CARDIOPULMONARY SUPPORT AND PHYSIOLOGY

RETROGRADE AUTOLOGOUS PRIMING FOR CARDIOPULMONARY BYPASS: A SAFE AND EFFECTIVE MEANS OF DECREASING HEMODILUTION AND TRANSFUSION REQUIREMENTS

Todd K. Rosengart, MD
William DeBois, BS, CCP
Maureen O'Hara, RN
Robert Helm, MD
Maureen Gomez, RN
Samuel J. Lang, MD
Nasser Altorki, MD
Wilson Ko, MD
Gregg S. Hartman, MD
O. Wayne Isom, MD
Karl H. Krieger, MD

Objectives: **The obligatory hemodilution resulting from crystalloid priming of the cardiopulmonary bypass circuit represents a major risk factor for blood transfusion in cardiac operations. We therefore examined whether retrograde autologous priming of the bypass circuit would result in decreased hemodilution and red cell transfusion.** ***Methods:*** **Sixty patients having first-time coronary bypass were prospectively randomized to cardiopulmonary bypass with or without retrograde autologous priming. Retrograde autologous priming was performed at the start of bypass by draining crystalloid prime from the arterial and venous lines into a recirculation bag (mean volume withdrawal: 880 ± 150 ml). Perfusion and anesthetic techniques were otherwise identical for the two groups. The hematocrit value was maintained at a minimum of 16% and 23% during and after cardiopulmonary bypass, respectively, in all patients. Patients were well matched for all preoperative variables, including established transfusion risk factors. Subsequent hemodynamic parameters, pressor requirements, and fluid requirements were equivalent in the two groups.** ***Results:*** **The lowest hematocrit value during cardiopulmonary bypass was 22% ± 3% versus 20% ± 3% in patients subjected to retrograde autologous priming and in control patients, respectively ($p = 0.002$). One (3%) of 30 patients subjected to retrograde autologous priming had intraoperative transfusion, and seven (23%) of 30 control patients required transfusion during the operation ($p = 0.03$). The number of patients receiving any homologous red cell transfusions in the two groups during the entire hospitalization was eight of 30 (27%; retrograde autologous priming) versus 16 of 30 (53%; control) ($p = 0.03$).** ***Conclusions:*** **These data suggest that retrograde autologous priming is a safe and effective means of significantly decreasing hemodilution and the number of patients requiring red cell transfusion during cardiac operations.**
(J Thorac Cardiovasc Surg 1998;115:426-39)

Homologous blood transfusions remain a persistent risk of cardiac operations. Two to four donor exposures are required in up to 70% of patients, despite the recent introduction of many innovative blood conservation techniques.[1-4] In fact, coronary bypass grafting has been associated with about 10% of all blood transfusions in the United States.[5] Hemodilution, the direct result of the mixing of the patient's blood volume with the crystalloid cardiopulmonary bypass (CPB) circuit prime, is a unique and obligatory feature of cardiac surgery as currently practiced that imposes a significant risk for red blood cell transfusions.[6, 7] In this regard, the decrease in hematocrit value associated with hemodilution may lead to obligatory red cell transfusions resulting from unacceptably lowered hematocrit values during or after cardiac operations. Incremental improvements have been made in decreasing the hemodilution associated with CPB, such as through the use of "low prime" oxygen-

From The New York Hospital–Cornell Medical Center, Department of Cardiothoracic Surgery, New York, N.Y.

This work was supported in part from a grant from Miles (Bayer) Pharmaceuticals, New Haven, Conn., to T.K.R.

Read at the Twenty-third Annual Meeting of The Western Thoracic Surgical Association, Napa, Calif., June 25-28, 1997.

Received for publication Feb. 14, 1997; revisions requested May 7, 1997; revisions received June 6, 1997; accepted for publication June 9, 1997.

Address for reprints: Todd K. Rosengart, MD, The New York Hospital–Cornell Medical Center, Department of Cardiothoracic Surgery, 525 East 68th St., F-2103, New York, NY 10021.

0022-5223/98 $5.00 + 0 **12/6/83788**

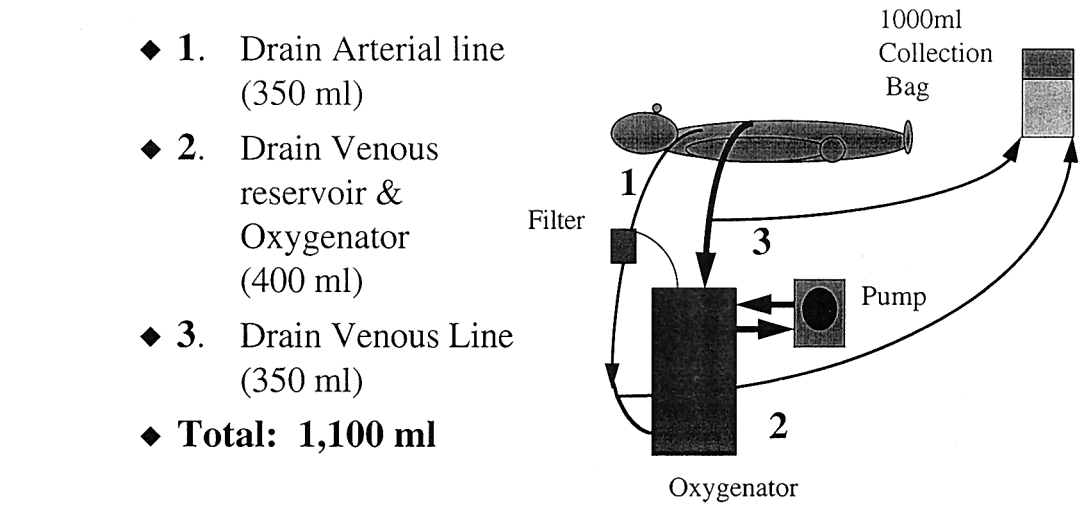

Fig. 1A. Schema of the RAP technique. *1,* Arterial line drainage. While systolic arterial blood pressure is being maintained greater than 100 mm Hg, the recirculation line clamp is slowly released, and blood travels through the pump arterial line from the aorta though the filter, into the recirculation line, and up into a 1000 ml transfer bag. *2,* Venous reservoir and oxygenator drainage. The line between the oxygenator and arterial line filter is clamped and the recirculation line is unclamped. The arterial pump is slowly advanced until the venous reservoir volume drops to 200 ml. At this time, the arterial line filter purge is opened and the arterial pump is again advanced until the fluid exiting the oxygenator outlet became sanguineous. The arterial pump is stopped and the pump outlet and recirculation lines are clamped. The recirculation line is then removed from the 1000 ml bag and attached to the recirculation port on the oxygenator reservoir. *3,* Venous line drainage. As bypass is commenced, the venous line prime is drained into the recirculation bag, and this ¼-inch line is clamped once the venous line fluid becomes sanguineous. The recirculation bag is rehung to allow for crystalloid transfusion as necessary.

ators.[6, 7] Nevertheless, we hypothesized that a significant margin for minimizing hemodilution and thereby decreasing homologous red cell transfusions could be achieved with the use of a technique called retrograde autologous priming (RAP). With this technique, the crystalloid CPB prime is evacuated from the pump circuit at the initiation of bypass in advance of the patient's blood column.

Our strategy would bring nearly full circle the technique of blood versus crystalloid priming. The CPB circuit had historically been primed with up to 8 units of whole blood. Subsequently, the virtues of moderate and even "extreme" hemodilution in terms of blood circulation, microcirculatory flow, and organ function were advanced,[8-12] and use of an asanguineous pump prime ultimately received widespread acceptance. In 1960, Panico and Neptune[13] described a technique to eliminate donor blood prime from the CPB circuit by instead substituting 1 L of physiologic saline solution. After arterial cannulation, the patient's blood was drained retrogradely into the CPB circuit. Panico and Neptune[13] demonstrated in a series of 25 patients that the use of a bloodless prime reduced homologous blood transfusions. Thirty-seven years later, we now report a modification of their technique in which we use currently available technologies that decreases the number of patients requiring homologous red cell transfusions associated with "excessive" hemodilution during CPB.

