through (v)). We recommend submitting the following information and data:
  - the device manufacturer
  - the device type
  - blood unit number
  - component description (i.e., leukocytes reduced)
  - date of collection
  - date of testing
  - result interpretation(s)
  - the identity of the person performing the testing

- the identity of the collection facility
- evidence of QA oversight, and
- expected component specifications.

- Additionally, we recommend two months of QC data for actual platelet yield and volume, pH, and residual WBC count (if requesting approval for Leukocytes Reduced platelets).

We further recommend that you provide an agreement to summarize bacterial contamination testing results for the first two hundred and fifty (250) Platelets, Pheresis collections in your Annual Report.

2. Comparability Protocol: If you are an establishment with multiple manufacturing sites and wish to submit a comparability protocol to justify a reduced reporting category for a manufacturing change at multiple sites (see Section X.C.4 below), you must submit that protocol as a PAS (21 CFR 601.12(e)). In addition to the information listed in Section X.C.1 above , we recommend that you include the following:

- implementation plan
- proposed reporting category for changes made under proposed Comparability Protocol

3. CBE-30 submissions (excluding new facilities under an approved Comparability Protocol): Under 21 CFR 601.12(c)(3) and 601.12(b)(3)(i) through (vii), the following information must be included in your CBE-30 submission:

- identification of the Platelets, Pheresis components involved (e.g., single plateletpheresis component, double plateletpheresis components, and/or triple plateletpheresis components) and manufacturing site(s) or area(s) affected, and a detailed description of the proposed manufacturing change (including device collection technology and the collection protocol(s)). We recommend that you document this information in a cover letter and FDA Form 356h. To permit assessment of the documented manufacturing change, we recommend that you include copies of any new or revised SOPs.

- relevant validation protocols and data. We recommend that you submit a summary of the validation protocol, including failure investigation.

- the data derived from such studies. We recommend two months of QC data for actual platelet yield and volume, pH, and residual WBC count (if requesting approval for Leukocytes Reduced platelets).

4. CBE-30 submissions for new facilities under an approved Comparability Protocol: To comply with 21 CFR 601.12(c)(3) and 601.12(b)(3)(i) through (vii), the following information must be included:

- identification of the components involved (e.g., single plateletpheresis component, double plateletpheresis components, and/or triple plateletpheresis components) and new manufacturing site(s) or areas(s) affected, and a detailed description of the proposed implementation plan (manufacturing change including device collection technology and the collection protocol(s)). Additionally, we recommend that this information be documented in a cover letter and FDA Form 356h.

- relevant validation protocols and data. We recommend a summary of the validation protocol, including failure investigations to meet the requirement.

- the data derived from studies. We recommend two months of QC data for actual platelet yield and volume, pH, and residual WBC count (if requesting approval for Leukocytes Reduced platelets).

In addition, you should include the submission tracking number (STN) of the approved Comparability Protocol, or the STN(s) of changes to the SOPs associated with an approved Comparability Protocol.

D. Submission of Platelets, Pheresis Sample(s) to CBER

To obtain a biologics license under Section 351 of the Public Health Service Act for any biological product, the manufacturer must submit an application to CBER, and sample(s) representative of the product must be listed in the application (21 CFR 601.2(a)).

We recommend that:

- applicants with no prior experience in the collection of Platelets, Pheresis schedule submission of Platelets, Pheresis products to CBER.
- applicants who submit a CBE-30 for an additional facility under an approved Comparability Protocol generally would not need to submit Platelets, Pheresis products to CBER.

CBER may request the submission of product samples by other applicants, as necessary, during the review process or at any other time (21 CFR 610.2(a)).

E. Shipping Platelets, Pheresis Sample(s) to CBER

If CBER has requested you to submit a Platelets, Pheresis sample(s) to CBER, you should contact CBER Division of Hematology, Laboratory of Cellular Hematology at (301) 496-2577 to schedule delivery of the products to arrive prepaid. Platelets, Pheresis sample(s) should be shipped to the following address between 8:30 a.m. and 4:00 p.m. Monday through Friday, excluding Federal holidays:

Center for Biologics Evaluation and Research (CBER)
Food and Drug Administration
8800 Rockville Pike
Building 29, Room 323
Bethesda, Maryland 20892

We recommend that you enclose a pre-paid, self-addressed shipping label to allow return of shipping boxes and coolants, if desired.

