Review

Perfusion

Perfusion
2020, Vol. 35(7) 574–586

DOI: 10.1177/0267659119895474
journals.sagepub.com/home/prf


Retrograde autologous priming to reduce allogeneic blood transfusion requirements: a systematic review

Nousjka PA Vranken,[1,2] Zaheer UD Babar,[1] Jesse A Montoya[3] and Patrick W Weerwind[1,2]

Abstract

Background: Efforts have been made to minimize transfusion of packed red blood cells in patients undergoing cardiac surgery with cardiopulmonary bypass. One method concerns retrograde autologous priming. Although the technique has been used for decades, results remain contradictory in terms of transfusion requirements.

Objective: This systematic literature review aimed to summarize the evidence for the efficacy of retrograde autologous priming in terms of decreasing perioperative packed red blood cell requirements in adults.

Methods: Two researchers independently searched PubMed for articles published in the past 10 years. The modified Cochrane collaboration Risk of Bias Tool and the Research Triangle Institute Item Bank were used to assess bias.

Results: Eight studies were included, of which two randomized and six observational studies. Five studies, including one randomized study, report a significant decrease in packed red blood cell use in the retrograde autologous priming group compared to no retrograde autologous priming used. All studies are flawed by at least a high risk bias of bias score on one item of the bias assessment.

Conclusion: Although most studies reported significantly fewer packed red blood cell transfusions in the retrograde autologous priming group, it is important to note that relatively few articles are available which are flawed by several types of bias. Prospective, randomized multi-center trials are warranted to conclude decisively on the benefits of retrograde autologous priming.

Keywords

retrograde autologous priming; packed red blood cells; allogeneic blood transfusion; intraoperative blood management

Introduction

Blood transfusion of red blood cells increases the oxygen-carrying capacity of the blood and can be lifesaving in cases of extreme blood loss or hypotension. Although blood transfusion is a commonly performed procedure in the operating theater, a wide range of transfusion-related complications should be taken into account in balancing the risks and benefits of the intervention. These complications include but are not limited to transfusion-associated immunomodulation and increased risk of infections,[1,2] which adversely affect postoperative morbidity and mortality rates. Illustrated by a dose-dependent relationship, patients receiving fewer blood transfusion products appear to have superior outcomes compared to patients receiving more blood products.[1,3] In addition to the clinical benefit, decreasing the consumption of blood products significantly reduces health care costs.[4]

In the cardiac surgery population specifically, transfusion rates may be as high as 88%.[5] This can be partially explained by the fact that the use of a cardiopulmonary bypass (CPB) circuit is inherently accompanied by

[1]Department of Cardiothoracic Surgery, Maastricht University Medical Center, Maastricht, The Netherlands
[2]Cardiovascular Research Institute Maastricht, Maastricht University Medical Center, Maastricht, The Netherlands
[3]Perfusion Sciences Program, Department of Pharmacology, The University of Arizona, Tucson, AZ, USA

Corresponding author:
Nousjka PA Vranken, Department of Cardiothoracic Surgery, Maastricht University Medical Center, P. Debyelaan 25, PO Box 5800, 6202 AZ Maastricht, The Netherlands.
Email: nousjka.vranken@mumc.nl

Presented at the 40th Annual Seminar of The American Academy of Cardiovascular Perfusion, Palm Coast, Florida, 6-9, February, 2019

hemodilution and reduction of plasma colloid osmotic pressure.[6] Besides the adverse effects of hemodilution by itself, that is, an increased risk of neurological complications,[7,8] the concomitant lowered hematocrit value below a certain threshold is considered a "transfusion trigger" exposing the patient to the potential harmful effects of blood transfusion. Apart from the obligatory hemodilution while using the CPB system, the cardiac surgical patient is often predisposed to an additional increase in risk of postoperative complications by receiving transfusion products.[1–3,9]

Accumulating evidence regarding the side effects of packed red blood cells (PRBC) transfusion resulted in an increasing interest in bloodless cardiac surgery. Several modifiable factors playing a role in the likelihood of a patient receiving blood transfusion have been identified, including the priming volume of the CPB circuit.[10,11] Measures used to avoid or minimize the use of transfusion products include preoperative iron and erythropoietin supplementation,[12] techniques to reduce the priming volume of the CPB circuit by means of a minimized system,[13] the use of cell salvage devices for autotransfusion,[14,15] and retrograde autologous priming (RAP). During the latter, a part of the patient's own blood is passively drained into the CPB circuit, replacing part of the crystalloid or colloid-based priming solution before initiating bypass. During initiation of CPB, a variable volume of blood is passively drained from the patients' circulation into the CPB circuit before initiating bypass.[16] The RAP technique was first described by Panico and Neptune,[17] then adapted by Rosengart et al.,[16] whose proposed RAP protocol is still being used in clinical practice to date. Compared to conventional priming of the CPB system, RAP appears effective in terms of decreasing the deleterious effects of hemodilution.[18,19] Although the technique has been applied in cardiac surgical centers since several decades, study results remain contradictory in terms of its effects on hematocrit level and transfusion requirements.[20]

The aim of this review was to assess whether adult patients undergoing cardiac surgery with CPB using RAP require fewer PRBC transfusions compared to patients undergoing CPB with conventional priming of the circuit.

Methods

This review was written according to the guidelines provided by the PRISMA statement for reporting systematic reviews.[21]

Types of studies and outcome measures

In this review, observational and experimental studies were assessed that met the following criteria: 1. patients underwent cardiac surgery with CPB using either the RAP technique or conventional priming of the circuit, and 2. studies reported any of the following outcome measures: use of allogeneic blood transfusion or use of PRBCs intraoperatively and/or perioperatively. The search was limited to original full-length articles written in English published between 14th February 2009 and 14th February 2019. Articles published over 10 years ago were not considered eligible for inclusion due to the use of outdated CPB techniques.

