The relative safety of automated two-unit red blood cell procedures and manual whole-blood collection in young donors

Richard J. Benjamin, Beth A. Dy, Jean M. Kennedy, Edward P. Notari IV, and Anne F. Eder

BACKGROUND: Automated red blood cell (RBC) apheresis offers the advantage of collecting 2 units of RBCs (2RBC) from one donation, but may expose donors to procedure-related risks. This study evaluated the relative safety of 2RBC compared to whole-blood (WB) donation with a focus on young donors.
STUDY DESIGN AND METHODS: Adverse reactions recorded at the collection site or requiring outside medical care were compared after 4,348,686 WB and 206,570 2RBC donations in 26 regional blood centers.
RESULTS: 2RBC donors were more likely than WB donors to be male (91.6% vs. 50.3%) and repeat donors (84.0% vs. 81.0%). The overall complication rate was higher for 2RBC than WB collections (627.9 vs. 435.1 per 10,000; odds ratio [OR], 1.44; 95% confidence interval [CI], 1.41-1.47), but more than 96% of all reactions were minor in severity. For donors younger than 20 years, adverse events were equally or less common after 2RBC than after WB donation, but were more common after 2RBC for donors 20 years or older. The rate of major systemic complications was significantly lower for 2RBC than WB donations in all age groups (10.2 vs. 14.3 per 10,000 collections; OR, 0.71; 95% CI, 0.62-0.82). Overall, the need for outside medical care was similar for 2RBC and WB collections (3.4 vs. 4.2 per 10,000 donations, respectively), but significantly less likely after 2RBC donation for donors less than 20 years old (3.8 vs. 7.0. per 10,000 donations; OR, 0.53; 95% CI, 0.32-0.89).
CONCLUSION: 2RBC collection procedures, as currently performed in the American Red Cross, are associated with fewer immediate adverse reactions in young donors and have a comparable safety profile in older donors. These data support the collection of 2RBC from young donors.

Automated collections now provide more than 10% of red blood cell (RBC) components transfused in the United States.[1] Two-unit RBC (2RBC) collection by apheresis offers several advantages over whole-blood (WB) donation, including better inventory management of needed blood types and more consistent and controlled component quality. Consequently, blood centers are increasingly recruiting 2RBC donors, and more procedures are being performed at high school and college drives.[2,3] In 2003, automated procedures accounted for only 1% of RBCs distributed for transfusion by the American Red Cross, which grew to more than 7% in 2006. With this trend, recruitment of donors younger than 20 years increased for both WB and 2RBC collections. By 2008, young (<20 years old) donors accounted for 15% of the WB donations and more than 19% of the 2RBC donations.

The introduction of 2RBC technology, however, requires careful consideration of donor safety issues, especially with respect to the loss of twice the RBC mass compared with WB collections and the risks inherent to apheresis, such as citrate toxicity and device-related complications. Accordingly, donation guidelines are more stringent for 2RBC than WB collection. Minimum weight, height (or calculated blood volume), and donor hemoglobin (Hb)/hematocrit (Hct) requirements are higher and the donation interval is twice as long for 2RBC donors

ABBREVIATIONS: 2RBC = 2-unit red blood cell collection procedure; LOC = loss of consciousness; WB = whole blood.

From the Biomedical Services, Medical Office, National Headquarters, American Red Cross, Washington, DC; and the Jerome H. Holland Laboratory, American Red Cross, Rockville, Maryland.

Address reprint requests to: Richard Benjamin, MD, PhD, Biomedical Services, National Headquarters, American Red Cross, 2025 E Street NW, Washington, DC 20006; e-mail: BenjaminR@usa.redcross.org.

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TABLE 1. Differences in donor selection criteria and collection processes between WB and 2RBC collections, as currently implemented in the American Red Cross*

Parameter	WB	2RBC†
Donor weight (lb)		
Male	≥110	≥150
Female	≥110	≥175
Donor height		
Male	NA	≥5 ft 1 in.
Female	NA	≥5 ft 5 in.
Donor Hct (%)	38	40
RBC volume collected (mL)	>180	~400
Needle gauge	16	17-18
Saline replacement	No	Yes
Duration (min)	4-15	~28-32
Donation interval	8 weeks	16 weeks

* The manufacturers' recommended criteria differ in that male donors greater than 130 lb and females greater than 150 lb are acceptable for 2RBC donation, and the RBC volume collected may vary from 360 to 420 mL, according to a FDA-approved nonogram based on sex, height, weight, and Hct.[25] The American Red Cross aimed for 400-mL RBC volume in all 2RBC collections.

† Donor criteria for MCS+ 8150 (Haemonetics) and Alyx (Fenwal) devices.

NA = not applicable

than WB donors (Table 1). Moreover, 2RBC procedures utilize saline replacement, employ smaller needles (17 or 18 gauge vs. 16 gauge), and take considerably longer (approx. 28-32 min vs. 4-15 min) than WB donation. In addition to the device manufacturers' restrictions for 2RBC collections, the American Red Cross implemented uniform RBC volume (~400 mL) criteria and more conservative weight restrictions (males, ≥150 lb; females, ≥175 lb) for all procedures, to standardize operations and meet component quality control requirements (Table 1).