Patients and methods

Study design. Sixty patients having first-time coronary bypass were prospectively randomized by envelope selection without replacement to CPB with (n = 30) or without (n = 30) RAP. Exclusion criteria were age less than 18 or greater than 85 years, left ventricular ejection fraction less than 30%, emergency procedure, history of stroke, hematocrit value less than 30%, and weight less than 55 or greater than 115 kg. Physicians ordering blood transfusions were blinded for randomization. Informed consent

The Journal of Thoracic and
Cardiovascular Surgery
February 1998

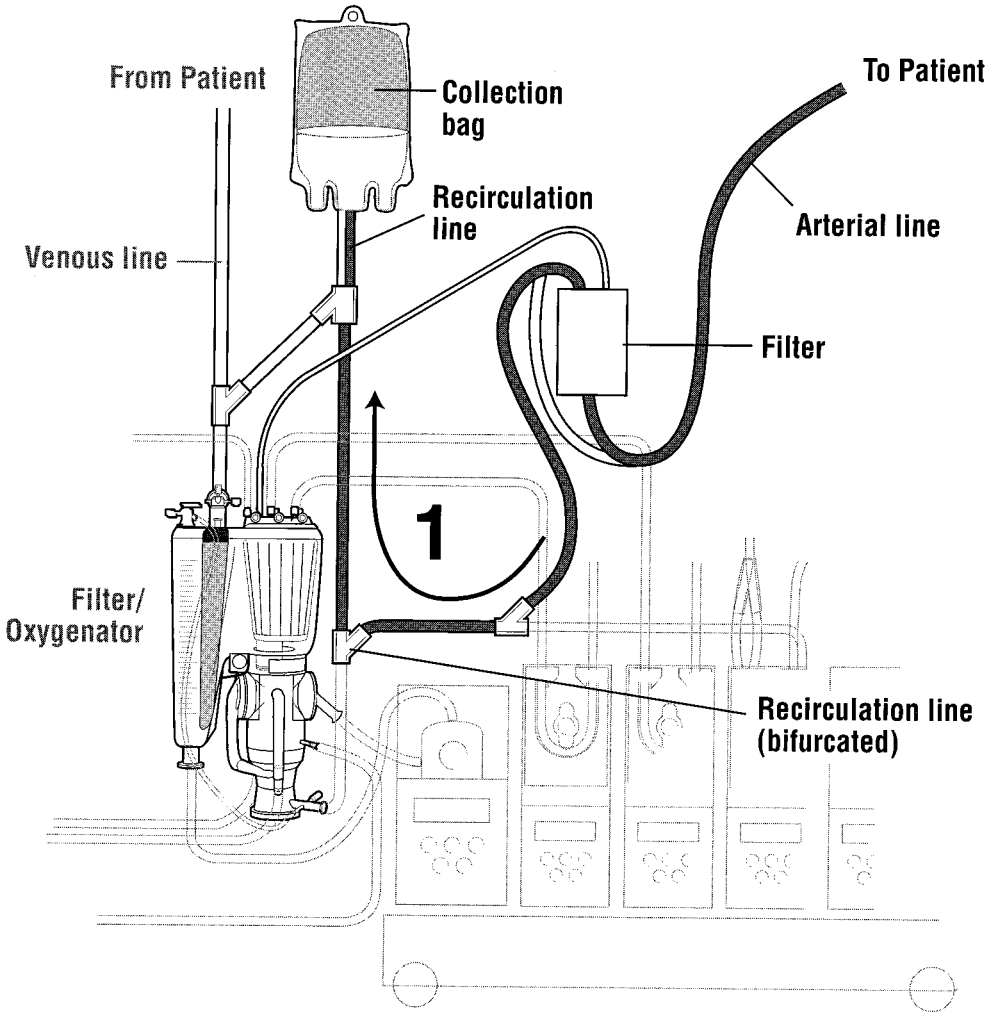

Fig. 1B. Detailed schema of drainage of arterial line.

and was obtained from each patient and the study was approved by the Investigational Review Board of The New York Hospital–Cornell Medical Center.

Anesthesia and CPB setup. Patients received lorazepam and morphine intramuscularly for premedication before arrival in the operating room. Anesthesia was induced with intravenous fentanyl, thiopental, and midazolam. Muscle relaxation was achieved with pancuronium. After intubation, anesthesia was maintained with a combination of fentanyl, midazolam, and isoflurane. Hemodynamic monitoring and blood sampling were obtained by means of radial and pulmonary artery catheters. A urinary catheter with indwelling temperature probe was used for urine output measurements and core temperature assessment.

The extracorporeal circuit consisted of a hollow-fiber membrane with integral cardiotomy (Terumo Medical Corporation, Somerset, N.J.), centrifugal arterial pump (Bio-Medicus, Medtronic Bio-Medicus, Eden Prairie, Minn.), 4:1 "coil in bucket" blood cardioplegia set (Gish Biomedical Incorporated, Irvine, Calif.), arterial line filter, and a polyvinylchloride tubing set. The total pump prime was 1400 ml, which consisted of 1100 ml of electrolyte solution (Plasma-Lyte 7.4, Abbott), 10,000 units U.S. Pharmacopeia porcine mucosa heparin, 100 ml normal serum albumin, and 200 ml 20% mannitol. A calculated volume of intraoperative autologous donation blood was withdrawn at the start of the operation to yield a CPB hematocrit value of at least 18%, as previously described.[14] Initial heparin dosing (300 units/kg) was followed by a standard cannulation of the ascending aorta and right atrium with 20F and 36/51F two-stage venous cannulas, respectively (Sarns/3M, Inc., Ann Arbor, Mich.).

RAP. For the implementation of RAP, a ¼-inch recirculation line was diverted off the arterial outlet line of the oxygenator. This line was attached to a 1000 ml blood transfer bag, which was hung on the pump mast 20 cm higher than the right atrium. In addition, a ¼-inch line was "y'd" off the venous line just before its connection to

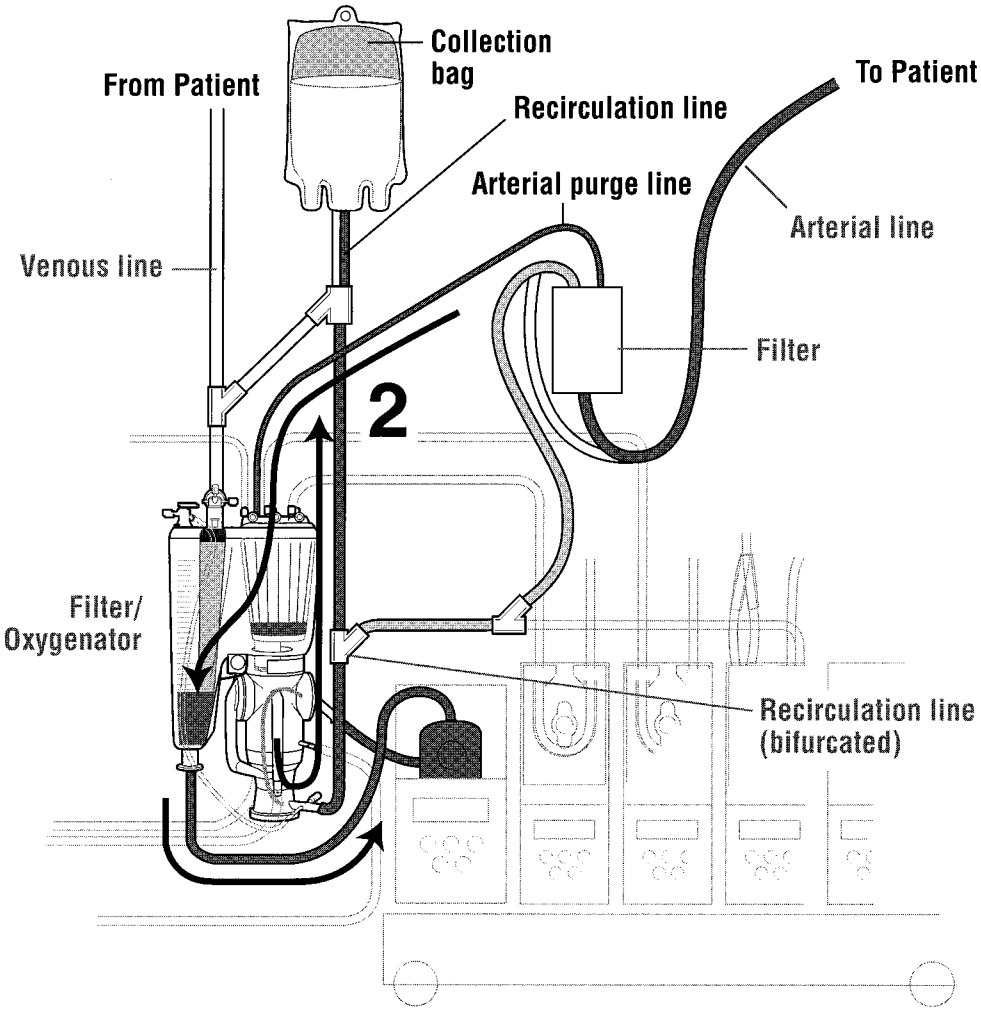

Fig. 1C. Detailed schema of venous reservoir and oxygenator.