The primary outcome measure was the intraoperative use of erythrocyte transfusion products and/or the proportion of patients receiving erythrocyte transfusion products.

Participants

Each study includes human adult patients undergoing elective cardiac surgery and each study includes both male and female patients.

Data source and search strategy

Using the PubMed database, original research articles were retrieved by the combination of MeSH terms and free search terms as shown in Table 1. Screening the references in the retrieved papers identified eventual studies that might have been missed. Studies that were not published as a full-length article were excluded. The detailed search strategy is provided in Figure 1.

Study inclusion

Two authors independently reviewed the studies for eligibility. First, the title and the abstract of all studies obtained from the PubMed search were screened. Articles that did not match the objective of this review were excluded. After initial screening, potentially relevant studies were read in full text.

Data collection

Data from the studies were extracted by one author and summarized in a data extraction sheet. The following items were collected: the first author's surname, year of publication, study design, the intraoperative blood pressure target, the PRBC transfusion trigger, type of surgery, blood pressure target while on CPB, type of priming solution (colloid or crystalloid), type and volume of cardioplegic solution, and the number of patients included (in total and per group). The following items were collected from each study group (RAP group and conventional priming of the CPB circuit, which will be referred to as the "conventional CPB" group): proportion of the male gender of patients, CPB duration, the patients' weight and/or body mass index (BMI), and/or

Table 1. PubMed search strategy.

Search terms	MeSH terms	Free terms
patients	Humans, Adult	adult, human
intervention		RAP, retrograde autologous priming, autologous priming, blood management, blood conservation
control	Hemodilution	conventional, conventional haemodilution, conventional hemodilution, normovolemic haemodilution, normovolemic hemodilution
setting	Coronary Artery Bypass, Cardiopulmonary Bypass, Extracorporeal Circulation, Thoracic Surgery, Cardiac Surgical Procedures	cardiac surgery, cardiothoracic surgery, CABG, coronary artery bypass, coronary artery bypass graft, coronary artery bypass grafting, open heart surgery
outcome	Blood transfusion, Erythrocyte Transfusion	blood transfusion, allogeneic blood transfusion, erythrocyte transfusion, red packed cell

CABG: coronary artery bypass graft; MeSH: medical subject headings; RAP: retrograde autologous priming.

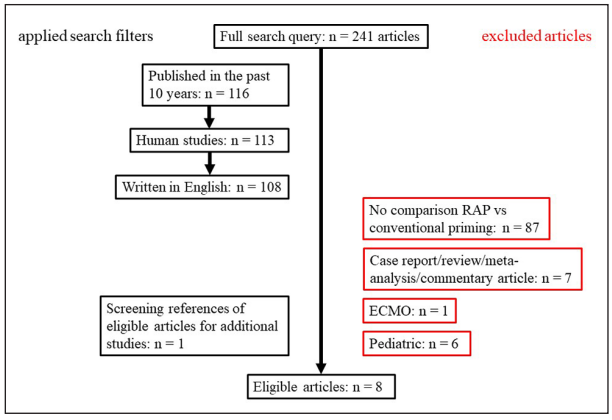

Figure 1. Study flow chart.

body surface area (BSA). With regards to the fluid balance, the following items were retrieved for both study groups: use (and volume) of hemofiltration, use (and volume) of autotransfusion, intraoperative blood loss, CPB priming volume, and preoperative hematocrit and/or hemoglobin values.

Primary study outcomes were the proportion of patients who received PRBC transfusions in the perioperative period in both study groups (RAP vs. conventional CPB) and/or the number or volume of PRBC transfusions in both study groups. Study outcomes have not been modified since no meta-analysis was performed.

Risk of bias assessment in individual studies

The methodological quality of the included observational studies was assessed using the modified Cochrane collaboration Risk of Bias Tool,[22] while the RTI Item Bank was used for the assessment of randomized studies.[23] In both bias assessment tools, several topics are assessed regarding the different types of bias. The author of this review assessed the risk of bias of each included study using either the 7 items of the Cochrane tool or the 13 items of the RTI tool. Each item was scored as follows: low risk of bias (LR), questionable risk of bias (QR), or high risk of bias (HR). No assessment of risk across studies was performed.

Results

The PubMed search resulted in 241 studies. After application of search filters (published in the past 10 years, human studies, and written in English), 108 studies remained eligible for inclusion as presented in Figure 1. After reading the titles and abstracts, eight studies were considered for data extraction. Of these eight, two were randomized studies, while the remaining six were observational studies.

Study characteristics

In Table 2, the study characteristics are shown, while Table 3 shows surgical and CPB data of all included studies and Table 4 shows a summary of the data concerning blood transfusions. All studies were single-center studies. The number of study participants ranges from 62 to 14,898 with a mean age of patients in the RAP group of 62.1 years old, and in the control group 60.9 years old. The study by Cheng et al.[19] included the youngest study participants with a mean age of 43 years in the RAP group and 32 years in the conventional CPB group. In all studies, proportionally more male than female patients were included; the average proportion of males was 74% in the RAP group and 73.4% in the control group. Some studies used exclusion criteria, which were mostly consisting of any other type of cardiac surgery than coronary artery bypass grafting (CABG) and emergency procedures. The study by Ševerdija et al.[24] used additional exclusion criteria related to the fluid balance, that is, fluids volume administered by the anesthesiologist >1,000 mL, cardioplegic volume >1,000 mL, and

Table 2. Characteristics of the included studies.