We recommend that you ensure that the Platelets, Pheresis sample(s) arrives at CBER prior to the expiration time. The Platelets, Pheresis sample(s) should not expire on Friday or Saturday at midnight, or at midnight on the day before a Federal holiday.

Labeling and processing, including required testing for evidence of infection due to communicable disease agents (21 CFR 610.40), should be complete prior to shipment.

When shipping to us, you should follow your SOPs for collection, processing, storage and distribution of blood components intended for transfusion.

XI. CONTACT INFORMATION

You may direct questions specific to Platelets, Pheresis application submissions to the Division of Blood Applications. You may also direct questions to the Office of Communications, Training, and Manufacturers Assistance (OCTMA) as an initial general point of contact. Submit all registration forms (Form FDA 2830) and licensure applications/supplements to the Director, CBER.

Table 3: FDA Contact Information

Submissions: Registrations License Applications	Director, Division of Blood Applications Center for Biologics Evaluation and Research, HFM-370, Food and Drug Administration, c/o Document Control Center, HFM-99, 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448.
General Questions	Director, OCTMA, HFM-40, Food and Drug Administration, c/o Document Control Center, HFM-99, 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, Voice (301) 827-2000; Fax (301) 827-3843.
Application Submission	Director, Division of Blood Applications, Center for Biologics Evaluation and Research, HFM-370, Food and Drug Administration, c/o Document Control Center, HFM-99, 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, Voice (301) 827-3543; Fax (301) 827-3534.
Platelets, Pheresis Samples to CBER	Center for Biologics Evaluation and Research (CBER) Food and Drug Administration 8800 Rockville Pike Building 29, Room 323 Bethesda, Maryland 20892

XII. REFERENCES

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(11)

[原著]

事前検査におけるヘモグロビン測定の導入

香川県赤十字血液センター
内田 立身，窪田 明美，中西 幸美，安藤 浩子
西村 拓史，白井 隆，小河 敏伸，西尾由美子
細川 和浩，木村 史子，三枝 明子，本田 豊彦

Implementation of measuring hemoglobin concentration at pre-donation test

Kagawa Red Cross Blood Center
Tatsumi Uchida, Akemi Kubota, Yukimi Nakanishi, Hiroko Andoh,
Takuji Nishimura, Takashi Shirai, Toshinobu Ogoh, Yumiko Nishio
Kazuhiro Hosokawa, Humiko Kimura, Akiko Saigusa and Toyohiko Honda

抄　録

香川県赤十字血液センターでは2003年10月に，事前検査として血液比重にかわって，ヘモグロビン(Hb)測定法を導入した。Hb法の最大の利点はその定量性にあり，献血者にHb値を数字として提示することができ，Hb低値者，高値者に対する対応を明確にし得た。また，懸念されていたHb不足による献血不適格者数，VVR発症率も比重法施行時と大差がなかった。今回の検討で，Hb12.5g/dL以上がほぼ比重1.053以上に，12.0g/dL以上が1.052以上に相当すること，Hbと赤血球指数との関係から，赤血球が正色素性から小球性低色素性に変わるHb値が12.5～12.0g/dLであることから現行の採血基準は妥当であると考えられた。Hb法は測定装置がHbの表示まで時間を要すること，温度差による配慮が必要であるなどの欠点はあるが，定量性，均一性を重視するGMPからみても従来の比重法より優れていると結論した。

Key words: Pre-donation examination, Hemoglobin determination
Blood donation criteria, HemoCue hemoglobin analyzer

