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Original Contribution

Preoperative Blood Volume Deficit Influences Blood Transfusion Requirements in Females and Males Undergoing Coronary Bypass Graft Surgery

Ketan Shevde, MD,* Murali Pagala, PhD,† Changa Tyagaraj, MS,‡ Chiedozie Udeh, MD,§ Mamatha Punjala, MD,§ Sunita Arora, MD,§ Abdelhamid Elfaham, PhD‖

Department of Anesthesiology, Maimonides Medical Center, Brooklyn, NY

Study Objective: *To evaluate whether preoperative blood volume and postoperative blood loss influence blood transfusion in females and males undergoing coronary artery bypass graft (CABG) surgery.*
Design: *Prospective study.*
Setting: *Anesthesiology department of a teaching hospital.*
Patients: *57 CABG patients (21 females and 36 males).*
Measurements: *Blood volume was determined using the radioactivity dilution method. Preoperatively, each patient received intravenous (IV) injection of 1 mL Albumin I_{131} tracer having 25 microcuries of radioactivity. Five-milliliter blood samples were collected at different intervals. From these samples, hematocrit (Hct) value, preoperative total blood volume, red blood cell (RBC) volume, and plasma volume were determined. Postoperatively, some consenting patients received another 1 mL dose of the tracer, and the postoperative blood volumes were determined. If a patient received a blood transfusion, the units of packed red blood cells (PRBCs), platelets, or fresh frozen plasma (FFP) transfused were recorded. For each patient we recorded the gender, age, weight, height, body surface area (BSA), preoperative Hct, duration of surgery, and discharge Hct.*
Results: *Preoperatively, the mean total blood volume, RBC volume, and plasma volume, respectively, were 2095 mL/m^2, 631 mL/m^2, and 1,465 mL/m^2 in females; and 2,580 mL/m^2, 878 mL/m^2, and 1,702 mL/m^2 in males. The preoperative blood volumes were significantly lower ($p < 0.01$) in females than in males. There was no significant difference between males and females in the extent of blood loss during CABG. Intraoperatively, females received PRBC transfusion of 1.38 units, significantly more ($p < 0.01$) than the 0.39 units received by males. During the entire hospital stay, females received 4.33 units of PRBC, significantly more than ($p < 0.02$) the 1.33 units received by males. Significantly more ($p < 0.01$) females (12 of 21) received intraoperative PRBC transfusion than did males (6 of 36). Multiple logistic regression analysis of the data*

*Chairman, Department of Anesthesiology

†Research Director

‡Research Assistant

§Resident

‖Radiation Safety Officer

Address correspondence to Dr. Shevde at the Department of Anesthesiology, Maimonides Medical Center, 4802 Tenth Avenue, Brooklyn, NY 11219.

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655 Avenue of the Americas, New York, NY 10010

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showed that PRBC transfusion was significantly correlated with the preoperative total blood volume and RBC volume.
Conclusion: *The greater need for blood transfusion in females than in males during CABG is primarily attributable to significantly lower preoperative total blood volume and RBC volume in females.*

Keywords: Blood transfusion; blood volume; coronary artery bypass graft surgery; gender difference; RBC volume.

Introduction

Females are known to receive more blood transfusion than males during coronary artery bypass graft (CABG) surgery.[1–4] The reason for such a gender difference in the requirement for blood transfusion is not fully understood. Previous studies have reported that blood transfusion in CABG patients was significantly influenced by age, gender, weight, body surface area (BSA), preoperative hematocrit (Hct), previous CABG, coagulation defects, insulin-dependent diabetes mellitus, and severe clinical complications.[4–8] Low Hct, which is characteristic of females, was suggested to be a major reason for the greater need for blood transfusion in females.[8] However, gender difference in transfusion need was persistent even when male and female CABG patients with similar preoperative Hct levels were compared.[4,9] Our previous studies further showed that differences in age, weight, and duration of surgery could not account for the gender difference in transfusion need, but gender by itself was an independent determining factor.[9]

The present study was aimed at understanding the characteristics by which gender can have an influencing role in determining the blood transfusion for CABG surgery. Calculations based on Hct and total body mass show that females have lower blood volume and red blood cell (RBC) mass than males.[2,10] Although these factors theoretically may account for the gender difference in the need for blood transfusion during CABG surgery, no direct measurements were made to establish such a relationship. In the present study, the volumes of total blood, RBC, and plasma were measured in female and male patients before CABG surgery, and their relationship to the transfusion of blood received by them was evaluated. The role of blood loss during the operation as a possible contributing factor to this gender difference in transfusion was also evaluated by measuring the blood volumes in some patients before and after CABG surgery.