First author	Year	Study	Type of cardiac surgery	Myocardial preservation (type/dose in mL)	n (RAP)	n (conv)	RAP: males (%)	Conv: males (%)	RAP: age (years)	Conv: age (years)	RAP: body weight (kg)/length (cm)/BMI (kg/m^2)/BSA (m^2)	Conv: body weight (kg)/length (cm)/BMI (kg/m^2)/BSA (m^2)
Cheng et al.[19]	2015	Random, double-blind	Septal defects and valve replacements	Cold blood cardioplegia/–	120	120	50.9	55.8	43.1 ± 10.1	32.5 ± 11.3	45.6 ± 3.6	48.9 ± 4.3
Reges et al.[25]	2011	Random	CABG	–/–	27	35	66.7	62.9	58.4 ± 2.1	58.3 ± 2.0	74.6 ± 2.7	75.7 ± 2.2
Kearsey et al.[26]	2013	Obs, case (historic) control	CABG	–/–	101	92	91	83	65.6 ± 9.7	65.5 ± 8.4	–	–
Nanjappa et al.[27]	2013	Obs, pros	CABG	Cold blood cardioplegia/–	73	128	73.9	85.9	68.0 (64.7-69.0)	68.0 (65.4-69.2)	–/–/28.8 (28.5-30.8)	–/–/28.3 (28.3-30.0)
Ševerdija et al.[24]	2011	Obs, retro	CABG	St. Thomas I/±800 mL	50	50	86	68	63 ± 9	65 ± 10	80 ± 9/–/26 ± 3	81 ± 11/–/27 ± 4
Stammers et al.[28]	2017	Obs, retro	All cardiac + CPB	Crystalloid cardioplegia/median 320 for controls; median 346 for RAP	12,677	2,221	70.1	69.4	65.9 ± 11	66 ± 10.9	–/–/–/1.99 ± 0.25	–/–/–/1.97 ± 0.25
Trapp et al.[18]	2015	Obs, retro	CABG	Warm blood cardioplegia/–	30	30	90	87	67.6 ± 10.5	68.30 ± 9.54	83.5 ± 7.3	79.8 ± 11.9
Vandewiele et al.[29]	2013	Obs, retro	CABG, CABG + valve, valve, other	St. Thomas II/600-1,000 mL	498	255	68.4	74.9	65.3 ± 14.6	63.8 ± 14.2	76.6 ± 15/168.9 ± 8.8	80.2 ± 15.9/170.2 ± 9.5

–: no values documented in this publication. CABG: coronary artery bypass graft; conv: conventional CPB group; obs: observational; RAP: retrograde autologous priming group; pros: prospective; random: randomized study; retro: retrospective study; BMI: body mass index; CPB: cardiopulmonary bypass.

Table 3. Study characteristics: surgical factors.

First author	RAP: CPB time (min)	Conv: CPB time (min)	RAP: actual priming volume (mL)	Conv: priming system (mL)	Priming solution	RAP: preop Hct (%)/ Hb (g/dL)	Conv: preop Hct (%)/ Hb (g/dL)	RAP: autotrans-fusion (% of patients)/mL	Conv: autotrans-fusion (% of patients)/mL	RAP: intraop blood loss	Conv: intraop blood loss	Mean ABP target during CPB (mm Hg)
Cheng et al.[19]	84.1 ± 22.1	78.1 ± 21.4	382.6 ± 118.3	1,190.9 ± 100.1	Crys	38.8 ± 2.6/–	41.5 ± 2.8/–	–	–	342.1 ± 125.1	378.6 ± 111.3	50-80
Reges et al.[25]	86.2 ± 7.0	89.9 ± 5.0	1,131.1 ± 82.4	2,415.1 ± 77.2	Crys	40.4 ± 1.0/13.2 ± 0.4	39.7 ± 1.2/12.9 ± 0.4	–	–	–	–	–
Kearsey et al.[26]	86 ± 27	80 ± 30	1,013 ± 189	2,450 ± 484	Crys	–/13.5 ± 1.6	–/13.9 ± 1.3	–	–	–	–	–
Nanjappa et al.[27]	81.0 (75.9-87.9)	81.0 (80.3-88.6)	1,188 ± 118	1,500	Crys	39.0 (38.2-40.0)	42.0 (40.5-42.0)	–	–	–	–	>55
Ševerdija et al.[24]	69 ± 18	72 ± 32	782 ± 96	1,627 ± 108	Coll	42 ± 1	41 ± 3	50/371 ± 499	50/982 ± 503	293 ± 161	348 ± 213	70-90
Stammers et al.[28]	100 [77-134]	106 [79-140]	705 [550-855]	960 [852-1,150]	Crys	35.7 ± 5.6	35.5 ± 6.0	0/0	0/0	–	–	–
Trapp et al.[18]	113.8 ± 24.7	108.3 ± 26.9	946.3 ± 212.1	1,620.0 ± 181.0	Crys	41.5[a]	39[a]	–	–	–	–	–
Vandewiele et al.[29]	89 ± 34	97 ± 39	747.8 ± 262	1,288 ± 170	Coll	38.9 ± 4.4/–	40.5 ± 4.6/–	6/144.8 ± 213	5.5/198.8 ± 329	–	–	>50

–: no values documented in this publication. ABP: arterial blood pressure; col: colloid; conv: conventional CPB group; CPB: cardiopulmonary bypass; coll: colloid; crys: crystalloid; Hb: hemoglobin; Hct: hematocrit; intraop: intraoperative; RAP: retrograde autologous priming group.

[a]Values estimated from graph in the publication.

Table 4. Outcomes regarding blood transfusion.