はじめに

香川県赤十字血液センターでは，2003年10月より，事前検査として硫酸銅法による比重測定にかわって，簡易ヘモグロビン(Hb)測定装置，ヘモキュウヘモグロビンシステム(以下Hb法)による方法に変更した。採血基準は，血液事業の根幹の一つであり，その判定には定量的なHb法が最も妥当と考えられるゆえである。自動血球算定装置がルーチン化したわが国において，貧血の診断はすべてHb，ヘマトクリット，赤血球数によっており，目視による比色法(ザーリ法)や比重法(硫酸銅法)は赤十字血液センターを除いて用いられていない。最近の献血の適否に関する世界の論文は，すべてがHb法を用いて判断しており[1)-3)]，比重法は

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掲載決定日：2005年12月5日

検査法として教科書の記載すらない現状である[4]。

今回，比重法とHb法の比較，変更前後の献血不適格者の比率，副作用，とくに血管迷走神経反応(Vasovagal Reflex：以下VVR)の比率，また，200mL献血12.0g/dL以上，400mL献血12.5g/dL以上とされている採血基準の妥当性についても検討した。さらに，Hb法の有用性を生かして，不適格者のHb濃度別による個人指導のありかたについても検討したので，これらの成績を報告する。

方　法

簡易Hb法(ヘモキュウ)によるヘモグロビン測定は，あらかじめ試薬が充填された専用マイクロキュベットに10μLの末梢血をサンプリングしアナライザーにセットして，表示されるHb量を読み取る。Hb測定はアザイドメトヘモグロビン法により570nmと880nmからなる2波長様式によっている。

200mL献血申込者63名，400mL献血申込者62名において，血液比重測定と同時に自動血球計数装置(STKS)によるHb測定を行い両法の比較を行った。次に，平成14年4月1日から15年3月31日の間に比重法によって判定した献血者と平成16年4月1日から17年3月31日の間にHb法で判定した献血者において，本社採血基準による献血不適格者の比率，VVRの発症比率を比較検討した。また，献血申込者男性1,472名，女性771名のHb法によるHb濃度別度数分布を作成した。次に，STKSによって得られたMCV，MCH，MCHCとHb値の関係をみることにより，Hb法採用時の採血基準の妥当性を検討した。

Hb法(ヘモキュウ)を導入して1年6カ月経過した時点で，献血バスで実際に使用している看護師17名にアンケート調査を行った。

結　果

1．比重法とHb法の関係

400mL献血申込者のうち，血液比重1.053以上を示した献血者62名のHb値は12.6～17.3g/dLの範囲になり，その平均値±1SDは14.96±1.12g/dLであった。同様に比重1.052以上の200mL献血申込者63名は12.1～16.4の範囲で平均値は13.64±1.16g/dLであった。以上から，400mLの採血基準1.053以上またはHb12.5g/dL以上，200mLの採血基準1.052以上または12.0g/dL以上は両者ともcut off値として妥当であると考えられた。また，比重法の結果はHb値で幅広い範囲に分布し，定量性がないことも明らかとなった。

2．簡易Hb法と自動血球計算装置との相関

簡易Hb法(ヘモキュウ)と自動血球算定装置(Coulter STKS)によって測定した結果の相関を図1に示した。相関係数0.951(Y＝0.8893X＋1.59)の高い相関がみられた。

3．Hb法による献血者ヘモグロビンの度数分布

Hb測定の定量性を生かして献血者ヘモグロビンの度数分布が得られた（図2）。献血申込者の男性1,472名，女性771名の解析で最も頻度が高いのは，男性15.0～15.5g/dL，女性12.5～13.0g/dLであった。

4．比重法およびHb法による献血不適格者の比較

表1に比重法(平成14年4月1日～15年3月31日)とHb法(16年4月1日～17年3月31日)で判定した比重あるいはHb不足による献血不適格者の比率を示す。両者の年齢区分毎不適格率で大きな差異は認めなかった。200mL，400mLの合計において比重法の男性申込者は23,985名，うち不適格者数(率)151名(0.6%)，女性申込者は21,715名，うち不適格者4,404名(20.3%)，Hb法の男性申込者22,749名，不適格者数(率)151(0.6%)，女性申込者20,504名，不適格者数3,958名(19.3%)で，いずれも差異を認めなかった。400mL申込女性で40歳代では，多数の(26～30%)不適格者がみられた。また，400mL申込女性でHb12.5g/dL未満431名のうち10.0g/dL未満が43名(10.0%)，8g/dL未満も4名みられ，治療を必要とすると考えられた。