Materials and Methods

After obtaining Maimonides Medical Center Institutional Review Board approval, 57 consenting patients undergoing CABG surgery were prospectively studied from June 1999 to March 2001. The patients included 21 females and 36 males. Pregnant women and patients who had multiple procedures or repeat operations were not included in this study.

Preoperatively, aspirin was stopped 10 days before elective surgery, and those patients taking coumadin were switched to heparin. Standardized anesthesia consisted of midazolam 2 to 4 mg, sufentanil 100 to 150 μg, and rocuronium 50 to 100 mg intravenously (IV) for induction and tracheal intubation. Anesthesia was maintained with incremental doses of midazolam, rocuronium, and isoflurane as needed, and remifentanil infusion (15–30 μg/min) intraoperatively. Inpatients who underwent CABG with the use of a cardiopulmonary bypass (CPB) pump, activated clotting times were maintained at approximately 500 seconds with heparin 3 mg/kg prebypass, and then as needed every 20 minutes on CPB. Cardiotomy suction and cell savers were used in all cases. Autologous blood (500 mL) was withdrawn from every patient on initiation of CPB and then re-transfused post-CPB. Hollow fiber oxygenators were used for all cases (Duroflow II, Jostra Bentley Corporation, Irvine, CA). Pump prime consisted of plasmacyte 500 mL and hetastarch 1,000 mL.

Blood volume was determined using the computerized BVA-100 Blood Volume Analyzer (DAXOR Corporation, New York, NY). In principle, this analyzer uses the dilution of injected I_{131}-labeled serum albumin to determine the plasma volume of the patient. Using the measured Hct value, it calculates the total blood volume and the RBC volume of the patient.[11] The blood volumes were determined preoperatively in all of the 21 females and 36 males, and both preoperatively and postoperatively in 6 females and 15 males who consented to take part in the extended study.

For preoperative determination of the blood volumes, approximately 45 minutes before surgery, each patient received IV injection of 1 mL Albumin I_{131} tracer containing 25 microcuries of radioactivity. Five-milliliter blood samples were collected at 12, 17, 22, 30, and 35 minutes after the injection, and placed in separate tubes. From each tube, 0.5 mL of the blood was used for determining the Hct value. Remaining blood was centrifuged at 3,500 rpm for 5 minutes, and 1 mL of the plasma sample was pipetted out into each of two tubes. The tubes were placed in opposite wells of the rotary sample tray in the BVA-100. This action was repeated for the other four blood samples collected. Two tubes with a control solution containing 25 microcuries of radioactivity were also placed in the sample tray to serve as standards. DAXOR blood volume analysis software ran the blood volume determination protocol. Each patient's I.D. number, age, gender, weight, height, exact times of the five blood sample collections, and the replicate Hct values were entered into the worksheet. The computer printed out the values for experimentally determined volumes of total blood, RBCs, and plasma; the calculated ideal volumes (V_Ts), and the percent deviation of each of the determined volumes from their respective V_Ts.

For postoperative determination of the blood volumes, approximately 2 to 4 hours after the CABG surgery, the patient received another IV dose of 1 mL Albumin I_{131} tracer containing 25 microcuries of radioactivity. Five-milliliter blood samples were collected at 12, 17, 22, 30, and 35 minutes after the injection, and processed as

Table 1. Clinical Data of the Coronary Artery Bypass Graft (CABG) Patients Included in the Study

Parameter	Females (n = 21)	Males (n = 36)	Significance of Difference
Age (yrs)	70.5 ± 8.4	66.6 ± 9.1	
Weight (kg)	72.3 ± 13.8	78.5 ± 14.8	
BSA (m^2)	1.73 ± 0.20	1.93 ± 0.21	$p < 0.001$
Duration of surgery (hrs)	4.3 ± 0.85	4.3 ± 0.96	
Preop Hct (%)	33.5 ± 3.4	37.8 ± 5.2	$p < 0.01$
Discharge Hct (%)	30.2 ± 4.5	29.2 ± 3.4	

Note: Values are means ± SD obtained from the number of patients indicated in parentheses. Significance of differences between females and males were calculated by Student's *t*-test for unpaired variates.