the venous inlet of the oxygenator. During the entire RAP process, a minimum systolic blood pressure of 100 mm Hg was maintained with oxymetazoline HCl (Neo-Synephrine), as needed. RAP was implemented in three stages, beginning after the activated clotting time (International Technidyne Corporation, Edison, N.J.) reached 400 seconds, as follows (Fig. 1):

1. Arterial line drainage. With the systolic arterial blood pressure maintained greater than 100 mm Hg, the recirculation line clamp was slowly released. This allowed for the patient's blood to travel through the pump arterial line from the aorta through the filter, into the recirculation line, and up into the 1000 ml transfer bag. Up to 400 ml was recovered from the pump circuit at this time.

2. Venous reservoir and oxygenator drainage. The line between the oxygenator and arterial line filter was clamped and the recirculation line was unclamped. The arterial pump was slowly advanced until the venous reservoir volume decreased to 200 ml. At this time, the arterial line filter purge was opened and the arterial pump was again advanced until the fluid exiting the oxygenator outlet became sanguineous. The arterial pump was stopped and the pump outlet and recirculation lines were clamped. An additional 300 ml was removed in this manner. The recirculation line was then removed from the 1000 ml bag and attached to the recirculation port on the oxygenator reservoir. After this, the 1000 ml bag was lowered to allow for additional drainage from the venous line.

3. Venous line drainage. As CPB was initiated, almost all of the 400 ml of pump prime from the venous line was drained into the recirculation bag. Once the venous line fluid became sanguineous, this ¼-inch line was clamped. The bag was then rehung to allow for crystalloid transfusion as necessary. The targeted RAP volume to be withdrawn was 1100 ml.

Performance of CPB. CPB was otherwise conducted as per standard practice in all patients. Mean arterial pressure was maintained at or greater than 50 mm Hg, and the venous reservoir was maintained at a level greater than

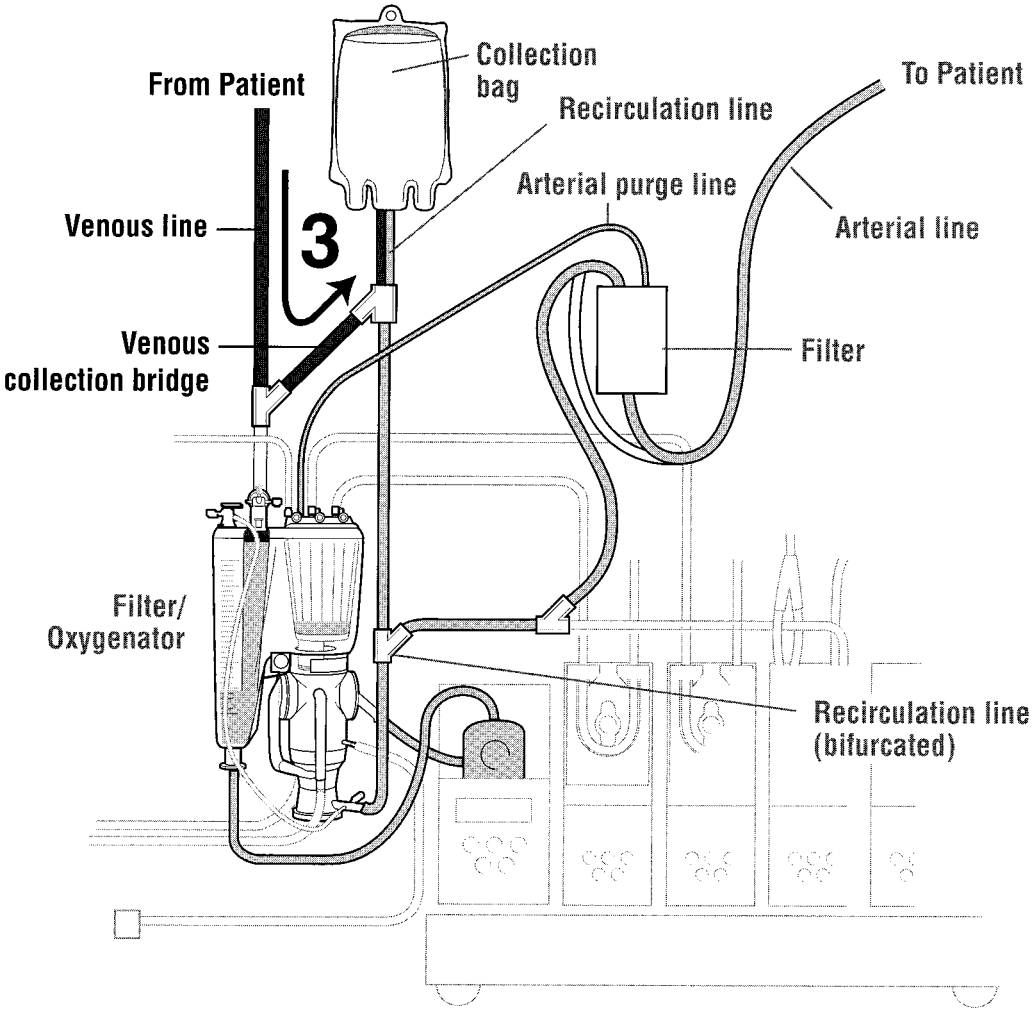

Fig. 1D. Detailed schema of venous line.

400 ml. Standard level sensor and air emboli detectors were used for protection against air embolism. Left ventricular venting was accomplished by means of the aortic root cannula. Pericardial blood was aspirated and collected in the reservoir. The hematocrit value was maintained at a minimum of 16%. Moderate hypothermia (bladder temperature $\geq$28° C) was used. Nonpulsatile flow rates during CPB ranged from 1.6 L/min per square meter during hypothermia up to 2.4 L/min per square meter during normothermia. The protocol mandated that hematocrit values be maintained at a level of 28% or less at all times during hypothermia by adding crystalloid solution, as needed. After aortic crossclamping, cold blood cardioplegic solution (15 ml/kg) was given at 15- to 20-minute intervals. Blood gases were managed by the alpha-stat method. Patients were slowly weaned from CPB when a bladder temperature of 35.5° C was reached. Heparin was neutralized with equal doses of protamine sulfate. Total fluid administration was measured. The pump contents and any additional fluid in the Cell Saver System (Sarns, Haemonetics Corp., Braintree, Mass.) were immediately processed and transfused after the patient's condition was deemed stable, and the aortic cannula was removed. The hematocrit value was maintained at a minimum of 23% after CPB.

Postoperative care. All patients were admitted to the intensive care unit and treated as per standard clinical practice. Platelets (6-unit pack) were transfused for chest tube drainage greater than 600 ml in the first 3 hours after the operation, followed by 2 units of fresh frozen plasma if subsequent drainage was greater than 100 ml/hr. Cardiac index was maintained greater than 2.0 L/min per square meter and mean arterial pressure was maintained at 60 mm Hg or higher by crystalloid infusion or vasoactive agents, as appropriate.