Several small studies and the published experience from one large blood center attest to the general safety of 2RBC procedures with respect to complications recorded at the donation site.[2,4] We previously reported safety data for calendar year 2006, showing the particular susceptibility of young donors to syncope-related (e.g., vasovagal) complications after WB donation.[5,6] We extend these observations in this study to compare WB and 2RBC complication rates to evaluate the relative safety of collection procedures as currently performed by the American Red Cross, in particular for young donors.

MATERIALS AND METHODS

Study population

The American Red Cross collects WB and 2RBC donations in 35 and 31 regional blood centers ("regions"), respectively. This analysis is restricted to the 26 regions that performed more than 50 2RBC procedures on 17-year-old donors in calendar year 2007.

Collection site procedures

WB is collected into 500-mL collection sets (Fenwal, Inc., Lake Zurich, IL; Pall Medical, Inc., East Hills, NY) following standard procedures from volunteer, allogeneic donors. 2RBC procedures are performed with Alyx (Fenwal, Inc.), Trima (CaridianBCT, Lakewood, CO), or MCS+ 8150 (Haemonetics, Braintree, MA) device systems according to manufacturers' operational instructions. Eleven regions used only Alyx devices, 13 regions used only MCS+ 8150 devices, and 2 regions used both. For the purposes of analysis of rates of adverse events, the equipment type was attributed by region and the two regions that used both devices were excluded from the analysis. During this period 4080 procedures (<2% of all procedures) were performed on the Trima device, most of which occurred in regions also using MCS+ 8150 (3798 procedures) rather than in regions using Alyx devices (282 procedures). Device type is not captured in the centralized database; therefore, the relative contribution of the procedures performed on the Trima on the rates of adverse reactions is not known.

The standardized classification system for donor complications defining 15 reaction categories and the functioning of the American Red Cross Hemovigilance Program has been described.[5,6] Complication rates were calculated per 10,000 collections for minor and major complications and for cases receiving outside medical care for different donor age groups. To facilitate further analysis, complications were grouped into three composite categories: minor events (allergic, citrate, small hematoma, presyncope reaction, and other reaction); loss of consciousness (LOC) and major systemic events (LOC [less than or greater than 1 min], LOC with injury, prolonged recovery, allergic, other reactions); and major phlebotomy-related events (large hematomas, arterial puncture, and nerve irritation).

Donor return rates

The effect of adverse events on the rate of return donation was assessed in young donors aged 17 to 19 years, for donations made between January 1, 2007, and June 30, 2007. An index donation during this period was the first 2RBC donation in which an adverse event was recorded for those donors who had an adverse reaction and the first 2RBC donation in the given time period for all those with an uneventful donation. Donors were then followed for 365 days and any subsequent presentation (i.e., for WB or apheresis donation) that resulted in a successful donation or deferral (including Hb deferrals), with or without an adverse event, was captured. Similar data were also recorded for any donations in the 365 days before the index donation. For this analysis major systemic and major phlebotomy-related events were combined, because they were rare events.

Statistical analysis

Multivariate logistic regression analysis with a stepwise selection of risk factors was used to compare 2RBC donations with minor reactions to those with no reactions and to compare 2RBC donations with major systemic reactions to those with no reactions. The multivariate model evaluated age, donation status, gender, and device (MCS+ 8150 vs. Alyx). Statistical analysis was done with computer software (SAS/STAT, Version 8.2 of the SAS System for Unix, SAS Institute, Inc., Cary, NC). The American Red Cross Institutional Review Board determined that the research was exempt under 45CFR46, 21CFR50.

RESULTS

In calendar year 2007, the American Red Cross collected 6,018,720 WB donations and performed 240,493 2RBC apheresis procedures in 35 regions in the United States. We limited the current analysis of immediate adverse reactions to 26 regions that performed a substantial number (>50/year) of 2RBC procedures in 17-year-old donors, to focus on the safety of these procedures in young donors. These regions performed 4,348,686 WB collections and 206,570 2RBC procedures (Table 2). 2RBC procedures preferentially involved male (91.6% vs. 50.3%) and repeat (84.0% vs. 81.0%) donors, compared with WB collections. The age distribution of 2RBC donors was similar to that of WB donors, except that a slightly higher proportion of 2RBC procedures were performed on donors less than 20 years of age (19.3% vs. 15.0%).

Adverse events after WB and 2RBC procedures were recorded by collection staff using 15 reaction categories (Table 3).[6] Overall 6.3% (627.9 per 10,000) of 2RBC procedures were associated with an adverse event at the collection site, compared to 4.4% (435.1 per 10,000) of WB donations (odds ratio [OR], 1.44; 95% confidence interval [CI], 1.41-1.47). The vast majority (>96%) of all reactions were minor reactions or symptoms regardless of procedure type; the most common events after WB collection were presyncopal reactions (277.2 per 10,000 collections) and small hematomas (140.3 per 10,000 collections); after 2RBC procedures, small hematomas (309.8 per 10,000 procedures), presyncopal reactions (185.6 per 10,000 procedures), and minor citrate reactions (117.4 per 10,000 procedures).

Hematomas (small and large) were more frequent after 2RBC procedures, whereas presyncope, LOC (<1 min), LOC with injury, prolonged recovery, and arterial puncture were more frequent after WB donation (Table 3). The rate of phlebotomy-related nerve injuries reported at the collection site was not different for WB and 2RBC collections; however, these events are often reported after the donation event. When delayed reports are included, the rate of nerve injury for automated collections is significantly but only marginally higher than for WB donations (4.0 vs. 3.2 per 10,000; OR, 1.25; 95% CI, 1.14-1.36; data not shown).