First author	Outcome definition	Tranfusion trigger	Univariate analysis				Multivariate analysis: OR (95% CI)/p value
			RAP: PRBC transfusion	Conv: PRBC transfusion	RAP superior	p value	
Cheng et al.[19]	Perioperative RBC transfusion (%)	–	54.2	95.8	Yes	<0.001	–
	Intraoperative RBC transfusion (%)	–	19.1	88.3		<0.001	–
Reges et al.[25]	Intraoperative RBC transfusion (%)	–	11.1	17.1	No	NS	–
	Postoperative RBC transfusion (%)	–	37.0	34.4		NS	
	Postoperative RBC transfusion (mL)	–	580.0 ± 80.0	500.0 ± 85.3		NS	
Kearsey et al.[26]	Blood transfusion (%)	Hb ⩽ 8 g/dL	36	40	No	NS	–
Nanjappa et al.[27]	Intraoperative RBC transfusion	Hct < 24% or Hb < 7.5 g/dL	–	–	No	0.43	–
Ševerdija et al.[24]	Perioperative RBC transfusion (%)	Hct < 23%	6	26	Yes	0.012	RAP (y/n): 6.12 (1.20-31.54)/0.012
	Intraoperative RBC transfusion (n)		4	22		0.041	–
Stammers et al.[28]	Intraoperative RBC transfusion (%)	Different triggers in the different hospitals, none reported	20	26.7	Yes	<0.001	–
Trapp et al.[18]	Mean intraoperative RBC transfusions (n)	Hb < 8 g/dL	0.27 ± 0.64	1.3 ± 1.41	Yes	<0.01	–
	Mean perioperative RBC transfusions (n)		1.13 ± 1.78	3.20 ± 2.66		0.01	–
Vandewiele et al.[29]	Mean intraoperative RBC transfusions (n)	Hct ⩽ 25%	0.58 ± 1.11	0.89 ± 1.42	Yes	0.001	RAP volume: 0.997 (0.996-0.999)/<0.001
	Intraoperative RBC transfusion (%)		26.1	33.3		0.038	–

–: no values documented in this publication. conv: conventional CPB or control group; Hb: hemoglobin; Hct: hematocrit; NS: non-significant; OR: odds ratio; PRBC: packed red blood cells; RAP: retrograde autologous priming.

blood loss during surgery >1,000 mL. In each study, the total volume of priming volume was significantly lower in the RAP group versus the conventional CPB group, approximately 862 and 1,631 mL, respectively, average volume for all eight studies (p = 0.001, Mann–Whitney U test).

Risk of bias within studies

The risk of bias was assessed using the modified Cochrane collaboration Risk of Bias Tool for the randomized studies, while the RTI tool was used for the observational studies. The randomized studies by Cheng et al.[19] and Reges et al.[25] were not entirely free of bias. Table 5 depicts a brief elucidation on the risk of bias for each predetermined type of bias in each study, whereas in Table 6 a overview of the risk of bias is presented. Only in the two randomized trials blinding was performed. This concerned the outcome assessor, meaning the staff at the intensive care unit who were responsible for administrating blood products whenever the transfusion trigger was exceeded. All observational studies reported the transfusion trigger administered in their hospital, varying from a hemoglobin level of <7.5 to <8 g/dL and/or a hematocrit level <23% to <25% (Table 4). Both randomized trials, on the other hand, did not report their transfusion trigger.

The assessment of bias in the observational studies is presented in Tables 7 and 8 using the same three categories of risk of bias. An overall assessment is provided by the last of the 13 items. All studies are flawed by at least a high risk bias of bias score on one item of the bias assessment. Multiple types of bias could not be excluded in all individual studies. Overall, reporting bias was likely to be present due to

Table 5. Assessment of bias of randomized studies.

	Random sequence generation—selection bias	Allocation concealment—selection bias	Blinding of participants and personnel—performance bias	Blinding of outcome assessment—detection bias	Incomplete outcome data—attrition bias	Selective reporting—reporting bias	Other bias
Cheng et al.[19]	Random number sequence generated by computer	Unclear whether researchers or study subjects could foresee allocation	Medical and nursing staff in the ICU and postoperative wards were blinded	ICU and ward staff administrating PRBC were unaware of the allocation	Number of PRBC transfusions solely in the postoperative period is unclear	The authors aimed to assess the safety or RAP, however, only lactate was used as a surrogate marker for postoperative morbidity. Not all factors that influence fluid balance are reported[a]	Selection bias: unclear whether any other factor than valve surgery was used to preselect patients
Reges et al.[25]	Unclear how randomization was performed	Unclear whether researchers or study subjects could foresee allocation	Physicians responsible for postoperative care were blinded with respect to the study group	ICU and ward staff administrating PRBC were unaware of allocation	Number of units PRBC transfusions as well as volumes are documented for intra- and postoperative use	Not all factors that influence fluid balance are reported[a]	Exclusion criteria are clearly formulated

ICU: intensive care unit; PRBC: packed red blood cells; RAP: retrograde autologous priming.
[a]At least one of the following factors which affect fluid balance was not taken into account or documented: type and/or dosage of cardioplegia used, the mean arterial blood pressure target during CPB, the use of autotransfusion, the use of hemofiltration, intraoperative blood loss, and the patients' weight/length/body mass index, and/or the transfusion trigger.

Table 6. Summary of assessment of bias of randomized studies.

First author	Random sequence generation—selection bias	Allocation concealment—selection bias	Blinding of participants and personnel—performance bias	Blinding of outcome assessment—detection bias	Incomplete outcome data—attrition bias	Selective reporting	
						Reporting bias	Other bias
Cheng et al.[19]	LR	QR	QR	LR	HR	HR	QR
Reges et al.[25]	QR	QR	QR	LR	LR	HR	LR

LR: low risk of bias; QR: questionable risk of bias; HR: high risk of bias.

the fact that none of the studies reported all possible factors which influence the patients' fluid balance: the type and dose of cardioplegic solution, the mean arterial blood pressure target during CPB, use and volumes of autotransfusion, use and volumes of hemofiltration, intraoperative and postoperative blood loss, urine output, and the patients' body weight/length/BMI.