Data analysis. Data were collected as indicated by a research nurse who was blinded to the randomization. All patients were followed up until the day of discharge. Safety data included continuous intraoperative hemodynamic and electrocardiographic monitoring and analysis

Table I. *Patient characteristics and surgical data for control and RAP groups*

	Control group (n = 30)	*RAP group (n = 30)*
Age (yr)	64 ± 8	60 ± 9
Female	5/30	8/30
Weight (kg)	82 ± 11	81 ± 10
BSA (m^2)	2.0 ± 0.2	2.0 ± 0.2
Red cell mass (ml)	2040 ± 320	2040 ± 390
Preoperative hematocrit (%)	40 ± 4	41.6 ± 4
NYHA class (III or IV)	16/30	18/30
Ejection fraction (%)	47 ± 10	46 ± 10
Pump time (min)	83 ± 22	76 ± 28
Aortic clamp time (min)	45 ± 15	41 ± 16
IV NTG	3/30	4/30
ASA	11/30	12/30
Distal anastomoses	3.0 ± 0.5	2.9 ± 0.5

There were no significant differences between groups. All values are mean ± standard deviation, except proportions. *BSA,* Body surface area; *NYHA,* New York Heart Association; *IV NTG,* intravenous nitroglycerin within 24 hours; *ASA,* aspirin taken within 7 days.

Table II. *Patient risk factors for control group and RAP group*

	Control group (n = 30)	*RAP group (n = 30)*
Diabetes necessitating medication	4 (13%)	9 (30%)
COPD	3 (10%)	2 (7%)
PVD	4 (13%)	2 (7%)
HTN	15 (50%)	17 (57%)
Smoking history	11 (37%)	8 (27%)

There were no significant differences between groups. *COPD,* Chronic obstructive pulmonary disease; *PVD,* peripheral vascular disease; *HTN,* hypertension; *Smoking history,* smoking within 1 year.

of the postoperative electrocardiogram for myocardial infarction, blood urea nitrogen and creatinine for renal dysfunction, and survey for clinical evidence of cerebrovascular accidents. Data were collected and analyzed with the use of spreadsheet and analytical software (Excel, Microsoft Corporation, Redmond, Wash., and STATISTIX, Tallahassee, Fla.). By way of normalizing for red cell transfusions, a corrected hematocrit value was generated by subtracting the number of packed red cell transfusions times three from the measured hematocrit value obtained at all time points after these transfusions. Comparisons between groups of numeric values were made by means of a two-sample t test. The χ^2 test was used for comparison of proportions.

Results

Definition of populations and performance of RAP. Sixty adult patients scheduled for nonemergency primary coronary artery bypass were enrolled in this study over a 3-month period and randomized to CPB with or without RAP. All enrolled patients were included in the data analysis. The RAP and non-RAP groups were closely matched for established risk factors for transfusion, including age, sex, preoperative hematocrit value and red cell mass, aspirin ingestion, and other intraoperative variables (Table I). Patients were also closely matched for coexisting disease (Table II). No patients required any forms of ventricular assist, such as intraaortic balloon pumping. No complications or deaths occurred in either the RAP or control group.

A significant fraction of the crystalloid prime volume was replaced by the circulating blood volume removed from patients in the RAP group (mean volume withdrawal: 880 ± 150 ml, range**:** 600 to 1100 ml). This mean volume withdrawal, which was less than the 1100 ml target volume, reflects the relative ability to complete RAP in these patients. So that hemodynamic compromise could be avoided, systolic blood pressure was maintained at a minimum of 100 mm Hg during the RAP process, as described in the *Patients and methods* section. Although oxymetazoline was used in 13 (43%) patients in the RAP group to facilitate the performance of RAP, the total oxymetazoline dose during CPB was not significantly different in the RAP group from that in the control patients (0.8 ± 1.5 mg vs 1.5 ± 2.6 mg, respectively, $p = 0.27$). The entire RAP process was generally accomplished in less than 1 minute, although occasionally it required up to 5 minutes to complete. The mean arterial pressure and systemic vascular resistance were not significantly different 5 minutes after initiation of CPB in RAP compared with control patients (Fig. 2). The CPB flow rate at this time point was also similar in the RAP and control groups (4.5 ± 0.6 vs 4.7 ± 0.5 L/min, respectively, $p = 0.18$).

Hemodynamic and clinical outcome. The venous reservoir volume at the onset of CPB was significantly lower in the RAP group than in the control group, but it was maintained well above a safety threshold of 400 ml (Table III). This difference in reservoir volume was equalized as CPB continued, despite the fact that total intraoperative infusion of crystalloid solution (Table III) and hemodynamic parameters (Fig. 2) were equivalent for the two groups. The CPB flow rates were also equivalent in RAP compared with control patients throughout CPB (data not shown). The mean arterial pressure was maintained well above minimal safety margins in both patient groups at all times, as defined in the clinical protocol (see *Patients and methods*). Intraoperative and postoperative vasopressor administra-

The Journal of Thoracic and
Cardiovascular Surgery
February 1998

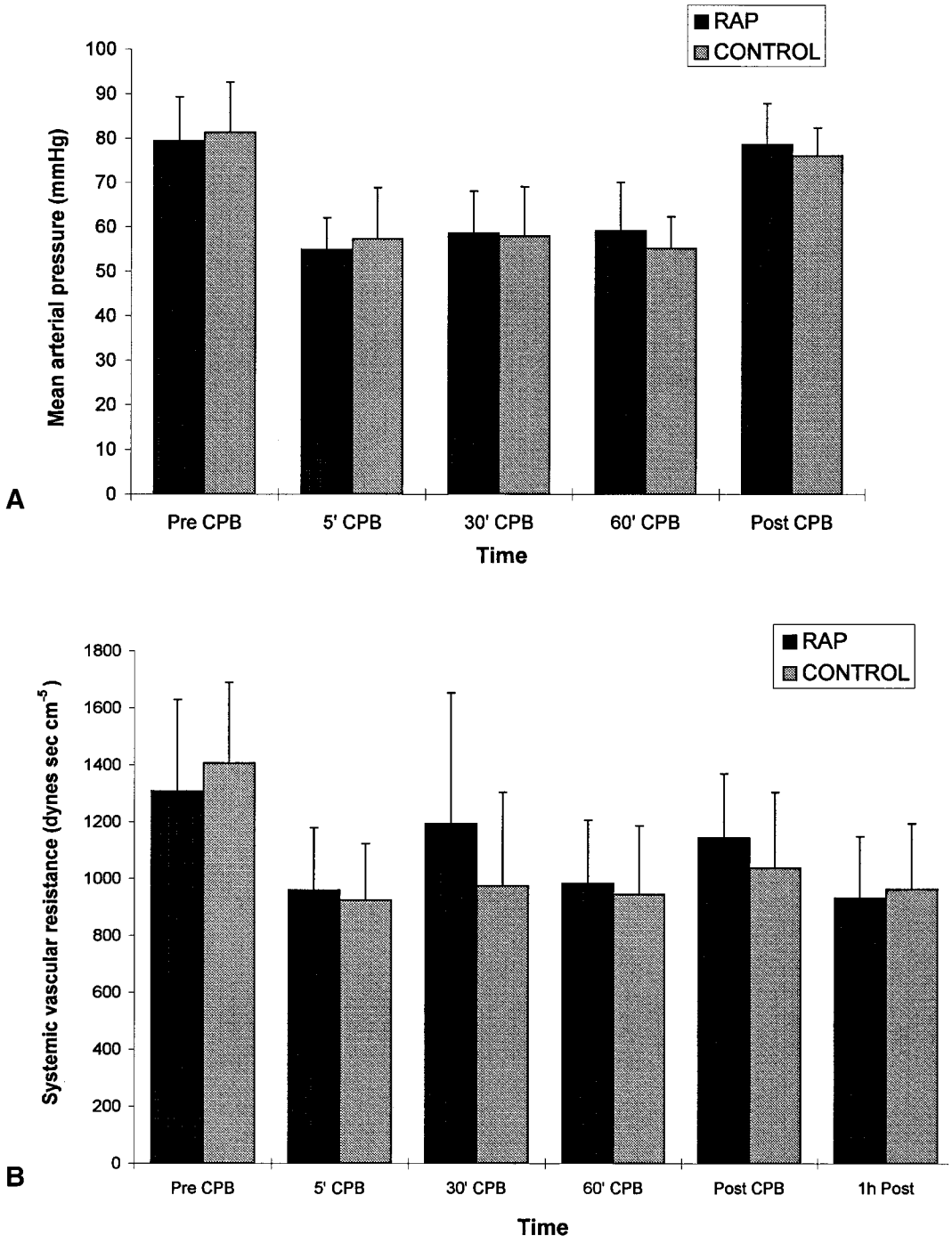

Fig. 2. A, Mean arterial pressure at various time points in RAP and non-RAP groups. **B,** Systemic vascular resistance at various time points in RAP and non-RAP groups.