BSA = body surface area, Hct = hematocrit.

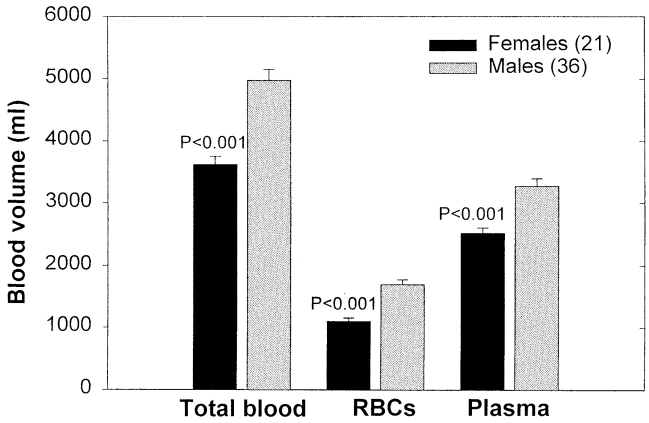

Figure 1. Preoperatively measured total blood volume, red blood cell (RBC) volume, and plasma volume in female and male patients who had coronary artery bypass graft (CABG) surgery. Each bar represents the mean value and the vertical line represents the standard deviation value obtained from the number of females and males indicated in parentheses. The difference between the mean values in females and males was evaluated by Student's *t*-test for unpaired variates.

described above. From the preoperative and postoperative values, percent loss in total blood volume, RBC volume, and plasma volume following surgery were calculated for each patient.

Blood transfusion was initiated if the patient's Hct decreased to 18% or less intraoperatively or postoperatively. Units of PRBCs, platelets, or fresh frozen plasma (FFP) transfused intraoperatively and/or postoperatively were recorded.

The experimental data were analyzed using SigmaStat and graphically represented using SigmaPlot software packages (SPSS Inc., Chicago, IL). The values of different parameters collected from the CABG patients are expressed as means ± SD. Significance of difference between females and males with respect to each parameter was evaluated by Student's *t*-test for unpaired variables. Difference between females and males with respect to preoperative and postoperative blood volumes, and thus the blood loss, was assessed by two-factor analysis of variance (ANOVA). Difference in the number of females and males who received transfusion of PRBCs was assessed using the Chi-square test. The relationship between transfusion and different blood volumes in females and males was assessed by multiple logistic regression analysis. The dependent variable transfusion had a value of 1 for "transfused" and 0 for "not transfused", and the independent variables—total blood, RBC, and plasma volumes—had continuous values, whereas gender had a value of 0 for "female" and 1 for "male".

Results

Clinical Features

Among the female and male CABG patients studied, there was no significant difference in the mean age, weight, and duration of surgery (*Table 1*). Mean BSA was 1.73 m^2 in females and 1.93 m^2 in males, and it was significantly lower ($p < 0.001$) in females than in males (*Table 1*). Mean preoperative hematocrit was 33.5% in females and 37.8% in males, and it was significantly lower ($p < 0.01$) in females than in males. There was no significant difference in discharge hematocrit between females and males.

Preoperative Blood Volumes

The experimentally determined mean total blood volume, RBC volume, and plasma volume were, respectively, 3,619 mL, 1,098 mL, and 2,520 mL in females; and 4,972 mL, 1,696 mL, and 3,276 mL in males (*Figure 1*). The total blood volume was 27.2% lower ($p < 0.001$), RBC volume was 35.2% lower ($p < 0.001$), and plasma volume was 23.1% lower ($p < 0.01$) in females than in males (*Figure 1*). When the blood volumes were normalized with respect to BSA of each patient, mean total blood volume, RBC volume, and plasma volume were, respectively, 2,095 mL/m^2, 631 mL/m^2, and 1,465 mL/m^2 in females; and 2,580 mL/m^2, 878 mL/m^2, and 1,702 mL/m^2 in males. These values were still significantly lower ($p < 0.01$) in females than in males.