Individual studies

Eight studies aiming at determining whether the use of RAP during CPB is beneficial in terms of minimizing PRBC requirements were included. Five studies, of which one randomized[19] and four observational studies,[18,24,28,29] reported a significant difference in PRBC transfusion in favor of the RAP group. All studies used the number of intraoperative transfusions per patient or the proportion of patients receiving intraoperative transfusions as an outcome measure. Ševerdija et al.,[24] Cheng et al.,[19] and Trapp et al.[18] also reported perioperative transfusions, which is the sum of all transfusion products used during and following the surgical procedure. Two observational studies also performed a multivariate analysis with either the use of RAP as a dichotomous variable or the RAP volume as a predictor for PRBC requirements.[24,29] Both studies report a significant contribution of RAP in the prediction model of PRBC transfusion.

Three studies,[25,26,27] of which one randomized trial, did not find any significant difference in PRBC transfusions between the RAP and conventional CPB group. Moreover, the three studies that found no effect of RAP all use higher priming volumes in both the RAP and control groups compared to the studies that found a significant benefit of RAP. More specifically, the priming

Table 7. Assessment of bias of observational studies.

Item		Kearsey et al.[26]	Nanjappa et al.[27]	Ševerdija et al.[24]	Stammers et al.[28]	Trapp et al.[18]	Vandewiele et al.[29]
1	Do the inclusion/exclusion criteria vary across the comparison groups of the study?	No	No	No	No	No	No
2	Does the strategy for recruiting participants into the study differ across groups?	No	No	Questionable: no information regarding patient selection other than the exclusion criteria is provided	No	No	No
3	Is the selection of the comparison group inappropriate?	No	No	Yes	Yes	No	No
4	Does the study fail to account for important variations in the execution of the study from the protocol?	No: authors reported that no changes in clinical practice occurred	Questionable: no documentation of deviations from the protocol	No: the authors minimized variations in execution of the study protocol by including data from one perfusionist	No: the authors performed the analysis on the database as described in the methods section	Questionable: retrospective documentation may have failed to include important variations in surgery protocol	Questionable: no documentation of protocol deviations
5	Was the assessor blinded to the outcome, exposure, or intervention status of the participants?	No	No	No	No	No	No
6	Were valid and reliable measures used or implemented consistently across all study participants?	Questionable: due to the retrospective data collection in control patients, data quality may be suboptimal	Yes	Yes	Yes	Questionable: due to the retrospective study design, data quality may be suboptimal	Questionable: due to retrospective data collection in control patients' data quality may be suboptimal
7	Was the length of follow-up different across study groups?	Yes: the hospital LOS was significantly shorter in the RAP group	No: all patients were followed until the end of the surgical procedure	Questionable: no information regarding hospital LOS provided	No: all data was recorded intraoperatively	No: hospitalization days were similar across groups	No
8	In cases of missing data, was the impact assessed?	NA: no record of missing data	NA: no record of missing data	NA: no record of missing data	No: parameters with missing data were excluded in regression analysis and patients with missing data were excluded	NA: no record of missing data	NA: no record of missing data
9	Are any important primary outcomes missing from the results?	No	Yes: the number of PRBC transfusions postoperatively is not documented	No: no primary outcomes are missing, however, the authors did not discriminate between intrao perative and postoperative transfusion	Yes: the number of PRBC transfusions postoperatively is not documented	Yes: the number of PRBC transfusions postoperatively is not documented	Yes: the number of PRBC transfusions postoperatively is not documented

(Continued)

Table 7. (Continued)

Item		Kearsey et al.[26]	Nanjappa et al.[27]	Ševerdija et al.[24]	Stammers et al.[28]	Trapp et al.[18]	Vandewiele et al.[29]
10	Are any important harms or adverse events that may be a consequence of the intervention/exposure missing from the results?	No	No	No	No	No	No
11	Did the study fail to balance the allocation between the groups or match?	Questionable: unclear whether matching was performed, no documentation of method of selection of control patients	Yes: no balancing of study group allocation was performed	Yes: no balancing of allocation was performed	No: study groups were not determined but observed in the database	Questionable: method of matching to study groups is not documented	Yes: no balancing of study group allocation was performed
12	Were important confounding variables taken into account in the design and/or analysis?	No: no description of the matching procedure is provided, no multivariate analysis performed. Not all factors that influence fluid balance are reported[a]	No: no matching or multivariate analysis were performed. Not all factors that influence fluid balance are reported[a]	Questionable: multivariate analysis was performed, however, not all important factors were included, nor did the authors justify why others factors that affect transfusion requirements were not included	No: no matching or multivariate analysis were performed. Not all factors that influence fluid balance are reported[a]	No: no description of the matching procedure is provided (considering size, weight, and age), no multivariate analysis performed, the factor fluid balance is not specified, and not all factors that influence fluid balance are reported[a]	Questionable: multivariate analysis was performed, however, not all important factors were included, nor did the authors justify why others factors that affect transfusion requirements were not included
13	Overall assessment: are results believable taking study limitations into account?	Questionable: the lack of information regarding fluid balance makes interpretation difficult, presence of several types of bias cannot be excluded	No: multiple types of bias might substantially affect the study results	Yes: the authors included not all but most important parameters regarding fluid balance	Questionable: the lack of information regarding fluid balance makes interpretation difficult, presence of several types of bias cannot be excluded	Questionable: the lack of information regarding fluid balance makes interpretation difficult, presence of several types of bias cannot be excluded	Questionable: the lack of information regarding fluid balance makes interpretation difficult, presence of several types of bias cannot be excluded

NA: not applicable; LOS: length of stay; PRBC: packed red blood cells; RAP: retrograde autologous priming.
[a]At least one of the following factors which affect fluid balance were not taken into account or documented: type and/or dosage of cardioplegia used, the mean arterial blood pressure target during CPB, the use of autotransfusion, the use of hemofiltration, intraoperative blood loss, and the patients' weight/length/body mass index, and/or the transfusion trigger.