tion was also similar for the RAP and non-RAP groups (Table IV). By the end of CPB, RAP volumes had to be reinfused in 19 (63%) of the patients (volume reinfused 720 ± 100 ml). Postoperative weight gain, measured as an indicator of third-space fluid sequestration, nevertheless demonstrated a statistically significant trend toward a lesser increase 36 hours after the operation in the RAP group as

Table III. *Fluid administration and RAP volumes during surgery*

	Control group (n = 30)	*RAP group (n = 30)*	*p Value*
Total crystalloid given (ml)	2330 ± 620	2420 ± 780	NS
RAP volume removed (ml)	0	880 ± 150	—
Intraoperative autologous donation (ml)	610 ± 360	780 ± 390	0.1
Postoperative weight gain (% increase from preop body weight)	2.4 ± 4.4	0.5 ± 2.5	0.075
Oxygenator reservoir volume			
Within 5 min of CPB	970 ± 490	480 ± 260*	0.001
Within 30 min of CPB	790 ± 490	600 ± 250	0.06
Within 60 min of CPB	610 ± 320	550 ± 330	0.6

Total crystalloid given, Crystalloid given by anesthesiologist or by CPB circuit in excess of pump prime before and during CPB; *RAP,* volume removed during RAP procedure (no volume was removed from control patients); *Postoperative weight gain,* measured 36 hours after operation; *Oxygenator reservoir volume,* volume in the venous reservoir during CPB; *NS,* not significant. Values reported are mean ± standard deviation.

compared with the control group (Table III). There were no deaths or clinical evidence of myocardial infarction, stroke, or renal dysfunction in either of the groups.

Transfusion and blood conservation indices. One (3%) of 30 patients in the RAP group received an intraoperative transfusion, compared with seven (23%) of 30 control patients ($p = 0.03$). Throughout the entire hospital stay, fewer patients in the RAP group (8 [27%] vs 16 [53%], $p = 0.03$) received packed red blood cells than did control patients. Among patients who received a transfusion, the number of homologous units of blood or blood products administered was similar in the RAP and the control groups (Table V).

Hematocrit values were equivalent or greater in the RAP group than in the control group from the time of initiation of CPB through the early postoperative period, despite the decrease in red cell transfusions in the former group (Fig. 3). The lowest hematocrit value during CPB was 22% ± 3% versus 20% ± 3% in the RAP and control groups, respectively ($p = 0.002$). Patients subjected to RAP, in fact, demonstrated even greater hematocrit values when this value was "corrected" for red blood cell transfusion (Fig. 4). Hematocrit values that exceeded the protocol limits were not encountered during CPB.

Postoperative platelet counts, prothrombin times, and partial thromboplastin times were not significantly different in RAP compared with control patients (data not shown), and although control patients demonstrated a trend toward greater chest drainage 6 and 24 hours after CPB, the difference between the groups was not statistically significant (Table V). Correspondingly, the transfusion of fresh frozen plasma and platelets was not significantly different between the two groups (Table V).

Table IV. *Supportive requirements in the operating room and ICU for control and RAP groups*

	Control group (n = 30)	*RAP group (n = 30)*
Vasopressors		
Operating room	20 (67%)	17 (57%)
ICU	6 (20%)	7 (23%)
Inotropic drugs		
Operating room	6 (20%)	5 (17%)
ICU	7 (23%)	8 (27%)
IABP	0 (0%)	0 (0%)

There were no significant differences between groups. *ICU,* Intensive care unit; *Vasopressor,* phenylephrine. *Inotropic drugs,* dobutamine and epinephrine; *IABP,* Intraaortic balloon pump.

Subset analysis. Additional analysis was performed on patients with a body surface area (BSA) less than 1.9 m^2 (lowest 30th percentile of study population). The decrease in the number of patients receiving transfusions in the low BSA group was not significantly greater than that for patients with a BSA greater than 1.9 m^2 (low BSA, 3 [30%] of 10 patients [RAP] vs 6 [67%] of 9 patients [control] receiving transfusions; high BSA, 5 [25%] of 20 patients [RAP] vs 10 [48%] of 21 patients [control] receiving transfusions).

Discussion

In the numerous recent trials, a variety of hemostatic agents have been demonstrated to result in dramatic reductions of postoperative blood loss and decreases in the number of transfusions associated with cardiac operations, but a significant number of patients in these studies have continued to require red cell transfusions.[4, 15-17] These findings highlight the critical contribution of factors other than bleed-

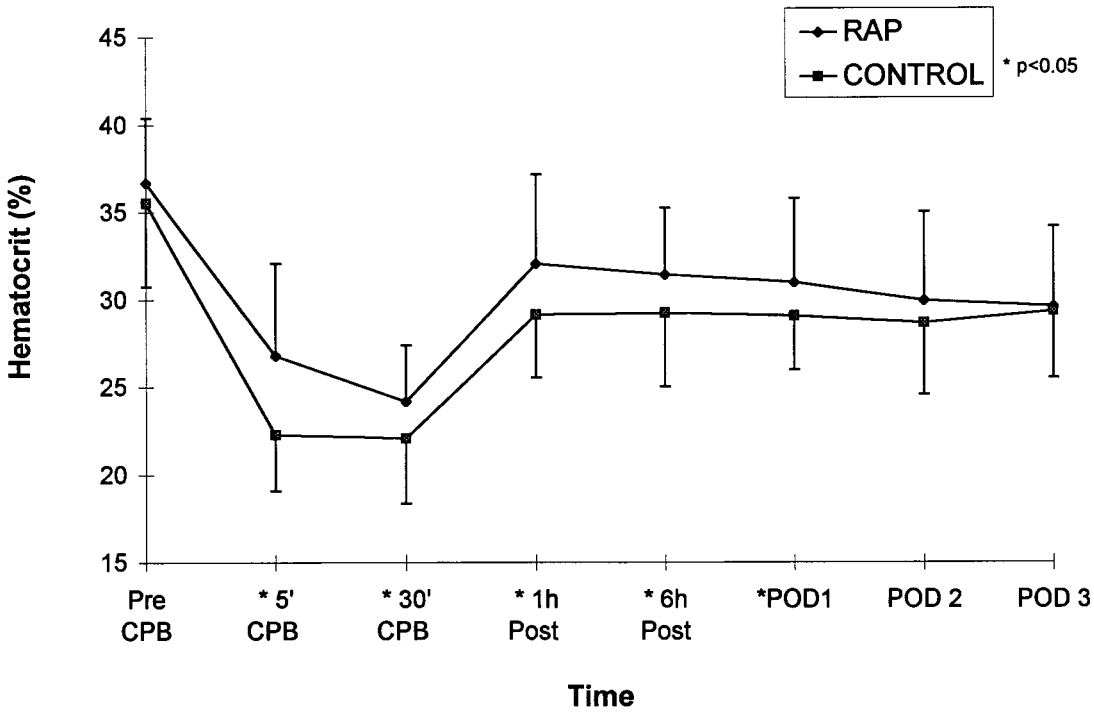

Fig. 3. Serial hematocrit values at various time points in RAP and non-RAP groups. *POD,* Postoperative day.

Table V. *Chest tube drainage and homologous transfusions*

	Control group (n = 30)	*RAP group (n = 30)*	*p Value*
Chest tube drainage (ml)			
6 hr	350 ± 330	325 ± 170	NS
24 hr	710 ± 470	660 ± 300	NS
Transfusions			
Patients given PRBCs intraop.	7 (23%)	1 (3%)	0.03
Patients given PRBCs during length of stay	16 (53%)	8 (27%)	0.03
Patients given platelets and/or FFP	6 (20%)	2 (7%)	0.13
PRBCs (units/patient transfused)	2.2 ± 1.1	2.0 ± 1.3	NS
Platelets (units/patient transfused)	9.0 ± 3.4	6.0 ± 0	NS
FFP (units/patient transfused)	2.3 ± 1.3	2.0 ± 0	NS

Values reported mean ± standard deviation. *PRBC,* Packed red blood cells; *FFP,* fresh frozen plasma; *NS,* not significant.

ing to the transfusion risk associated with cardiac operations. The hemodilution associated with the use of an asanguineous (crystalloid) CPB prime results in decreased intraoperative and postoperative hematocrit values in patients undergoing cardiac operations.[6, 7, 12] The current study demonstrated that RAP could safely be used to decrease the crystalloid pump prime and the hemodilution associated with this prime volume; in this way the number of patients requiring red blood cell transfusions could be reduced by avoiding the obligatory transfusions triggered by hematocrit values decreased below minimum safety triggers.