Postoperative Loss of Blood Volumes

Following surgery, the mean loss in total blood volume was 3.1% in the 6 females and 8.9% in the 15 males who consented to undergo blood volume determinations both before and after CABG (*Table 2*). The mean loss in RBC volume was 6.5% in females and 23.7% in males, and the mean loss in plasma volume was 0.5% in females and 0.7% in males (*Table 2*). Two-factor ANOVA showed that there was no significant difference between female and male CABG patients in postoperative loss of blood volumes.

Among the 21 patients who consented to undergo blood volume determinations both before and after CABG, 12 had CABG performed on-pump and 9 had it performed off-pump. However, unpaired *t*-test showed no

Table 2. Postoperative Blood Loss in Male and Female Coronary Artery Bypass Graft (CABG) Patients

Parameter	Preoperative	Postoperative	Postoperative Loss (%)
Females (n = 6)			
Total blood volume (mL/m^2)	2269 ± 268	2189 ± 373	−3.1 ± 15.2
RBC volume (mL/m^2)	681 ± 58	635 ± 121	−6.5 ± 18.9
Plasma volume (mL/m^2)	1589 ± 263	1554 ± 275	−0.5 ± 20.0
Males (n = 15)			
Total blood volume (mL/m^2)	2909 ± 451	2599 ± 297	−8.9 ± 16.2
RBC volume (mL/m^2)	996 ± 228	733 ± 100	−23.7 ± 16.9
Plasma volume (mL/m^2)	1913 ± 287	1866 ± 224	−0.7 ± 17.8

Note: Values are means ± SD obtained from the number of patients indicated in parentheses. Two-way analysis of variance showed no significant difference in blood loss between males and females following CABG surgery.

RBC = red blood cells.

significant difference between these two groups in the percent loss of different blood volumes in connection with the CABG procedure (*Table 3*). Of the 12 on-pump cases, four were females and eight were males. Of the nine off-pump cases, two were females and seven were males. Two-way ANOVA showed no significant difference between these four groups in the percent loss of different blood volumes in connection with the CABG procedure (*Table 3*).

PRBCs Transfused

The mean PRBCs transfused intraoperatively were 1.38 units for females and 0.39 units for males, and the intraoperative transfusion was significantly higher ($p < 0.01$) for females than for males (*Figure 2*). For the entire hospital stay, the mean PRBCs transfused were 4.33 units for females and 1.33 units for males, and the entire hospital stay transfusion was also significantly higher ($p < 0.02$) for females than for males (*Figure 2*). Two-way ANOVA showed that females received significantly more ($p < 0.05$) PRBC transfusion than males both in on-pump and off-pump cases, although there was no significant difference between the two procedures in transfusion. There was no significant difference between female and male CABG patients in transfusion of platelets or FFP.

Number of Patients Who Received PRBC Transfusion

Intraoperatively, 12 of 21 (57.1%) females and 6 of 36 (16.7%) males received PRBC transfusion (*Figure 2*). Chi-square analysis showed that significantly more ($p < 0.01$) females than males received blood transfusion intraoperatively. During the subsequent stay in the hospital, additional patients received a PRBC transfusion. As a result, during the entire hospital stay, 15 of 21 (71.4%) females and 17 of 36 (47.2%) males received PRBC transfusion (*Figure 2*). However, there was no significant difference in the number of females and males who received PRBC transfusion during the entire hospital stay.