Table 8. Summary of the assessment of bias of observational studies.

Item		Kearsey et al.[26]	Nanjappa et al.[27]	Ševerdija et al.[24]	Stammers et al.[28]	Trapp et al.[18]	Vandewiele et al.[29]
1	Do the inclusion/exclusion criteria vary across the comparison groups of the study?	LR	LR	LR	LR	LR	LR
2	Does the strategy for recruiting participants into the study differ across groups?	LR	LR	QR	LR	LR	LR
3	Is the selection of the comparison group inappropriate?	LR	LR	LR	LR	LR	LR
4	Does the study fail to account for important variations in the execution of the study from the proposed protocol?	LR	QR	LR	LR	QR	QR
5	Was the assessor blinded to the outcome, exposure, or intervention status of the participants?	HR	HR	HR	HR	HR	HR
6	Were valid and reliable measures used or implemented consistently across all study participants to assess inclusion/exclusion criteria, intervention/exposure outcomes, participant benefits and harms, and potential confounders?	QR	LR	LR	LR	HR	QR
7	Was the length of follow-up different across study groups?	HR	LR	QR	LR	LR	LR
8	In cases of missing data, was the impact assessed (e.g. through sensitivity analysis or other adjustment method)?				HR		
9	Are any important primary outcomes missing from the results?	LR	HR	LR	HR	HR	HR
10	Are any important harms or adverse events that may be a consequence of the intervention/exposure missing from the results?	LR	LR	LR	LR	LR	LR
11	Did the study fail to balance the allocation between the groups or match groups (e.g. through stratification, matching, propensity scores)?	QR	HR	HR	LR	QR	HR
12	Were important confounding variables not taken into account in the design and/or analysis (e.g. through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment such as instrumental variables)?	HR	HR	QR	HR	QR	QR
13	Are results believable taking study limitations into consideration?	QR	HR	LR	QR	QR	QR

LR: low risk of bias; QR: questionable risk of bias; HR: high risk of bias.

volumes in the RAP groups were significantly higher in the studies that concluded RAP was not beneficial in terms of lowering blood transfusions (Mann–Whitney U test, median priming volume in RAP groups 1,131 vs. 748 mL, $p = 0.036$).

From the eight included studies, seven used the intraoperative PRBC transfusion rate as an outcome measurement, of which some also report the transfusion rate in the entire perioperative period. Three studies only reported the intraoperative transfusion rate without any information regarding the total perioperative or postoperative transfusion rate.

Discussion

This systematic literature review assessed the evidence for the relationship between RAP and the reduction of allogeneic blood transfusions. The hypothesis was that RAP results in a decreased need of blood transfusions, which is beneficial in terms of the risk of complications associated with transfusion as well as costs. Eight studies were included, of which two randomized and six observational trials. Five studies including one randomized trial found that application of RAP is associated with a significant decrease of blood transfusion in the perioperative period.

In the three studies reporting no significant benefit of RAP in terms of blood transfusion requirements, the priming volumes were surprisingly higher as compared to the five studies that did report a decreased transfusion rate in the RAP group. One may hypothesize that the absolute priming volume in the RAP groups was too high in the studies in which no decrease in transfusions was found, resulting in comparable rates of blood transfusions across

groups. Moreover, it is possible that patient management strategies in these three studies did not allow for using lower priming volumes, resulting in the inability to find a significant difference in blood transfusion rate between the RAP and control groups.

When taking a closer look at these three studies, it becomes apparent that the study by Reges et al.[25] is a prospective but small-scale pilot study. The small sample size (n = 27 in the RAP group) may be the reason the authors could not identify a significant difference between the RAP and non-RAP group.

Second, the study by Kearsey et al.[26] consists of part prospectively (RAP group) and part retrospectively (control group) collected data. The authors found no difference in blood transfusion rates between groups, even though the difference in priming volume between groups is large, approximately 1,400 mL, which is translated to the significant difference in hemoglobin values at initiation of CPB, 9.1 g/dL in the RAP group versus 7.8 g/dL in the control group. Although the authors report that no changes in clinical care occurred during the prospective inclusion period, a defined care pathway was lacking, potentially resulting in small but significant changes leading to improved patient care and shorter hospital stays, as they observed in the RAP group.

Finally, the third study in which RAP appeared to have no benefit in terms of blood transfusions,[27] the use of RAP was included in a univariate logistic regression model, while no testing based on differences in means or medians between study groups was conducted.

The study by Ševerdija et al.[24] reported a significant benefit of RAP in terms of blood transfusions. The authors showed that patients in the RAP group received significantly fewer transfusion products as compared to the control group. The patients in the RAP group also had less postoperative blood loss, which may have been a potential source of bias, since blood loss is one of the major reasons for postoperative blood transfusion. The multivariate regression analysis, on the other hand, did not include postoperative blood loss. Hence, its influence may be only marginal as compared to other apparently more relevant factors such as age and preoperative hematocrit.