RAP and hemodilution. Patients undergoing cardiac operations who will require transfusions can be predicted before the operation by a number of variables, including red cell mass.[14, 18-20] This is consistent with the assumption that patients with a low red cell mass are more likely to have low hematocrit values and therefore require transfu-

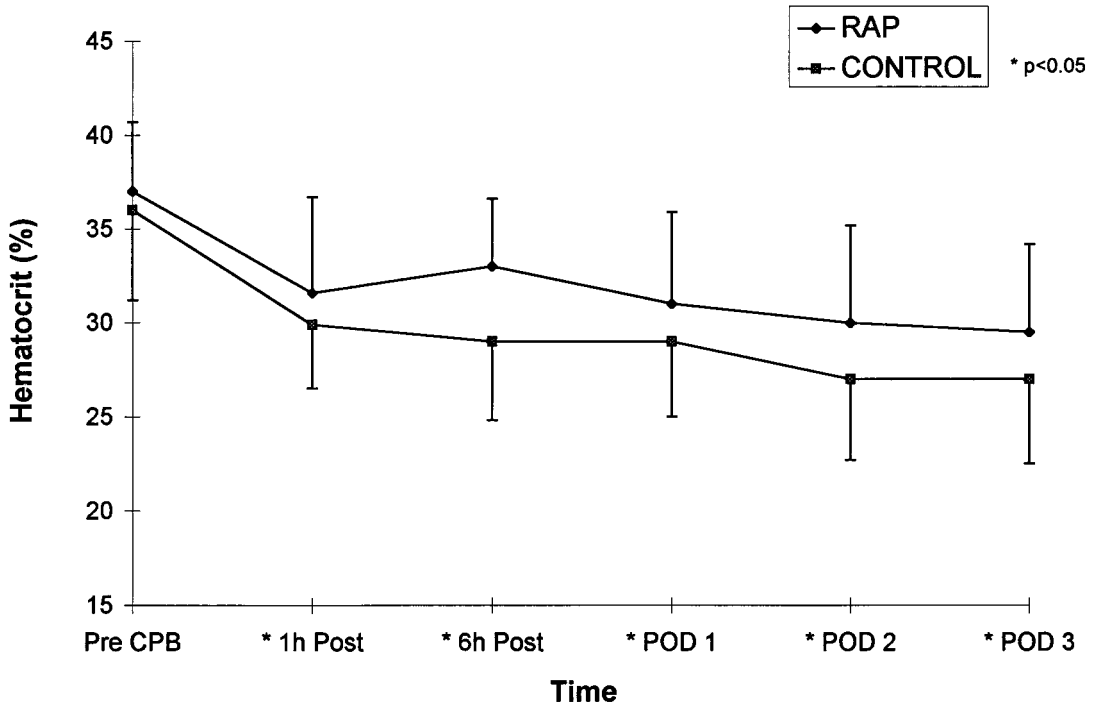

Fig. 4. Serial hematocrit values at various time points in RAP and non-RAP groups, "corrected" for homologous blood transfusions (three percentage points were subtracted from the hematocrit value for each unit of homologous red blood cells transfused to that time interval). *POD,* Postoperative day.

sions after CPB as a result of the proportionately greater hemodilution caused by CPB in these patients. For example, a 60 kg woman with a 30% hematocrit value at the start of CPB would be more likely than a 90 kg man with the same hematocrit value to require a transfusion on or shortly after CPB because of a profound degree of relative hemodilution. Our own experience has similarly confirmed that patients weighing less than 70 kg expended 60% of all the homologous blood products transfused, although they comprised only 40% of the caseload.[7]

This was a pilot study designed to determine whether RAP would be of benefit in the general cardiac surgery population. Patients were not specifically preselected into high- or low-risk groups on the basis of BSA, although patients with extremely low hematocrit values or red cell mass (as determined by weight) were eliminated because transfusion probably could not be avoided in these patients even with maximal RAP. With these exceptions, it can be concluded from this study that RAP successfully reduces transfusions in the general coronary bypass population.

It is not intuitively obvious whether RAP would be of greater benefit to patients with low BSA compared with the general population. Successful implementation of RAP would likely be more difficult in patients with a low BSA because the red cell mass withdrawn would represent a proportionately greater amount of the patient's total intravascular volume and therefore would cause more hemodynamic compromise. On the other hand, the pump prime volume would equivalently represent a greater proportion of these patients' intravascular blood volumes and therefore would produce more profound hemodilution and greater likelihood of hematocrit values low enough to mandate obligatory transfusions. A limited analysis was performed on patients in the current study with a BSA of less than 1.9 m^2 (lowest 30th percentile). In fact, the transfusion risk in patients with a low BSA was improved to a somewhat greater extent than that in patients with a larger BSA, although greater numbers would be required to achieve statistical significance in this analysis.

The hematocrit value resulting from the hemodilution associated with CPB can be directly calcu-

lated as the product of the patient's hematocrit value and the patient's red cell mass (volume) as a fraction of the crystalloid CPB prime volume plus the red cell volume (appendix). Red cell mass, the product of blood volume times hematocrit value, can be determined with the use of a nomogram based on the initial hematocrit value, height, weight, and gender. Thus the patients in whom RAP may play a critical role in avoiding transfusion may be predictable before the operation.

RAP as a blood conservation modality. Although erythropoietin can be used to minimize hemodilution by enhancing the total red cell mass,[21, 23] RAP is a more expeditious, inexpensive technique, which minimizes hemodilution by modifying the inverse aspect of the hemodilution equation: that is, the CPB prime volume rather than the red cell mass. Despite this demonstrated efficacy, patients with exceedingly low red cell masses, such as severely anemic patients or those, such as elderly patients, women, or others with small BSAs, will experience excessive hemodilution, significantly decreased hematocrit values, and increased transfusion risk despite maximal RAP. These patients may therefore be viewed as remaining candidates for preoperative erythropoietin therapy, despite the potential application of RAP. Although hemoconcentration may also cause increased concentrations of platelets and clotting factors and thereby reduce postoperative bleeding, no direct evidence of this was provided by our results. RAP can thus not be viewed as a hemostatic modality.

Safety. As described in this article, RAP is safe and extremely well tolerated. One potential risk of RAP, paradoxically, is related to the efficiency of RAP in minimizing hemodilution in patients undergoing CPB. Early investigators had demonstrated that an inverse linear relationship exists between temperature and blood viscosity; blood viscosities can increase 10% to 30% under the hypothermic conditions associated with CPB.[24-26] Therefore moderate hemodilution during CPB has been considered desirable in avoiding this increased viscosity and potential compromise of the microcirculation, and such a degree of hemodilution has generally been provided by a total crystalloid prime.[9-11] Because of these considerations, we maintained a hematocrit value less than 28% ("less than the blood temperature") during CPB by using intraoperative autologous donation before CPB or by adding crystalloid prime during CPB, as required. In fact, with the use of intraoperative autologous donation, "excessive" hematocrit values were not encountered during CPB.

A second theoretical risk of RAP is related to the potential of hemodynamic instability caused by the large volumes of crystalloid solution withdrawn during the RAP process.[6] It is somewhat unexpected in considering the relative hypovolemia induced by RAP that a significant volume or pressor requirement was not subsequently observed in patients subjected to RAP to "fill up" or "shrink" the intravascular space, respectively, and thereby avoid hypotension. In fact, withdrawal of RAP volumes was well tolerated, with hemodynamic parameters and pressor requirements that were equivalent to those in control patients. Although some patients did require reinfusion of RAP volumes, clinical experience suggested that correction of preoperative dehydration minimized the incidence of RAP reinfusion.