5．献血時副作用の比較

輸血副作用のうち採血基準が関係すると思われるvaso-vagal reaction(VVR)の発症率を比較した。ヘモキュウが用いられる献血バス200mL，400mL採血のVVRはHb法で男性が減少していたが，女性での頻度の差は認められなかった（表2）。いずれにしてもHb法を導入してVVRが増加することはなかった。

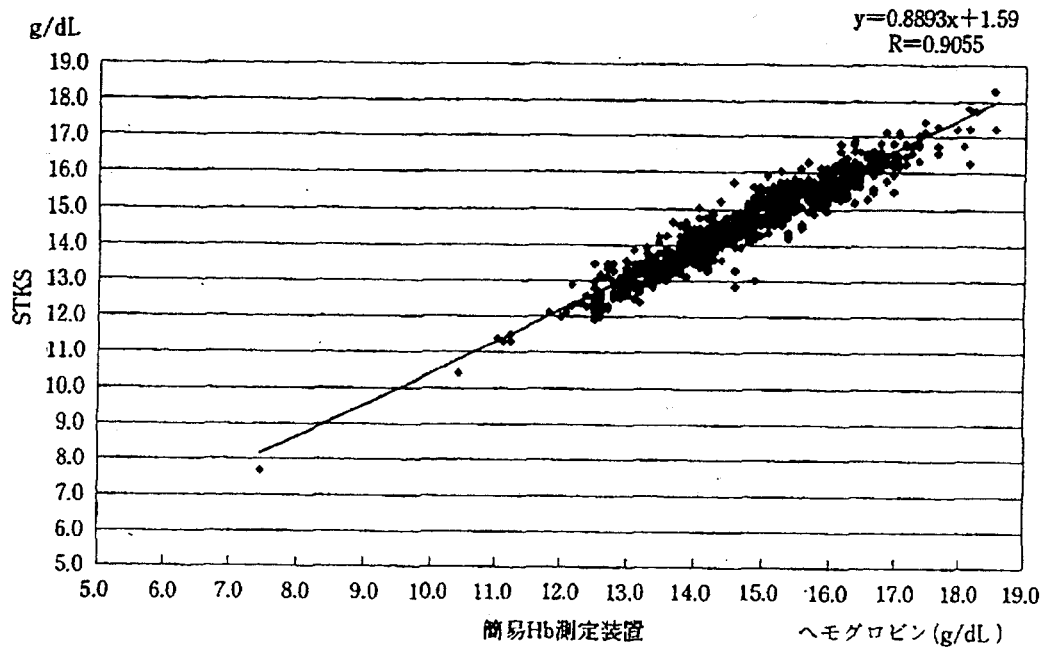
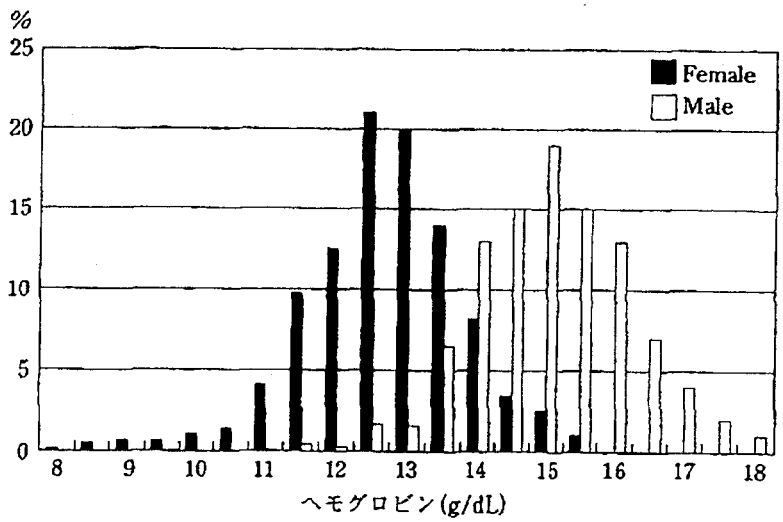