Multiple Logistic Regression Analysis of PRBC Transfusion

Multiple logistic regression analysis showed that intraoperative PRBC transfusion had a significant correlation with preoperative total blood volume ($p < 0.005$) and RBC

Table 3. Postoperative Percent Blood Loss in On-pump and Off-pump Coronary Artery Bypass Graft (CABG) Patients

	Total Blood Volume	RBC Volume	Plasma Volume
All on-pump patients (12)	−5.8 ± 13.9	−18.6 ± 21.0	1.8 ± 15.8
All off-pump patients (9)	−9.2 ± 18.6	−18.9 ± 16.7	−3.9 ± 20.9
On-pump females (4)	4.6 ± 9.2	0.5 ± 19.7	7.8 ± 16.7
Off-pump females (2)	−18.4 ± 14.0	−20.5 ± 4.2	−17.1 ± 18.3
On-pump males (8)	−11.0 ± 13.3	−28.3 ± 14.5	−1.2 ± 15.6
Off-pump males (7)	−6.6 ± 19.8	−18.5 ± 19.2	−0.1 ± 21.3

Note: Values are means ± SD obtained from the number of patients indicated in parentheses.

Unpaired *t*-test showed no significant difference in blood loss between all on-pump and all off-pump patients following CABG surgery.

Two-way analysis of variance showed no significant difference in blood loss between on-pump and off-pump female and male patients following CABG surgery.

RBC = red blood cells.

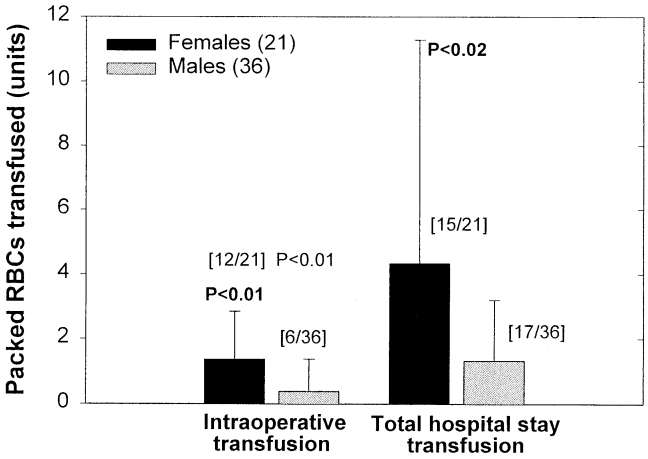

Figure 2. Packed red blood cells (PRBCs) transfused intraoperatively and during the entire hospital stay in females and males who underwent coronary artery bypass graft (CABG) surgery. Each bar represents the mean value and the vertical line represents the standard deviation value obtained from the number of females and males indicated in parentheses. The difference between the mean values in females and males was evaluated by Student's *t*-test for unpaired variates. The number of female and male CABG patients who received transfusion is shown in brackets, and the difference between the relative numbers was evaluated using the Chi-square test.

volume ($p < 0.002$) (*Table 4*). Similarly, entire hospital stay transfusion also had a significant correlation with preoperative total blood volume ($p = 0.039$) and RBC volume ($p < 0.010$). The odds ratios for total blood volume and RBC volume were close to 1 for both intraoperative and entire hospital stay transfusions (*Table 4*), indicating that the odds of transfusion increases by 1 with a unit decrease in RBC volume or total blood volume. Preoperative plasma volume was not included in the regression model, because it showed co-linearity with total blood volume. Intraoperative transfusion or entire hospital stay transfusion did not have a significant correlation with gender. The probability of transfusion intraoperatively or during the entire hospital stay can be determined using the logistic equations derived from the constants and the coefficients of the independent variables shown in *Table 4*.

Discussion

In the present study, we employed the "gold standard" radioactive tracer dilution method[11–13] to determine experimentally the preoperative blood volume, and we evaluated its relationship to the blood transfusion received by female and male CABG patients. This study clearly showed that among patients scheduled for CABG surgery, preoperative volumes of total blood, RBCs, and plasma were significantly lower in females than in males (*Figure 1*). This finding is consistent with the lower RBC volume calculated for females based on body weight and preoperative Hct.[2,10] The differences in blood volumes were not due to significantly lower body mass of the females compared with males (*Table 1*), because even when the blood volumes were normalized with respect to BSA, females still had significantly lower total blood, RBC, and plasma volumes. These results clearly show that females had markedly lower total blood and RBC volumes than males even before the start of the CABG procedure, indicating that preoperative blood and RBC volumes may have a significant influence on the greater need for blood transfusion in female CABG patients.