Increased vascular tone induced by neuroendocrine mechanisms and intravascular fluid shifts from the extravascular compartment are two of the normal adaptive responses to intravascular hypovolemia and may thus be regarded as potential physiologic responses to RAP. Because the mean arterial pressure and the systemic vascular resistance were demonstrated to be similar in the RAP and non-RAP groups in the current study, it would appear that fluid shifts, as opposed to an endogenous pressor response, may account for the lack of an exogenous volume or pressor requirement noted in patients undergoing RAP. Such fluid shifts from the extravascular into the intravascular compartment, compensating for the volume depletion occurring during the RAP process, may furthermore explain the relative postoperative fluid "loss" noted in RAP versus control groups, as denoted by the difference in weights noted in these patients 36 hours after the operation. A relatively greater colloid oncotic pressure, produced by substitution of the crystalloid prime with autologous blood, may also be responsible for a net extravascular fluid loss and relative weight decrease in the RAP compared with control patients. Either or both of these effects may result in decreased lung water accumulation and expedited ventilator weaning after cardiac operations, as has been previously suggested.[6, 27] Thus RAP may generate additional clinical benefits apart from decreased homologous blood transfusions.

Limitations. The study was designed to be a small-scale pilot study to assess the safety and

efficacy of RAP in patients undergoing coronary bypass. Although a more rigorous randomization procedure would be appropriate for larger studies, the technique employed in this study provided the unbiased creation of equivalent study populations in this trial.

We used a lower limit on-CPB and post-CPB hematocrit value of 16% and 23%, respectively, based on previous consensus findings regarding minimum safe hematocrit values with hypothermia and our own review of neurologic sequelae correlated with hematocrit values during CPB.[28-30] On the basis of these data, we did not think that hematocrit values lower than those adopted in this study were acceptable. We therefore do not believe that our control transfusion rate was "excessively" increased as a result of inappropriate transfusion triggers or that our RAP results were consequently significant only in reference to inappropriately increased control transfusion rates. Although the transfusion rate in our non-RAP group would nevertheless appear to be excessive, it is consistent with the results from a number of other trials.[1-5]

One potential modification of the RAP technique as described in this study might have included slower RAP withdrawal, which might have improved the volume of RAP withdrawn and/or pressor requirements. However, the RAP technique performed as described in this study, with withdrawal over 1 to 5 minutes and with incremental administration of usually one to three boluses of 100 μgm of oxymetazoline, appeared to be both effective and well tolerated.

RAP can be viewed as one of a number of synergistic techniques that can be used to avoid transfusions during cardiac operations. Either alone or as component of a multimodality blood conservation protocol, RAP would appear to be a safe and inexpensive technique of minimizing hemodilution and red cell transfusions that are associated with cardiac operations.

We thank Genia Podwojski, Marie Kilcullen, Pat Esposito, Barbara Elmer, Youram Sukhram, James McVey, and Laura Deffeo, for their able assistance in completing this trial, and Leah Dinozo for her constant attention to detail.

REFERENCES

1. Belisle S, Hardy J-F. Hemorrhage and the use of blood products after adult cardiac operations: myths and realities. Ann Thorac Surg 1996;62:1908-17.
2. Scott WJ, Rode R, Castlemain B, Kessler R, Follis F, Pett SB, et al. Efficacy, complications, and cost of a comprehensive blood conservation program for cardiac operations. J Thorac Cardiovasc Surg 1992;103:1001-7.
3. D'Ambra MN, Akins CW, Blackstone EH, Bonney SL, Cohn LH, Cosgrove DM, et al. Aprotinin in primary valve replacement and reconstruction: a multi-center, double-blind, placebo-controlled trial. J Thorac Cardiovasc Surg 1996;112: 1081-9.
4. Goodnough LT, Despotis GJ, Hogue CW, Ferguson TB. On the need for improved transfusion indicators in cardiac surgery. Ann Thorac Surg 1995;60:473-80.
5. Surgenor DM, Wallace EL, Churchill WH, Hao SHS, Chapman RH, Collins JJ. Red cell transfusions in coronary artery bypass surgery (DRGs 106 & 107). Transfusion 1992;32:458-64.
6. Jansen PG, te Velthuis H, Bulder ER, Paulus R, Scheltinga MRM, Eijsman L, et al. Reduction in prime volume attenuates the hyperdynamic response after cardiopulmonary bypass. Ann Thorac Surg 1995;60:544-50.
7. DeBois WJ, Sukhram Y, McVey J, Helm RE, Gold JP, Rosengart T, et al. Reduction in homologous blood transfusions using a low prime circuit. J Extracorporeal Technol 1996;28:58-62.
8. Hellstrom G, Björk VO. Hemodilution with Rheomacrodex during total body perfusion. J Thorac Cardiovasc Surg 1963; 45:395.
9. Roe BB, Swenson EE, Hepps SA, Bruns DL. Total body perfusion in cardiac operations. Arch Surg 1964;88:128.
10. Neville WE, Faber LP, Peacock H. Total prime of the disc oxygenator with Ringer's and Ringer's lactate solution for cardiopulmonary bypass. Dis Chest 1964;45:320.
11. Cooley DA, Beall AC, Grondin P. Open heart operations with disposable oxygenators, 5 per cent dextrose prime, and normothermia. Surgery 1962;52:713.
12. Lilleaasen P. Moderate and extreme haemodilution in open-heart surgery. Scand J Thorac Cardiovasc Surg 1977;11:97-103.
13. Panico FG, Neptune WB. A mechanism to eliminate the donor blood prime from the pump oxygenator. Surg Forum 1960;10:605-9.
14. Helm RE, Klemperer J, Rosengart TK, Gold JP, Peterson P, DeBois W, et al. Intraoperative autologous blood donation preserves red cell mass but does not decrease postoperative bleeding. Ann Thorac Surg 1996;62:1431-41.
15. Casas JI, Zuazu-Jausoro I, Mateo J, Oliver A, Litvan H, Muniz-Diaz E, et al. Aprotinin versus desmopressin for patients undergoing operations with cardiopulmonary bypass: a double-blind placebo-controlled study. J Thorac Cardiovasc Surg 1995;110:1107-17.
16. Horrow JC, Hlavacek J, Strong MD, Collier W, Brodsky I, Goldman SM, et al. Prophylactic tranexamic acid decreases bleeding after cardiac operations. J Thorac Cardiovasc Surg 1990;99:70-4.
17. Schonberger JPAM, Everts PA, Ercan H, Bredee JJ, Bavnick JH, Berreklouw E, et al. Low-dose aprotinin in internal mammary artery bypass operations contributes to important blood saving. Ann Thorac Surg 1992;54;1172-6.
18. Utley JY, Wallace DJ, Thomason ME, Mutch DW, Staton L, Brown V, et al. Correlates of preoperative hematocrit value in patients undergoing coronary artery bypass. J Thorac Cardiovasc Surg 1989;98:451-3.
19. Ferraris VA, Gildengorin V. Predictors of excessive blood

use after coronary artery bypass grafting: a multivariate analysis. J Thorac Cardiovasc Surg 1989;98:492-7.
20. Cosgrove DM, Loop FD, Lytle BW, Gill CC, Golding LR, Taylor PC, et al. Determinants of blood utilization during myocardial revascularization. Ann Thorac Surg 1985;40: 380-4.
21. Fullerton DA, Campbell DN, Whitman GJR. Use of human recombinant erythropoietin to correct severe preoperative anemia. Ann Thorac Surg 1991;51:825-6.
22. Helm RE, Gold JP, Rosengart TR. Erythropoietin in cardiac surgery. J Card Surg 1993;8:579-606.
23. Rosengart TK, Helm RE, Klemperer J, Krieger K, Isom OW. Combined aprotinin and erythropoietin use for blood conservation: results with Jehovah's Witnesses. Ann Thorac Surg 1994;58:1397-403.
24. Reemtsma K, Creech O. Viscosity studies of blood, plasma, and plasma substitutes. J Thorac Cardiovasc Surg 1962;44: 674-80.
25. Rand PW, Lacombe E, Hunt HE. Viscosity of normal blood under normothermic and hypothermic conditions. J Appl Physiol 1964;19:117-22.
26. Merril EW. Rheology of blood. Physiol Rev 1969;4:863-88.
27. Butler J, Rocker GM, Westaby S, et al. Early extubation after coronary bypass surgery: effects on oxygen flux and haemodynamic variables. J Cardiovasc Surg 1992;33:276-80.
28. Baron JF. Which lower value of haematocrit or haemoglobin concentration should guide the transfusion of red blood cell concentrates during and after extracorporeal circulation? Ann Fr Anesth Reanim 1995;14(Suppl):21-7.
29. Schill, D. The optimal preservation of the patient's hematocrit when cardiopulmonary bypass is required. J Extracorp Technol 1991;21:157-9.
30. Fang C, Helm RE, Krieger KH, Rosengart TK, DeBois WJ, Sason C, et al. The impact of minimum hematocrit during cardiopulmonary bypass on mortality in patients undergoing coronary artery surgery. Circulation 1996;94(Suppl):I70-1.