図1　簡易Hb測定装置(ヘモキュウ)と自動血球算定装置(STKS)との比較



献血申込者，男性1,472名，女性771名のヘモグロビン分布。男性で最も多いのは15.0～15.5g/dL，女性で最も多いのは12.5～13.0g/dLであった。

図2　献血申込者のヘモグロビン値の分布

6．ヘモグロビンと赤血球指数の関係

Hb値と赤血球指数(MCV，MCH，MCHC)の平均値の関係を表3に示す。Hbの低下に伴って赤血球指数も低下してくる。低下傾向が認められるのは男性で，MCV，MVH，MCHCともHb12.5g/dL未満から，女性12.0g/dL未満からであり，小球性低色素性の傾向が認められるのは男性が0.5g/dL高かった。以上から，Hbの低下にともなって赤血球は12.5～12.0g/dLで正色素性から小球性低色素性に変わることが判明した。

7．Hb低値による献血不適格者への対応

Hb測定の定量性を生かして献血者のHb値に応じた指導を行うこととした。Hb値10g/dL未満の献血者には医療機関を受診し治療を受けるよう医

表1　比重法およびHb法による献血不適格者の比較

			年齢区分	19～19	20～29	30～39	40～49	50～59	60～69	計
比重法	男性	200	申込数	1,091	286	346	550	517	210	3,000
			不適数	8	0	5	5	15	1	34
			不適率	0.7	0	1.4	0.9	2.9	0.5	1.1
		400	申込数	1,040	4,464	5,683	5,198	3,659	941	20,985
			不適数	5	14	21	29	30	18	117
			不適率	0.5	0.3	0.4	0.6	0.8	1.9	0.6
	女性	200	申込数	2,240	3,139	2,938	1,976	1,904	689	12,877
			不適数	399	602	689	448	239	67	2,444
			不適率	17.8	19.2	23.5	22.8	12.6	9.7	19.0
		400	申込数	601	1,923	2,097	1,923	1,771	523	8,838
			不適数	110	446	588	582	198	36	1960
			不適率	18.3	23.2	28.0	30.3	11.2	6.9	22.2
Hb法	男性	200	申込数	1,050	298	340	421	448	224	2,781
			不適数	7	1	1	4	5	8	26
			不適率	0.7	0.3	0.3	1.0	1.1	3.6	0.9
		400	申込数	1,147	4,183	5,510	4,832	3,373	923	19,968
			不適数	2	9	17	24	31	18	101
			不適率	0.2	0.2	0.3	0.5	0.9	2.0	0.5
	女性	200	申込数	2,422	2,579	2,825	1,762	1,510	612	11,710
			不適数	461	425	593	386	140	64	2,069
			不適率	19.0	16.5	21.0	21.9	9.3	10.5	17.7
		400	申込数	601	2,038	2,286	1,786	1,584	499	8,794
			不適数	176	454	596	467	163	33	1,889
			不適率	29.3	22.3	26.1	26.1	10.3	6.6	21.5

表2　比重法およびHb法によるVVR発症率の比較

		男　性	女　性
比重法	軽症	83	53
	重症	1	1
	計	84	54
	発症率（%）	0.44	0.43
Hb法	軽症	44	50
	重症	3	2
	計	47	52
	発症率（%）	0.27	0.44

師が指導し，12g/dL未満，10g/dL以上の献血者には食事指導用のパンフレットを作成し配布すると同時に，月に1度栄養士会による個別栄養指導も開設した。

8．Hb高値の献血者の頻度

採血可能であった男性1,472名，女性771名について（図2），Hb17.0g/dL以上の比率は，17.5＞Hb≧17.0：30例(3.0%)，18.0＞Hb≧17.5：3例(0.3%)，18.5＞Hb≧18.0：3例(0.3%)，19.0＞Hb≧18.5：1例(0.1%)の計37例で，いずれも男性で女性にはみられなかった。また，赤血球指数は正常であった。