Female CABG patients received significantly more units of PRBC transfusions both intraoperatively and during the entire hospital stay compared with males (*Figure 2*). In addition, significantly more females than males received PRBC transfusion intraoperatively, and considerably more females than males received PRBC transfusion during the entire hospital stay (*Figure 2*). However, females were not over transfused compared with males because there was no significant difference between females and males in the discharge Hct (*Table 1*).

This greater blood transfusion received by females was not due to greater loss of blood during surgery, because our measurements in 6 female and 15 male CABG patients showed a similar change in the postoperative total blood,

Table 4. Multiple Logistic Regression Analysis of the Relation between Packed Red Blood Cell (PRBC) Transfusion and Preoperative Blood Volumes in Male and Female Coronary Artery Bypass Graft (CABG) Patients

Parameter	Coefficient	*p*-value	Odds Ratio	95% Confidence Interval
Intraoperative PRBC transfusion				
Constant	−0.433			
Total blood volume	0.00512	0.005*	1.005	1.002–1.009
RBC volume	−0.0158	0.002*	0.984	0.974–0.994
Gender	−1.519	0.104	0.219	0.035–1.370
Entire hospital stay PRBC transfusion				
Constant	1.259			
Total blood volume	0.0025	0.039*	1.003	1.00–1.005
RBC volume	−0.0089	0.010*	0.991	0.985–0.998
Gender	−0.176	0.815	0.839	0.193–3.652

RBC = red blood cells.

*Significant correlation between PRBC transfusion and the independent variable.

RBC, and plasma volumes compared with the respective preoperative volumes (*Table 2*). This finding is consistent with an earlier report indicating that intraoperative blood loss was approximately equal in males and females for similar surgical procedures.[14] The blood losses were not significantly different between females and males who had the CABG performed on-pump or off-pump (*Table 3*).

Hence, the greater PRBC transfusion in female CABG patients may be closely related to the differences in their preoperative blood and RBC volumes. This relationship was evaluated using multiple logistic regression analysis. Logistic regression was preferred over linear regression because it enabled assessment of the role played by binary variables such as female/male in determining the transfusion outcome. This analysis showed that the total blood volume and RBC volume were significantly correlated with the outcome whether or not a patient received a PRBC transfusion (*Table 4*). The plasma volume varied co-linearly with total blood volume, and thus it did not have an independent influence on the transfusion. Contrary to our earlier finding,[9] in the present study gender did not have an independently significant correlation with the outcome for transfusion. In the present study, the preoperative blood volumes were actually measured rather than calculated on the basis of body weight and Hct as in the previous study. It has been shown that Hct could not reliably predict the RBC mass in individual patients.[15] Hence, the gender difference in blood transfusion during CABG surgery may be attributable mainly to preoperative differences in actual blood and RBC volumes. Although there may be few other factors that might account for the gender difference in the need for blood transfusion, based on the results of the present study, it can be suggested that greater need for blood transfusion in females compared with males during CABG surgery is primarily attributable to significantly lower preoperative total blood volume and RBC volume in females than in males. Because of the reduced oxygen carrying capacity, deficit in RBC volume is more critical than the deficit in total volume of the blood.

The reasons for the lower RBC volume in females compared with males are not clear. RBCs are derived from stem cells in the bone marrow, and need the hormone erythropoietin for differentiation into functional RBCs.[16] Synthesis of erythropoietin requires vitamin B_{12} and folic acid,[16] and deficiency in these factors can lead to deficiency in RBC volume. The action of erythropoietin also needs iron, and it is known that normal men have approximately 50 mg/kg iron while normal women have approximately 35 mg/kg iron.[16] The lower iron content can also contribute to lower RBC volume in females compared with males. Our future research would involve determination of the levels of iron, vitamin B_{12}, folic acid, and erythropoietin in the blood samples from female and male CABG patients, and to assess whether preoperative treatment of these patients with these agents would reduce the need for blood transfusion.

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