Adverse events at the collection site were further grouped in composite minor, LOC and major systemic, and major phlebotomy-related categories, to facilitate subsequent analysis. Overall, the rate of minor reactions after 2RBC collections was 50% greater than WB collection (OR, 1.50; 95% CI, 1.47-1.53), but the rate of LOC and major systemic adverse events was 29% lower (OR, 0.71; 95% CI, 0.62-0.82) than WB collections. The rate of major phlebotomy-related events recorded at the collection site was not significantly different for 2RBC compared to WB donations (Tables 2 and 3).

Analysis of risk factors for 2RBC adverse events

To further identify variables that predicted reactions after 2RBC donation, we performed multivariate logistic

TABLE 2. Donor demographics after WB and 2RBC donations in calendar year 2007*

	WB		2RBC	
Demographics	Number of donations	Percent	Number of procedures	Percent
Total, 26 regions	4,348,686	100.0	206,570	100.0
Sex				
Male	2,185,438	50.3	189,208	91.6
Female	2,158,526	49.6	17,159	8.3
Status				
First-time	828,000	19.0	33,075	16.0
Repeat	3,520,686	81.0	173,495	84.0
Age (years)				
16	41,144	0.9	62	0.0
17	302,145	6.9	19,929	9.6
18	199,802	4.6	13,889	6.7
19	111,945	2.6	6,106	3.0
20-29	588,499	13.5	27,987	13.5
30-29	566,642	13.0	25,988	12.6
>40	2,538,440	58.4	112,609	54.5

* Age data not available on 35 WB donors; sex data not available for 4722 WB and 203 2RBC donors.

TABLE 3. Total adverse event rates after WB and 2RBC donations in calendar year 2007

	WB		2RBC		
Adverse events	Events	Rate per 10,000	Events	Rate per 10,000	OR (95% CI)
Minor reaction categories					
Presyncope	120,561	277.2	3,833	185.6	0.67 (0.64-0.68)
Hematoma (small)	61,029	140.3	6,400	309.8	2.25 (2.19-2.31)
Citrate (minor)*	31	0.1	2,428	117.5	ND
Other (minor)	165	0.4	20	1.0	2.55 (1.57-3.99)
Allergic (minor)	30	0.1	11	0.5	7.72 (3.87-15.40)
Composite minor reaction categories	*181,816*	*418.1*	*12,692*	*614.4*	*1.50 (1.47-1.53)*
LOC and major reaction categories					
LOC (<1 min)	4,269	9.8	150	7.3	0.74 (0.63-0.87)
LOC (>1 min)	591	1.4	21	1.0	0.75 (0.48-1.16)†
Prolonged recovery	842	1.9	19	0.9	0.48 (0.30-0.75)
LOC with injury	438	1.0	3	0.1	0.14 (0.05-0.45)
Other (major)	82	0.2	9	0.4	2.31 (1.16-4.60)
Citrate (major)*	3	0.0	8	0.4	ND
Allergic (major)	2	0.0	1	0.0	ND
Composite major systemic	*6,227*	*14.3*	*211*	*10.2*	*0.71 (0.62-0.82)*
Major phlebotomy-related					
Hematoma (large)	387	0.9	53	2.6	2.88 (2.16-3.84)
Nerve irritation	314	0.7	11	0.5	0.73 (0.40-1.35)†
Arterial puncture	449	1.0	4	0.2	0.18 (0.07-0.50)
Composite major phlebotomy-related	*1,150*	*2.6*	*68*	*3.3*	*1.24 (0.97-1.59)†*
All adverse events	189,193	435.1	12,971	627.9	1.44 (1.41-1.47)
Outside medical care	1,814	4.2	71	3.4	0.82 (0.65-1.04)†

* Citrate reactions after WB donations represent errors in classification.
LOC = loss of consciousness; ND = not determined; † 95% confidence interval includes 1.0.

regression analysis. We previously reported that the risk of any adverse event after 2RBC donation in calendar year 2006 was independently associated with young donor age, first-time donation status, female sex, and collection site.[5,6] This analysis reflects the most common reactions, which are minor in severity and account for more than 95% of adverse events. Consequently, the current analysis evaluated minor complications separately from major systemic complications after 2RBC donation. In addition, we included device type (MCS+ 8150 vs. Alyx) in the models because the majority (74.9%) of 2RBC procedures (154,769 of 206,570) were performed in 24 study regions that used either Alyx (11 regions) or MCS+ 8150 (13 regions) technology. The two regions that used both devices were excluded from the models.

The multivariate logistic regression analysis compared 2RBC donations with no reaction to those with minor reactions using the composite endpoint (Tables 4 and 5). The risk factors previously determined to be significantly associated with minor adverse reactions (young age, first-time donation status, female sex)[5,6] as well as device type (MCS or Alyx), were entered into the final logistic regression model. Compared to the reference group (20- to 29-year-old donors), the rate of minor reactions was not different for younger donors (<19 years old) but the rate of reactions decreased for donors in older age groups. First-time donation status, female sex, and device type were also significantly associated with minor reactions.