9．ヘモキュウ使用者のアンケート結果

ヘモキュウを使用している看護師のアンケート結果は以下のとおりであった。まず，利点としては①感染性廃棄物としての後始末が簡単になった(100%)，②測定法が簡単である(74%)，③献血者にHb値を示すことで説得力がある(63%)，などであった。欠点としては①外気温や光線の影響

表3　Hbと赤血球指数の関係

Hb(g/dL)	男性			女性		
	MCV (fl)	MCH (pg)	MCHC (g/dL)	MCV (fl)	MCH (pg)	MCHC (g/dL)
16.0>Hb≧15.5	93±4	32±2	34±0			
15.5>Hb≧15.0	93±5	32±2	34±1	93±4	32±2	35±1
15.0>Hb≧14.5	92±3	32±2	34±1	92±3	32±1	35±0
14.5>Hb≧14.0	92±5	32±2	34±1	91±3	31±1	35±0
14.0>Hb≧13.5	92±4	32±2	35±1	91±1	32±1	35±0
13.5>Hb≧13.0	92±6	32±2	34±0	90±4	31±2	35±1
13.0>Hb≧12.5	92±5	32±2	34±1	90±3	31±1	34±0
12.5>Hb≧12.0	84±6	28±3	34±1	91±6	31±2	34±0
12.0>Hb≧11.5	83±5	28±2	34±0	87±5	30±2	34±1
11.5>Hb≧11.0*	77±0	25±0	33±0	83±5	28±2	34±0
11.0>Hb≧10.5				83±6	27±2	34±1

n=20 (*n=2)

を受けやすい(94%)．②測定に時間がかかる(94%)．③新たに精度管理が必要になった(69%)．などであった。

考　察

従来から採血基準として用いられている硫酸銅法による血液比重は，献血者を1.052未満，1.052以上(200mL)，1.053以上(400mL)と3区分して可否を判定するもので，各区分内に様々なヘモグロビン濃度が含まれる定性法であり，血液事業が始まって以来半世紀あまりずっと用いられている。しかしながら，比重法は測定者により±0.001程度のバラツキがあることが指摘されている[5]。一般に，赤血球沈降速度は，高温で促進，低温で遅延し補正が必要とされている[6]。佐野らの検討では，10℃で20℃に比し，0.001～0.002低い値，30℃で0.001～0.002高い値が得られるとしている[5]。また，Jamesら[7]は比重法の方がHb法よりも偽の適判定(false-pass)が多いことを証明した。以上から，現在のGMPに準拠した血液事業の理念からすれば，いつ，誰が，どう行っても一定した数値が得られるHb法の方が理想的であることは明白である。今回，簡易ヘモグロビン測定装置(ヘモキュウ)を導入して2年あまりになるので，従来の比重法との比較を様々の面から試みた。

ヘモキュウによるHb測定は，自動血球計算装置との相関で高い相関があり，とくに問題がないことが示された。これは過去の報告のとおりである[8)～10)]。また，比重法とHb法で献血不適格者の比率が異なるか否かを検討した。比重法とHb法の比較検討では，時期が異なるため厳密な比較ではないが，献血不適格者の増減はなく，現行の採血基準で有意の差はないと思われた。男性のVVRは，軽症でHb法の方が少なくヘモグロビン値以外の原因が考えられる。

Hb法の利点は，献血者のHb値を数字として表示できることであり，度数分布を知ることができる。この度数分布によって，女性献血申込者の中に，10g/dL未満の要加療者が不適格者の10%近くみられることが判明した。従来の比重法では，低比重以外の情報がなくそのまま放置されるわけであるが，Hb法ではHb値を提示できるので医療機関への受診を勧めることができた。また，10.0～12.5g/dLの方には栄養指導や食事のアドバイスができた。すなわち，貧血の予防と治療の双方を区別して指導することが可能である。