In the study by Stammers et al.,[28] the SpecialtyCare Operative Procedure rEgistry (SCOPE) was used, analyzing data from 171 hospitals throughout the United States, of which 12,677 patients undergoing cardiac surgery with RAP and 2,221 patients undergoing surgery without blood conservation strategies. A significantly lower intraoperative transfusion rate was noted in patients undergoing RAP compared to those who did not. Several factors affecting fluid balance, that is, postoperative transfusion rate and blood loss volume, were not reported and thus not included in the analysis. This might have introduced bias in the obtained results. Another potential risk of bias can be found in the fact that the transfusion trigger was not reported but known to vary between the different hospitals included in the database. Moreover, the authors note a potential gender-specific difference in the efficacy of blood conservation modalities. Patients who are anemic or lower in BSA may benefit more from RAP in terms of intraoperative hematocrit values.[30] One could argue that RAP should always be performed since the harmful effects of hemodilution are more pronounced in this subset of patients.[16] However, there are a few practical implications that must be considered. First and foremost, it is not possible to safely perform RAP in (imminent) hemodynamically unstable patients due to the fact that the volume of blood withdrawal during the procedure will cause further deterioration of the patient's status.[16] Usually, 500 to 1,000 mL of oxygenated autologous blood is withdrawn via the arterial cannula, depending on the patient's hemodynamic status.[16] Most cardiac surgical centers use a RAP protocol in which the systolic blood pressure is kept above 100 mm Hg, using boluses of phenylephrine during RAP.[16,20,24] Due to the prerequisite of a hemodynamically stable patient, RAP cannot be used in emergency procedures and patients with a low volume status.

Regardless of the fact that RAP is not possible for all cardiac surgical patients undergoing on-pump surgery, the blood-sparing technique does seem to reduce the need of perioperative blood transfusions in appropriate cases.[31] Taking into account that RAP is considered safe with no increased risk of complications,[31,32] one could argue that RAP should be implemented as standard CPB practice in order to decrease the negative effects of hemodilution and concomitant anemia.[9]

Inherent to the type of intervention, it is not possible blind all relevant parties when conducting a study on the effects of RAP. This means that blinding of the administrator of the intervention (the clinical perfusionist) is simply not possible. Hence, none of the studies scored a "low risk of bias" in terms of blinding. In randomized trials, the intensive care unit staff members who are responsible for administrating postoperative blood transfusions were blinded, which is beneficial in terms of limiting bias in the postoperative period. Given the fact that neither of both randomized studies report their transfusion trigger, there is a questionable risk of performance bias in these studies.

Several types of bias could not be excluded in any of the individual studies. Consequently, one may question the credibility of the study results. Although complete blinding of all staff who can administer blood products in a study aiming at determining the efficacy of RAP for diminishing PRBC use is impossible, other sources of bias should be excluded in future studies to increase the level of evidence. Prospective, multi-center trials are

necessary to increase the level of evidence for the relationship between RAP and PRBC use in the cardiac surgical patient.

Important to note is that all of the included studies lacked information on at least one parameter related to fluid balance. These may include but are not limited to the volume administrated by the anesthesiologist, the type and dose of cardioplegic solution, intraoperative and postoperative blood loss, the use of hemofiltration, use of autotransfusion, urine output, and the patient's BMI. During bypass, the clinical perfusionist can utilize several tools to influence the patient's fluid balance, such as administrating medication to regulate blood pressure, the Trendelenburg position to recruit blood volume from the lower extremities, hemofiltration of the circulating volume to eliminate volume, and autotransfusion to administer washed autologous blood back to the patient.[24] In case differences exist between study groups in one or more of these factors, this is likely to affect the risk of blood transfusion and thereby the observed PRBC use. Differences in total bias between the individual studies could therefore not be established.

When interpreting the results of this systematic review, several limitations have to be taken into account. On the level of the included studies, only two randomized controlled trials were included in this review. Although randomized controlled trials are considered the highest level of evidence besides a meta-analysis and systematic literature review, to date, the plurality of studies are observational and mostly use a retrospective design. Costs and time available to conduct a study are factors that in many cases outweigh the benefits of a prospective randomized trial. Moreover, no multicenter studies were found, which would have added to the justification of RAP as a standard in CPB technique. As for the risk of bias in individual studies, we found that none of the studies was considered to have none or an overall "low risk of bias." One important note is that most studies lack a complete description of the factors affecting fluid balance and intraoperative patient management. In addition, not all studies reported the transfusion trigger used in their institution, which directly affects the number of blood products transfused in the operating theater and the postoperative care unit. Due to the limited number of publications available, it remains difficult to find a clear answer on the research question.

Conclusion

Application of RAP resulted in a significant decrease in PRBC transfusions in the majority of studies. However, it is important to note that relatively few articles are available, which are flawed by several types of bias. Therefore, a prospective, randomized multi-center trial is warranted in which all parameters affecting volume status are taken into account to ultimately gain better insight in the contribution of RAP in bloodless cardiac surgery.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Nousjka PA Vranken https://orcid.org/0000-0002-6547-7008

References

1. Vranken NPA, Weerwind PW, Barenbrug PJC, et al. The role of patient's profile and allogeneic blood transfusion in development of post-cardiac surgery infections: a retrospective study. *Interact Cardiovasc Thorac Surg* 2014; 19: 232–238.
2. Youssef LA, Spitalnik SL. Transfusion-related immunomodulation: a reappraisal. *Curr Opin Hematol* 2017; 24: 551–557.
3. Santos AA, Sousa AG, Piotto RF, et al. Mortality risk is dose-dependent on the number of packed red blood cell transfused after coronary artery bypass graft. *Rev Bras Cir Cardiovasc* 2013; 28: 509–517.
4. Murphy GJ, Reeves BC, Rogers CA, et al. Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. *Circulation* 2007; 116: 2544–2552.
5. Brouwers C, Hooftman B, Vonk S, et al. Benchmarking the use of blood products in cardiac surgery to stimulate awareness of transfusion behaviour: results from a four-year longitudinal study. *Neth Heart J* 2017; 25: 207–214.
6. Hwang NC. Preventive strategies for minimizing hemodilution in the cardiac surgery patient during cardiopulmonary bypass. *J Cardiothorac Vasc Anesth* 2015; 29: 1663–1671.
7. Mathew JP, Mackensen GB, Phillips-Bute B, et al. Effects of extreme hemodilution during cardiac surgery on cognitive function in the elderly. *Anesthesiology* 2007; 107: 577–584.
8. Severdija EE, Vranken NP, Simons AP, et al. Hemodilution combined with hypercapnia impairs cerebral autoregulation during normothermic cardiopulmonary bypass. *J Cardiothorac Vasc Anesth* 2015; 29: 1194–1199.
9. Loor G, Rajeswaran J, Li L, et al. The least of 3 evils: exposure to red blood cell transfusion, anemia, or both. *J Thorac Cardiovasc Surg* 2013; 146: 1480–1487.