The analysis of major systemic reactions included only donor age and device as risk factors, because donation status and sex were not significantly associated with major systemic reactions and were not entered into the final logistic regression model. As with minor reactions, young donors were not at increased risk of major systemic reactions compared to donors age 20 to 29 years. With increasing age above 30 years, the rate of major systemic reactions was lower than that observed for donors age 20 to 29 years. Device type was also significantly associated with major systemic reactions in this analysis. The infrequent occurrence of major phlebotomy-related adverse events after 2RBC procedures precluded multivariate analysis, but none of the factors were significantly associated with these reactions in univariate (unadjusted) analysis (data not shown).

Effect of age on event rates

This multivariate analysis of 2RBC donations demonstrates that age is a strong and independent risk factor for minor and major reactions, as was similarly demonstrated for WB donation,[5,6] but suggests that younger donors are differentially affected by the 2RBC procedure, as currently performed in the American Red Cross. Recognizing the differences in donor selection criteria and the multiple technical differences between WB and 2RBC collections, the relative safety profile for different age groups after WB was evaluated alongside 2RBC donation for all 26 regions (Fig. 1).

TABLE 4. Multivariate logistic regression analysis of variables associated with minor reactions after 2RBC donation*

Variable	Donations	Events	Reaction rate/10,000	Adjusted OR (95% Wald CI)
Donor age (years)				
17	15,641	1039	664.3	0.98 (0.85-1.11)
18	10,806	769	711.6	1.11 (0.97-1.27)
19†	4,469	344	769.8	1.20 (1.00-1.44)
20-29	20,816	1361	653.8	1.00 Reference
30-39†	19,112	1028	537.9	0.81 (0.72-0.92)
40-49†	31,068	1417	456.1	0.69 (0.61-0.77)
50-59†	32,235	1403	435.2	0.66 (0.59-0.74)
60+†	20,160	900	446.4	0.68 (0.60-0.78)
Donation status				
First†	26,004	1770	680.7	1.19 (1.08-1.30)
Repeat	128,303	6491	505.9	1.00 Reference
Sex				
Female†	13,113	1043	795.4	1.69 (1.52-1.86)
Male	141,194	7218	511.2	1.00 Reference
Device (MCS vs. Alyx)				
MCS†	98,392	5442	553.1	1.17 (1.09-1.26)
Alyx	55,915	2819	504.2	1.00 Reference

* Regions using both devices (MCS and Alyx; two regions; 51,801 donations) and 16-year-olds (62 donations) who experienced seven minor reactions were excluded from the analysis.
† Significant differences between the group and the reference.

TABLE 5. Multivariate logistic regression analysis of variables associated with LOC and major systemic reactions after 2RBC donation*

Variable	Donations	Events	Reaction rate/10,000	Adjusted OR (95% Wald CI)
Donor age (years)				
17	14,636	34	23.2	1.66 (0.99-2.67)
18	10,051	14	13.9	0.95 (0.50-1.80)
19	4,133	8	19.4	1.31 (0.60-2.85)
20-29	19,484	29	14.9	1.00 Reference
30-39‡	18,098	14	7.7	0.52 (0.27-0.97)
40-49‡	29,667	16	5.4	0.35 (0.19-0.65)
50-59‡	30,850	18	5.8	0.37 (0.21-0.67)
60+‡	19,266	6	3.1	0.20 (0.08-0.47)
Donation status				
First	24,280	46	19.0	†
Repeat	121,905	93	7.6	†
Sex				
Female	12,085	15	12.4	†
Male	134,100	124	9.3	†
Device (MCS vs. Alyx)				
MCS‡	93,048	98	10.5	1.63 (1.13-2.36)
Alyx	53,137	41	7.7	1.00 Reference

* Regions using both devices (MCS and Alyx; two regions; 51,801 donations) and 16-year-olds (62 donations) who experienced seven minor reactions were excluded from the analysis.
† Donation status and sex did not select into the model.
‡ Significant differences between the group and the reference.

For young donors, 2RBC collections are associated with substantially lower rates of minor and major systemic reactions than WB collections, principally because the rate of adverse reactions after 2RBC procedures is relatively constant for donors under the age of 20 years while the rates after WB donation are inversely related to age (Fig. 1). At age 19 years, there is no difference in reaction rates, and at younger ages, 2RBC procedures are associated with fewer minor adverse reactions than WB collections for 17-year-old donors (754.2 vs. 1102.9 per 10,000 donations; OR, 0.66; 95% CI, 0.62-0.69) and 18-year-old donors (789.1 vs. 910.6 per 10,000 donations; OR, 0.86; 95% CI, 0.80-0.91; Fig. 1). The overall incidence of minor reactions is higher after 2RBC procedures than WB donation for donors 20 years or older. For major phlebotomy-related events, no difference was seen between 2RBC and WB collections, except in 2RBC donors older than 40 years of age (3.4 vs. 2.2 per 10,000 donations; OR, 1.55, 95% CI, 1.12-2.15), who are more likely to suffer large hematomas (data not shown).