Discussion

Dr. Bradley J. Harlan *(San Francisco, Calif.).* This is a well-designed prospective randomized study. The surgical results were very good, there being no deaths in the 60 patients. This interesting technique, which Dr. Rosengart describes as having been rediscovered, is essentially a method of priming with autologous blood, as the crystalloid volume is deprimed before and right at the beginning of CPB. Despite this technique, by the time the patients left the operating room, the amount of crystalloid solution that each group had received was exactly the same. The authors conclude from their data that RAP is a safe and effective means of decreasing red blood cell transfusion in cardiac operations, and this is certainly the case at New York Hospital. However, would it be the case for most patients undergoing coronary artery bypass, in whom intraoperative autologous blood donation is not used? The reason I ask is that the control group had an unusually high incidence of blood transfusion during hospital stay, 53%, and a remarkably high incidence of intraoperative transfusion, 23%, despite the fact that the average preoperative hematocrit value of this group was 40%. I suspect that the use of intraoperative autologous blood donation may explain this. Dr. Rosengart, during CPB in the control group, when the hematocrit value reached your trigger level for transfusion, why didn't you reinfuse the autologously donated blood rather than expose the patient to a homologous transfusion?

Dr. Rosengart. We did reinfuse the patient's intraoperative autologous donation blood before transfusing homologous units of blood.

Dr. Harlan. That was not clear from the manuscript. At Sutter Memorial, we use a standard crystalloid prime and autotransfusion in the operating room after CPB, and most patients receive autotransfusion from the chest tube drainage in the postoperative period. We tried to find a similar group of patients, but obviously ours are not exactly the same as your control group. A very small proportion of these patients received aprotinin. In 470 patients in whom these techniques were used, our incidence of blood transfusion during hospitalization was 38% and the incidence of intraoperative transfusion was extremely low. In the postoperative period, did you use the patient's chest drainage for autotransfusion?

Dr. Rosengart. We do use mediastinal blood autotransfusion as a technique at New York Hospital; we did not in the completion of this cohort.

Dr. Harlan. You have shown that the technique is effective, but I am not sure you have shown that it is safe yet, because your study comprised a relatively small, highly selected group of good-risk patients. I wonder whether you have expanded your indications or the use of the technique since this study and whether, despite this expansion, the patients seem to tolerate this hypovolemia well.

Dr. Rosengart. We first started using RAP several years ago. We now perform RAP on essentially every patient that we operate on, with the caveat that if the patient is high risk or we are concerned about hypovolemia or hypotension, we will not perform RAP.

We probably attempt to perform RAP on 95% of the patients, and we are probably successful in delivering a significant amount of RAP volume in the majority of patients, at least 75% or 80%. About half of the patients require retransfusion of some of the RAP volume, and on average about half of the RAP volume is retransfused or readministered at some time. It is impressive, however, that the hematocrit values during CPB are higher than they would be without the technique. I think RAP is allowing the patients to avoid being in the operating room with hematocrit values of 15% or 16%, in which case we would be compelled to transfuse. Whether we really need to transfuse at a hematocrit value of 15% or 16% is an unresolved issue.

Dr. Harlan. This study should stimulate us to review our methods of perfusion.

Dr. Neal W. Salomon *(Lutherville, Md.).* We have been doing the same procedure exactly as you described it for the past year and have had the same results. However, we have not done a randomized study. At the meeting of The American Association for Thoracic Surgery in April 1997, Richard Engelman's group from Bay State in Massachusetts reported similar results with a resurrection of an old technique. It is extremely simple, and they have had no problems. Neither of our groups has done a randomized trial because we use the technique on almost every patient and there is no need for an institutional review board

protocol. We found that we have saved blood in the operating room, and the perfusionists and operating room personnel are very enthusiastic about the technique. However, a significant number of patients will require blood later during their hospital stay. You do get to an irreducible minimum. The patients who need transfusion the least are the ones in whom this technique provides the best results, and the patients with a small body mass who are already anemic have less red cell mass, and they are going to need a blood transfusion regardless. They do require less blood, however, and I think this simple procedure should generate considerable enthusiasm. I do not know whether is more effective than 40 or 80 mg of furosemide (Lasix) or a hemoconcentrator, but it is free. You also have to make sure that your anesthesiologist does not try to compensate for a reduced prime by infusing 2 L of saline solution.

Dr. Rosengart. I would add that RAP is just one of a number of techniques that can be used in combination to decrease blood transfusion. If RAP is successfully accomplished and the patient subsequently loses 2 L of blood because of a coagulopathy, the technique has accomplished nothing. One thing that we therefore try to accomplish with our program is to combine different synergistic and complementary aspects of blood conservation to help prevent such a scenario. We therefore focus on coagulopathy and use aprotinin, aminocaproic acid (Amicar), and so on, which all play important roles.

Dr. Salomon. And you have to make sure that your anesthesiologist does not compensate by adding 2 L of saline solution.

Dr. Thomas A. Pfeffer *(Los Angeles, Calif.).* You mentioned that one of your exclusion criteria was the history of stroke. Is that still considered?

Dr. Rosengart. No, it is not. That was initially an exclusion criteria because we initiated this protocol so that we could implement it as cautiously as possible.

Dr. Pfeffer. You also did not accept patients with asymptomatic carotid stenosis. Was the reason for originally excluding those patients concern about hypotension during the period of RCP?

Dr. Rosengart. Yes. Neurologic complications are of the gravest concern, and because this was a preliminary trial, we wanted to err on the side of caution. At this point, we try to perform RAP on essentially every patient.

Dr. Pfeffer. One of your slides indicated that there was no significant difference in the mean arterial pressure in the immediate prebypass period. Yet you also described the use of oxymetazoline. Were the pressures the same because those patients automatically received phenylephrine while the blood was being withdrawn?

Dr. Rosengart. About half of the patients received 100 μg boluses of phenylephrine as we started the RAP process. The total amount of pressor requirements was the same, however, and the hemodynamics were essentially the same. Whatever compensatory mechanism ensues that allows compensation for the net blood withdrawal associated with RAP is unknown. I presume it is either an extravascular fluid shift or a change in the venous capacitance that compensates for this net volume loss.

Dr. Pfeffer. Finally, what time frame is involved in withdrawing the blood and priming the circuit this way? Have there been any patients in whom the procedure was abandoned because of hemodynamic instability?

Dr. Rosengart. The entire RAP process requires from 1 to 5 minutes (maximum). The procedure is quickly done.

Appendix

The following equations were used to determine on-CPB hematocrit levels with intraoperative autologous donation (IAD) and retrograde autologous primine (RAP). The estimated blood volume was determined from a previously published nomogram* (abbreviations: CPB = cardiopulmonary bypass; HCT = hematocrit; CPV = (circuit prime volume – RAP volume); EBV = estimated blood volume; $HCT_{initial}$ = HCT before IAD; $HCT_{pre\text{-}CPB}$ = HCT after IAD.

$$HCT_{on\ bypass} = HCT_{preCPB}(EBV)/(EBV + CPV)$$

$$\text{IAD volume} = EBV(HCT_{initial} - HCT_{pre\ CPB})/HCT_{initial}$$

*Albert SN, editor. Blood volume and extracellular fluid volumes. Springfield [IL]: Charles C Thomas; 1972. p. 281-2.