採血基準では，真性赤血球増加症(多血症)は採血しないことになっているが，比重法ではHb高値者を除外することができない。Hbを測定することによって，17g/dL以上は男性で3.7%にみられ，女性にはみられなかった。また，これらは白血球数，血小板数，赤血球指数が正常で，相対的(ストレス)赤血球増加症と考えられた。真性赤血

球増加症は白血球増加，血小板増加，小球性低色素性赤血球の傾向を示すことから，今回の検討で，Hb19.0g/dL未満で白血球数，血小板数，赤血球指数が正常であれば，採血可能と判断した．

今回Hb測定の定量性を生かして，従来の採血基準の妥当性を検討した。まず，比重法とHb法の比較で，1.052以上はHb12.1g/dL以上を，1.053以上はHb12.6g/dL以上を示した。また，Hb値の低下に伴って赤血球指数が低下してくるが，平均値の低下開始に相当するHb値は，小球性低色素性赤血球に移行する点で，女性の成分採血の際の可否判定に用いられているところである。低下開始点は男性12.5g/dL，女性12.0g/dLで，男性が0.5g/dL高かった。また，12.5g/dL以下の男性献血申込者の比率は0.6%と少なく，あえて男性の採血基準を引き上げる必要はないと考えられる。以上および米国FDAの基準[11]を勘案して，私たちはHb法の判定に男女差を設けず，従来の採血基準を用いることで問題がないと考えた。

今回用いたヘモキュウによるHb測定法は，英国のNational Quality Assessment Schemeの精度管理で正確性の保証が得られている[11]。また，静脈血採血と耳朶あるいは指尖毛細血管穿刺との間に差異があるとの議論がある。これは，サンプリングが不適切な場合で，血流が十分保たれ，穿刺が正確に行われた場合は有意の差がないとの見解が一般的である[12]。また，指尖穿刺の方が，静脈穿刺より正確性を欠くとの報告もある[13]。

献血の可否を決定する検査は，大別して，血液学的検査，生化学検査，感染症関連検査が行われている。生化学，感染症関連検査は1953年血液事業が開始されて以来，次々と改良，改善が加えられ，NAT検査の導入によって世界的水準を保つにいたっている。一方，採血基準の根幹である貧血の有無判定については，当初の硫酸銅による比重法が現在にいたるも用いられ，一向に改良の気配がない。その間，比重不足による献血不適格者は増加の一途であり，女性の400mL献血で本社の調査で，1990年 9.9%，2000年 18.1%，2003年 21.3%である[14),15]。輸血によるウイルス性肝炎が激減したのと極めて対照的である。いうまでもなく比重法は測定者の目視による定性的判定法であり，温度・湿度の影響，使用滴下回数や蒸発，観察者の主観を無視できない。臨床の場においても，かつては比重法や比色法(ザーリ法)が用いられたが，現在はHb,ヘマトクリットに統一され，比重，比色によっている医療機関は皆無である。したがって，血液センターと医療機関の間で貧血に関するかぎり整合した議論が全くできていない。国は献血者の確保の推進として，献血の検査結果を健康診査，人間ドック，職場検診で活用するとともに，地域の保健指導に用いるよう求めているが[16]，比重で表示される献血不適格者の成績は利用し得ない状況である。以上から，血液センターにおいてもHb法を早急に導入し，定量的な評価によって献血者の健康を守る配慮をすべきである。

結　論

1．献血の可否判定にHb法を導入した。従来の比重法に比して，不適格者率，副作用発症率とも差異はなかった。

2．Hbおよび赤血球指数の度数分布から，従来の採血基準(400mL：12.5g/dL以上，200mL：12.0mg/dL以上)を用いて差し支えないことが判明した。

3．Hb低値の献血申込者に対して，Hb値に応じた栄養指導，医療機関への受診指導を行うことができた。

4．Hb法は定量性，客観性において比重法に優っており，Hb法に統一すべきであることを提言した。

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