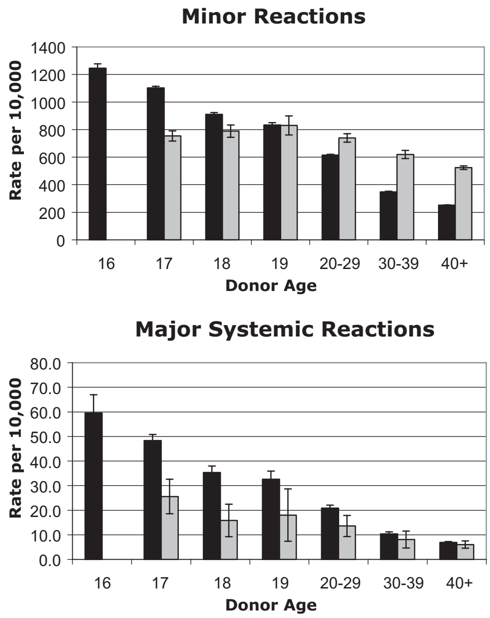

Fig. 1. The rates (95% CI) of adverse events after WB (■) and 2RBC (□) collections per 10,000 donations, analyzed by age group (years). The number of collection procedures performed in each age group is shown in Tables 2 and 3.

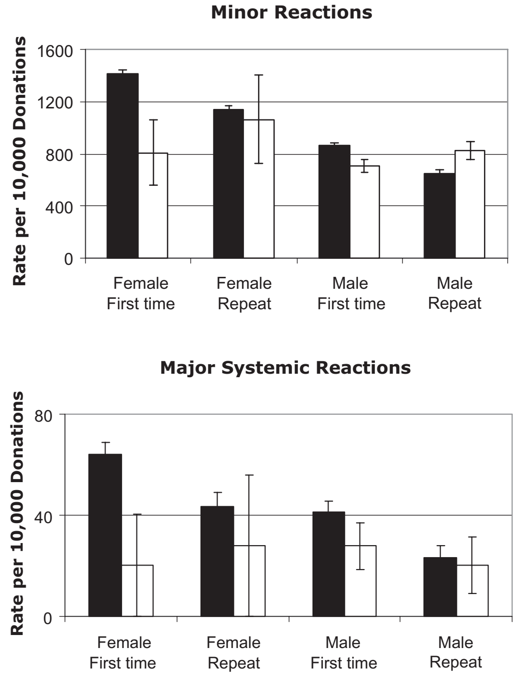

Fig. 2. Rates of adverse events per 10,000 collections in 17-year-old WB (■) and 2RBC (□) donors.

Outside medical care after 2RBC donations was sought by 71 2RBC and 1814 WB donors for minor, major systemic, or major phlebotomy-related issues. The need for outside medical care after WB and 2RBC donations was similar among all donors (4.2 vs. 3.4 per 10,000 collections; OR, 0.82; 95% CI, 0.65-1.04) and among donors 20 years or older (3.4 vs. 3.7 per 10,000 donations; OR, 0.92; 95% CI, 0.70-1.20). Donors younger than 20 years, however, were significantly less likely to require outside medical care after 2RBC procedures than WB collections (3.8 vs. 7.0 per 10,000 donations; OR, 0.53; 95% CI, 0.32-0.89).

Analysis of 17-year-old donors

We further characterized reactions experienced by 17-year-old donors after WB and 2RBC donations. Minor adverse events were significantly less likely after 2RBC procedures compared to WB donation for both female first-time (808.1 vs. 1420.1 per 10,000 donations; OR, 0.53, 95% CI, 0.38-0.73) and male first-time (709.2 vs. 870.4 per 10,000 donations; OR, 0.80, 95% CI, 0.75-0.86) donors, but more frequent among male repeat donors (827.2 vs. 654.2 per 10,000 donations; OR, 1.29, 95% CI, 1.17-1.42; Fig. 2). The rate of major systemic reactions tended to be lower for 2RBC procedures compared to WB donation, although the difference only reached significance in male first-time donors (27.8 vs. 41.4 per 10,000 donations; OR, 0.67, 95% CI, 0.47-95). Finally, major phlebotomy-related events were rare in all subgroups precluding meaningful comparisons (data not shown).

Return rates after 2RBC donations in donors 17 to 19 years of age

To assess the effect of adverse reactions on the likelihood of return donation, we identified a cohort of 18,308 17- to 19-year-olds who donated 2RBC between January 1, 2007, and June 30, 2007, and evaluated return donations in the following 365 days. The cohort contained 9132 (50%) individuals who had previously donated blood (i.e., repeat donors), including 3073 prior 2RBC donations (data not shown). In the year after the index 2RBC donation, 6166 (33.7%) donors presented to donate either WB or 2RBC again and there was no significant difference in return rates for those donors who experienced a minor reaction during the index donation compared with those who had no reaction (Table 6). Because of the rarity of major complications after 2RBC donations, only 16 donors were identified for this cohort, of which only 3 (18.8%) donors returned to donate blood. This rate of return after a major reaction was not statistically different compared to the rate of return of donors who had no reaction (OR, 0.46; 95% CI, 0.10-1.49). Forty-five percent (2774 of the 6166) of returning donors had a successful, second 2RBC donation in the year after their index donation. Overall return rates showed significant differences by age group, with 60.9% of 17-year-olds (1264/2077), 32.1% of 18-year-olds (3279/10,215), and 27.0% of 19-year-olds (1623/6016) presenting to donate again within 1 year (Table 6).