10. Balachandran S, Cross MH, Karthikeyan S, et al. Retrograde autologous priming of the cardiopulmonary bypass circuit reduces blood transfusion after coronary artery surgery. *Ann Thorac Surg* 2002; 73: 1912–1918.
11. Campbell JA, Holt DW, Shostrom VK, et al. Influence of intraoperative fluid volume on cardiopulmonary bypass hematocrit and blood transfusions in coronary artery bypass surgery. *J Extra Corpor Technol* 2008; 40: 99–108.
12. Hogan M, Klein AA, Richards T. The impact of anaemia and intravenous iron replacement therapy on outcomes in cardiac surgery. *Eur J Cardiothorac Surg* 2015; 47: 218–226.
13. Chatterjee S, Hoff WJ, Pearson PJ. Advantages to miniaturized cardiopulmonary bypass for adult cardiac surgery. *Clin Exp Cardiolog* 2011; S7: 1–4.
14. McKay C. Perfusion approaches to blood conservation. *Semin Cardiothorac Vasc Anesth* 2007; 11: 252–255.
15. Esper SA, Waters JH. Intra-operative cell salvage: a fresh look at the indications and contraindications. *Blood Transfus* 2011; 9: 139–147.
16. Rosengart TK, DeBois W, O'Hara M, et al. Retrograde autologous priming for cardiopulmonary bypass: a safe and effective means of decreasing hemodilution and transfusion requirements. *J Thorac Cardiovasc Surg* 1998; 115: 426–438.
17. Panico FG, Neptune WB. A mechanism to eliminate the donor blood prime from the pump-oxygenator. *Surg Forum* 1960; 10: 605–609.
18. Trapp C, Schiller W, Mellert F, et al. Retrograde autologous priming as a safe and easy method to reduce hemodilution and transfusion requirements during cardiac surgery. *Thorac Cardiovasc Surg* 2015; 63: 628–634.
19. Cheng M, Li JQ, Wu YC, et al. Short-term effects and safety analysis of retrograde autologous blood priming for cardiopulmonary bypass in patients with cardiac valve replacement surgery. *Cell Biochem Biophys* 2015; 73: 441–446.
20. Murphy GS, Szokol JW, Nitsun M, et al. The failure of retrograde autologous priming of the cardiopulmonary bypass circuit to reduce blood use after cardiac surgical procedures. *Anesth Analg* 2004; 98: 1201–1207.
21. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *International Journal of Surgery* 2010; 8: 336–341.
22. Higgins JPT, Green S. *Cochrane handbook for systematic reviews of interventions* (Appendix F Cochrane Risk of Bias Tool). London: The Cochrane Collaboration, 2011.
23. Viswanathan M, Berkman ND, Dryden DM, et al. *Assessing risk of bias and confounding in observational studies of interventions or exposures: further development of the RTI Item bank*. Methods research report, Prepared by RTI–UNC Evidence-based practice center under contract no. 290-2007-10056-I, AHRQ Publication no. 13-EHC106-EF, August 2013. Rockville, MD: Agency for Healthcare Research and Quality. www.effectivehealthcare.ahrq.gov/reports/final.cfm
24. Ševerdija EE, Heijmans JH, Theunissen M, et al. Retrograde autologous priming reduces transfusion requirements in coronary artery bypass surgery. *Perfusion* 2011; 26: 315–321.
25. Reges RV, Vicente WV, Rodrigues AJ, et al. Retrograde autologous priming in cardiopulmonary bypass in adult patients: effects on blood transfusion and hemodilution. *Rev Bras Cir Cardiovasc* 2011; 26: 609–616.
26. Kearsey C, Thekkudan J, Robbins S, et al. Assessing the effectiveness of retrograde autologous priming of the cardiopulmonary bypass machine in isolated coronary artery bypass grafts. *Ann R Coll Surg Engl* 2013; 95: 207–210.
27. Nanjappa A, Gill J, Sadat U, et al. The effect of retrograde autologous priming on intraoperative blood product transfusion in coronary artery bypass grafting. *Perfusion* 2013; 28: 530–535.
28. Stammers AH, Mongero LB, Tesdahl E, et al. The effectiveness of acute normolvolemic hemodilution and autologous prime on intraoperative blood management during cardiac surgery. *Perfusion* 2017; 32: 454–465.
29. Vandewiele K, Bove T, De Somer FM, et al. The effect of retrograde autologous priming volume on haemodilution and transfusion requirements during cardiac surgery. *Interact Cardiovasc Thorac Surg* 2013; 16: 778–783.
30. Hou X, Yang F, Liu R, et al. Retrograde autologous priming of the cardiopulmonary bypass circuit reduces blood transfusion in small adults: a prospective, randomized trial. *Eur J Anaesthesiol* 2009; 26: 1061–1066.
31. Sun P, Ji B, Sun Y, et al. Effects of retrograde autologous priming on blood transfusion and clinical outcomes in adults: a meta-analysis. *Perfusion* 2013; 28: 238–243.
32. Murphy GS, Szokol JW, Nitsun M, et al. Retrograde autologous priming of the cardiopulmonary bypass circuit: safety and impact on postoperative outcomes. *J Cardiothorac Vasc Anesth* 2006; 20: 156–161.