Finally, 55 of 286 (19.2%) female and 26 of 5880 (0.4%) male 17- to 19-year-old 2RBC donors who returned to

TABLE 6. Return donation behavior of donors after an index 2RBC donation in the period January 1, 2007, to June 30, 2007*

		Proportion of 2RBC donors with subsequent presentation to donate WB or 2RBC			
Variable	Age (years):	17	18	19	17-19
Total		1,264/2,077 60.9%	3,279/10,215 32.1%	1,623/6,016 27.0%	6,166/18,308 33.7%
No reaction		1,195/1,950 61.3%	3,070/9,595 32.0%	1,507/5,647 26.7%	5,772/17,192 33.6%
Minor reaction		68/125 54.4%	208/608 34.2%	115/367 31.3%	391/1,100 35.5%
OR (95% CI)		NS	NS	NS	NS
No reaction vs. minor		1.33 (0.92-1.91)	0.90 (0.76-1.08)	0.80 (0.64-1.00)	0.92 (0.81-1.04)

* Seventeen-year-olds were more likely to return than 18-year-olds (OR, 1.90; 95% CI, 1.75-2.05), who were more likely to return than 19-year-olds (OR, 1.19; 95% CI, 1.11-1.27).

donate again were deferred for low Hb/Hct (data not shown). An independent survey of 547,366 17- to 19-year-old WB donors who presented to the same American Red Cross regions in 2007 showed that 19.3% (58,233 of 301,377) of females and 0.4% (1016 of 245,989) of males were deferred for low Hb/Hct, indicating no significant difference ($p > 0.05$) in the rate of Hb/Hct deferral subsequent to a 2RBC or WB donation.

DISCUSSION

Blood donation is generally considered a safe procedure, a conclusion substantiated by early wartime studies and decades of subsequent experience.[7,8] Most blood donors do not experience adverse reactions and immediate complications are usually minor discomforts such as small hematomas and mild presyncope reactions. Several studies, however, have demonstrated that WB donors who experience even minor reactions are less likely to return to donate again.[6,9-14] Of further concern are reports showing that the risk of adverse reactions is highest in young, first-time donors, during a period when more and more donations are solicited at high schools and many states have reduced their minimum donation age (usually with parental consent) to 16 years.[5,15] A renewed focus on donor safety and more comprehensive study of adverse events associated with current blood center practices is warranted to identify possible interventions to protect donors from harm and to encourage return donation.

The donor selection criteria and donation interval for 2RBC collections are more stringent than for WB donation (Table 1). Despite these precautions, automated procedures continue to receive closer regulatory scrutiny than manual WB collection. 2RBC donations expose donors not only to the risks of phlebotomy, but also to those of an apheresis procedure (e.g., citrate toxicity), and the theoretical harm of losing twice as much RBC mass and iron than WB donation. The acute effects of 2RBC donation were previously compared with WB donation in a large multicenter study of 249,154 2RBC procedures.[4] Focusing on "moderate" and "severe" events, these authors demonstrated a reaction rate of 47.1 per 10,000 donations, which was significantly lower than the rate recorded for WB collections. These findings complement several smaller studies of 2RBC donation by autologous donors, some of whom had a history of myocardial infarction.[2,16,17] Although the results of published studies cannot be directly compared because of differences in donor selection criteria and classification schemes for donor reactions, hemovigilance data from 228,183 2RBC collections performed in 2006 in the American Red Cross system also support the safety of automated collections.[5,6] The overall rate of reactions after 2RBC procedures was 538.3 per 10,000 procedures, which was significantly higher than WB collections (OR, 1.57; 95% CI, 1.54-1.60). However, this data set, unlike others reported in the literature, captures the most common adverse events after 2RBC donation, which are mild reactions such as small hematomas, presyncopal reactions, and minor citrate reactions (217.9, 195.2, and 112.8 per 10,000 procedures, respectively).[4] Major reactions occurred at a rate of 3.3 per 10,000 procedures and were significantly less frequent after 2RBC procedures than WB collections (OR, 0.45; 95% CI, 0.36-0.57). The need for outside medical care after automated procedures compared to WB donation was not significantly different.

Herein, we report a more detailed analysis of complications after 2RBC procedures compared to WB donation, with the focus on the potential safety advantage for young donors, with respect to immediate reactions. This analysis was limited to 206,570 procedures in 26 regions that performed more than 50 procedures in 17-year-old donors and hence is not directly comparable to that previously reported from 2006 that incorporated all Red Cross regions. A total of 91.6% of 2RBC collections were performed on male donors, which reflects the donor selection criteria utilized and a slightly higher proportion of 2RBC collections was performed on young donors compared to WB.

The overall adverse event rate was 627.9 per 10,000 procedures, which was significantly greater (OR, 1.44; 95%

CI, 1.41-1.47) than that seen after WB collections. The most frequent events were minor citrate reactions (117.4 per 10,000 procedures) and small hematomas that were 2.2-fold more common than WB collections (309.8 per 10,000 procedures; OR, 2.25; 95% CI, 2.19-2.31). Presyncopal reactions were significantly less common (185.6 per 10,000 procedures; OR, 0.67; 95% CI, 0.64-0.68) than WB collections. Consistent with the observations of Wiltbank and Giordano,[4] we found that major systemic events, especially those related to vasovagal reactions, (LOC, LOC with injury, prolonged recovery) were less common in 2RBC collections (10.2 per 10,000 procedures; OR, 0.71; 95% CI, 0.62-0.82). Large hematomas (2.6 per 10,000 procedures; OR, 2.88; 95% CI, 2.16-3.84) were more common and arterial punctures were less common (0.2 per 10,000 procedures; OR, 0.18; 95% CI, 0.07-0.50) with 2RBC procedures than WB donation, with the net effect being no significant difference in major phlebotomy-related events recorded at the collection sites. By including reports of phlebotomy-related injuries called back to blood centers, the rate of nerve injury for automated collections is significantly but only marginally higher than for WB donations (4.0 vs. 3.2 per 10,000; OR, 1.25; 95% CI, 1.14-1.36; data not shown). The basis for this difference is not clear. Adverse events classified as minor allergic, minor "other" and major "other" were all rare, but statistically more common in 2RBC procedures than WB collections.

Taken together, 2RBC collections are associated with lower risk of vasovagal-type reactions but an increased risk of hematomas (small and large) and citrate reactions. Hematomas are almost certainly related to the need to reinfuse blood during the apheresis procedure and the longer duration of phlebotomy. Inadequate needle placement during this phase is more likely to lead to extravasation of blood into perivascular tissue than with conventional phlebotomy for WB donation. Citrate reactions are related to the rate and concentration of acid-citrate-dextrose anticoagulant infusion and are usually mild and managed without a need to discontinue the procedure. The multivariate analysis identified device type (defined by blood region) as a significant predictor of minor and major reactions. The devices differ with respect to several procedural variables (e.g., anticoagulant WB ratio, extracorporeal volume per cycle, return flow rate, anticoagulant type); however, we recognize significant variability in the reported reaction rates among our regions, and a major limitation of the current analysis is the inability to analyze device type independently of variation in regional reporting. Our results are therefore hypothesis generating and support the need for controlled prospective studies comparing the rates of adverse reactions with different 2RBC technologies.

The most interesting observation in this study is the effect of age on the relative difference on reactions after 2RBC compared to WB donation. Donors younger than 20 years are less likely to experience a minor or major reaction during 2RBC donation than WB donation. In contrast, donors 20 years or older are more likely to experience a minor reaction during 2RBC than WB donation, but are at no greater risk for a major reaction. These data suggest that 2RBC procedures, with the current restrictions in place in the American Red Cross, are safer than WB collections for young donors and support the recruitment of young donors for 2RBC collections. This safety margin may reflect either the different selection criteria or other factors such as the use of saline replacement and the smaller needle used with 2RBC procedures. Our data cannot directly answer this question; however, it is interesting that even among 17-year-old male first-time donors, a group in which approximately 75% of donors would meet the Red Cross 2RBC selection criteria,[18] minor and major systemic events are significantly less likely with 2RBC procedures than WB donation. Similarly, Kamel and colleagues[19] have recently reported that 2RBC collections have a lower rate of moderate and severe adverse outcomes in a population of male donors with blood volumes of more than 3.9 L, all of whom would meet the eligibility criteria for 2RBC donation.

Furthermore, while our data do not directly address donations by 16-year-old donors, it is likely that 2RBC donation would also be associated with fewer immediate complications than WB donation. Most states require parental consent for a donation by a 16-year-old; consequently, parental consent should be obtained specifically for 2RBC donation in this age group.

The further advantage of 2RBC donation for young donors is supported by the high rate of return to donate again within 1 year of an index donation, even in donors who suffer minor adverse events. Similarly, in a much smaller study examining only male 2RBC donors, Rader and coworkers[20] showed no effect of minor reactions on the return rate on repeat donors, while first-time donors were less likely to return after a minor reaction. An overall rate of return of 33.7% in 17- to 19-year-old donors is remarkable, given the 16-week deferral after 2RBC donation, while a decline in return rates from 60.9% in 17-year-olds to 27.0% in 19-year-olds is in keeping with a similar trend seen in WB donors.[21] The fact that 45% of returning donors chose to again donate using the 2RBC procedure is also encouraging, as an opportunity to donate with this technology is not always available at every blood drive.

The relevance of our findings for older donors deserves careful consideration. We and others have observed increased reactions among 2RBC donors compared to WB donation, even among repeat donors, primarily due to the relatively higher incidence of minor or light reactions with 2RBC procedures.[20,22] In this study, minor reactions were more common in 2RBC donors 20 years and older and major phlebotomy-related events were more common in donors 40 years and older than in WB donations. Major systemic events, however, are lower for 2RBC donations in all age groups, including LOC with injury and prolonged recovery, which lead to some of the most potentially dangerous outcomes. The fact that most events in older donors are minor discomforts, including citrate toxicity and small hematomas, and that the overall incidence of major phlebotomy-related complications is very low (approx. 3.5 per 10,000 procedures in donors >40 years old) again argues for the overall acceptability of 2RBC donation in older donors.

Finally, we have not addressed the issue of iron balance in blood donors, which deserves special attention in adolescents who have particular iron requirements during a period of growth. Young donors are known to have especially marginal iron stores.[23] 2RBC or WB donation may provoke an iron depletion state in donors with borderline stores and inadequate diets. Latent iron depletion, even in the absence of iron deficiency anemia, may be associated with fatigue, low physical endurance, and impaired cognition.[24] Clearly, 2RBC donors, especially young donors, must be encouraged to replace iron lost through blood donation with appropriate diet or possibly iron supplementation. Radtke and coworkers[25] have shown that daily iron supplementation between 2RBC donations resulted in stable ferritin levels and reduced the deferral rates due to low Hb. The transfusion community has an incomplete understanding of the optimal approach to Hb screening and iron balance in blood donors; consequently, several studies, including the NIH-funded RISE (REDSII Donor Iron Status Evaluation) study are currently under way.

Overall, our data support the general safety of 2RBC procedures with the donor selection criteria in place in the American Red Cross and provide a strong rationale for recruitment of young donors. We support the further evaluation of iron status in susceptible blood donor populations and endorse clear educational messages to young donors about the importance of good nutrition and adequate iron status, as well as further study on refining the current donor selection criteria for the minimum Hb/Hct and donation interval to reduce the risk of iron depletion with frequent blood donation.

CONFLICT OF INTEREST

RJB is a scientific advisor and consultant to Fenwal, Inc. The other authors report no conflict of interest with respect to the work reported here.

REFERENCES

1. Whitaker B, Sullivan M. The 2007 national blood collection and utilization survey report. Rockville (MD): The United States Department of Health and Human Services; 2008. Available from URL: http://www.hhs.gov/ophs/bloodsafety/2007nbcus_survey.pdf
2. Popovsky MA. Safety of 2-RBC donation: donor and recipient considerations. Transfus Apher Sci 2006;35:3-4.
3. Popovsky MA. Guest editor's introduction to transfusion and apheresis science: red cell automation. Transfus Apher Sci 2006;34:203-4.
4. Wiltbank TB, Giordano GF. The safety profile of automated collections: an analysis of more than 1 million collections. Transfusion 2007;47:1002-5.
5. Eder AF, Hillyer CD, Dy BA, Notari EP, Benjamin RJ. Adverse reactions to allogeneic whole blood donation by 16- and 17-year-olds. JAMA 2008;299:2279-86.
6. Eder AF, Dy BA, Kennedy JM, Notari EP IV, Strupp A, Wissel ME, Reddy R, Gibble J, Haimowitz MD, Newman BH, Chambers LA, Hillyer CD, Benjamin RJ. The American Red Cross donor hemovigilance program: complications of blood donation reported in 2006. Transfusion 2008;48:1809-19.
7. Poles FC, Boycott M. Syncope in blood donors. Lancet 1942;240:531-5.
8. Popovsky MA, Whitaker B, Arnold NL. Severe outcomes of allogeneic and autologous blood donation: frequency and characterization. Transfusion 1995;35:734-7.
9. Halperin D, Baetens J, Newman B. The effect of short-term, temporary deferral on future blood donation. Transfusion 1998;38:181-3.
10. Newman BH. Vasovagal reactions in high school students: findings relative to race, risk factor synergism, female sex, and non-high school participants. Transfusion 2002;42:1557-60.
11. Newman BH. Vasovagal reaction rates and body weight: findings in high- and low-risk populations. Transfusion 2003;43:1084-8.
12. Newman BH, Roth AJ. Estimating the probability of a blood donation adverse event based on 1000 interviewed whole-blood donors. Transfusion 2005;45:1715-21.
13. Newman BH, Newman DT, Ahmad R, Roth AJ. The effect of whole-blood donor adverse events on blood donor return rates. Transfusion 2006;46:1374-9.
14. Custer B, Johnson ES, Sullivan SD, Hazlet TK, Ramsey SD, Hirschler NV, Murphy EL, Busch MP. Quantifying losses to the donated blood supply due to donor deferral and mis-collection. Transfusion 2004;44:1417-26.
15. Wiltbank TB, Giordano GF, Kamel H, Tomasulo P, Custer B. Faint and prefaint reactions in whole-blood donors: an analysis of predonation measurements and their predictive value. Transfusion 2008;48:1799-808.
16. Axelrod FB, Catton P, Beller SA. A comparison of post donation reactions in 2 unit automated red cell apheresis collections using the Haemonetics MCS+ with 1 unit manual whole blood collection in autologous donors. Transfusion 1995;35 Suppl l:65S.

17. Schmidt AL, Randels J, Wieland M, Strauss RG. Collection of 2 unit autologous or allogeneic red blood cells by apheresis using Haemonetics MCS+. J Clin Apher 1997;12:41.
18. Newman BH, Satz SL, Janowicz NM, Siegfried BA. Donor reactions in high-school donors: the effects of sex, weight, and collection volume. Transfusion 2006;46:284-8.
19. Kamel H, James R, Bravo M, Tomasulo P, Custer B. Adverse reactions in whole blood and automated 2-unit red cell donations among 2RBC-eligible allogeneic male donors: a multivariate analyis. Vox Sang 2009;96 Suppl 1; P-187 (abstract).
20. Rader AW, France CR, Carlson B. Donor retention as a function of donor reactions to whole-blood and automated double red cell collections. Transfusion 2007;47:995-1001.
21. Notari EP IV, Zou S, Fang CT, Eder AF, Benjamin RJ, Dodd RY. Age-related donor return patterns among first-time blood donors in the United States. Transfusion 2009. In press.
22. Chambers LA, Kennedy JM, Dy BA. Increased rate of prefaint reactions to double red cell collections. Transfusion 2005;45 Suppl:23A (abstract).
23. Halterman JS, Kaczorowski JM, Aligne CA, Auinger P, Szilagyi PG. Iron deficiency and cognitive achievement among school-aged children and adolescents in the United States. Pediatrics 2001;107:1381-6.
24. Moore SB, Winters JL. Multiple blood donations and iron deficiency in patients with restless legs syndrome. Mayo Clin Proc 2003;78:654-5.
25. Radtke H, Mayer B, Rocker L, Salama A, Kiesewetter H. Iron supplementation and 2-unit red blood cell apheresis: a randomized, double-blind, placebo-controlled study. Transfusion 2004;44:1463-7.