Avoiding Transfusions in Children Undergoing Cardiac Surgery: A Meta-Analysis of Randomized Trials of Aprotinin

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Aprotinin, a potent antifibrinolytic drug, reduces the proportion of adults who receive blood transfusions during cardiac surgery, although the effect in children remains unclear. We performed a systematic review of the literature to identify all English language, randomized controlled trials of aprotinin involving children undergoing corrective or palliative cardiac surgery with cardiopulmonary bypass. All studies were assessed for methodological quality, and sources of heterogeneity were examined. We measured the effect of aprotinin on the proportion of children transfused, the volume of blood transfused, and the volume of chest tube drainage. Twelve trials enrolling 626 eligible children met the inclusion criteria. Aprotinin reduced the proportion of children who received red blood cell or whole blood transfusions during cardiac surgery by 33% (relative risk = 0.67; 95% confidence interval, 0.51 to 0.89). Aprotinin did not have a significant effect on the volume of blood transfused or on the amount of postoperative chest tube drainage. Most of the studies were of poor methodological quality and predefined transfusion triggers were infrequently used. Overall, aprotinin reduced the proportion of children who received blood transfusion during cardiac surgery with cardiopulmonary bypass. Further high-quality trials with clinically important outcomes may be warranted before aprotinin can be routinely recommended in this population.

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Children with congenital heart defects (CHD) often require corrective or palliative cardiac surgery. Perioperative bleeding frequently complicates this procedure as a result of the acquired hemostatic defects associated with cardiopulmonary bypass (CPB) (1) as well as low levels of clotting factors associated with blood volume dilution (2). Thus, allogeneic blood products are often administered to these children, exposing them early in their lives to the small but important risks associated with blood transfusion.

Aprotinin, a serine protease inhibitor, is a potent antifibrinolytic medication that rapidly inhibits human plasmin, trypsin, and kallikrein. It is indicated for the prevention and treatment of the bleeding diatheses associated with profibrinolytic states and mitigates CPB-induced platelet dysfunction by preserving glycoprotein Ib and glycoprotein IIb/IIIa function on the platelet surface (3). Side effects of aprotinin include hypersensitivity reactions in 0.3% to 0.6% of patients upon re-exposure to the drug (4–6), an increased risk of perioperative myocardial infarction (7) and venous thrombosis (8).

A meta-analysis of 61 trials (n = 7027) of adults undergoing elective surgery demonstrated that aprotinin reduced the proportion of patients exposed to at least one unit of allogeneic red blood cells (RBC) by 30% (relative risk [RR] = 0.70; 95% confidence interval [CI], 0.64–0.76) compared with controls (9). Similarly,

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a meta-analysis of 35 trials ($n = 3879$) of adult patients undergoing coronary artery bypass grafting showed that aprotinin reduced the proportion of patients transfused by 39% (RR = 0.61; 95% CI, 0.58–0.66) (10). The effectiveness of aprotinin in children undergoing cardiac surgery is unclear, as randomized clinical trials (RCTs) in this population have reported conflicting results. The objective of this systematic review was to determine the effect of IV aprotinin administered perioperatively to children undergoing cardiac surgery with CPB on the proportion of children requiring allogeneic RBC or whole blood transfusions, the volume of blood transfused, and the amount of chest tube drainage in the immediate postoperative period.

Methods

We searched the electronic databases of MEDLINE (1966 to November Week 3 2004) and EMBASE (1980 to 2005 Week 02) using the following keywords and textword search terms: *antifibrinolytic agents, aprotinin, antagosan, antilysin, fase, gordox, kir, repulson, pantinol, kallikrein-trypsin, bovine pancreatic trypsin, cardiopulmonary bypass, thoracic surgery, cardiac surgery, blood transfusion, hemorrhage, transfusion$, bleed$, blood loss$, hemorrhag$*. Citations were limited to RCT (11). The "related article search" of the PUBMED search engine was used to search citations relating to a representative article (12). The Cochrane Registry for Controlled Trials was searched using the terms "aprotinin" and "child." We conducted a cited reference search of the Boldt et al. article (13) through the Web of Science portal. We identified abstracts through the PapersFirst portal by searching the keywords "aprotinin" and "bypass;" and proceedings were identified through ProceedingsFirst using the keyword "blood conservation." Finally, we hand-searched bibliographies of relevant citations and reviews.

After initial screening, two independent reviewers examined the abstracts of potentially eligible RCT and selected those which met all of the following predefined inclusion criteria: 1) random allocation of all study treatment arms; 2) enrollment of children <18 yr of age; 3) primary or redo open-heart surgery with CPB for repair or palliation of CHD; 4) preoperative or intraoperative administration of IV aprotinin in any dose; 5) use of placebos, no aprotinin or other antifibrinolytic drugs as controls; 6) clinical outcomes that included the proportion of children requiring blood transfusion, the amount of transfused blood and/or the amount of chest tube drainage. RBC or whole blood transfusions were counted as the outcome unless the type of "blood transfusion" was not specified. The only exclusion criterion was non-English language publications.

We abstracted the following data: study design and source of funding; patient inclusion and exclusion criteria; number of patients screened and enrolled; average age, weight, and body mass index; number of patients with cyanotic heart disease; types of corrective surgical procedures; CPB variables; details of transfusion protocols; and doses of aprotinin. Outcome data we abstracted were the number of children requiring transfusion of any blood product (in excess of pump prime); volume of blood transfused; volume of postoperative chest tube drainage; therapy-related complications; and mortality. We contacted the corresponding authors to obtain missing data when possible.

Methodologic quality of the included trials were judged by two independent reviewers blinded as to the authors, affiliated institutions, sponsors, journal name, date of publication, and study results. We used the Jadad quality assessment scale (14), which assigns 1 point for each of the following criteria: 1) randomized treatment allocation; 2) appropriate methods of randomization; 3) the use of a double-blind study maneuver; 4) appropriate methods for double-blinding; and 5) a description of all withdrawals and dropouts. An overall score of 2 or lower was considered "poor" methodological quality (14). Furthermore, reviewers were asked to judge the adequacy of the method of allocation concealment and the use of an objective, predefined transfusion protocol.

When measures of variance were unavailable, they were imputed using mathematical formulae assuming a normal distribution of the data. The reported volumes of blood transfused and chest tube drainage were standardized by converting to mL/kg using the mean body weight or average body surface area of the study population where necessary. For multiarmed studies comparing different doses of aprotinin, the proportion of children transfused was determined by the total number of cases in all aprotinin arms divided by the total number of children; the amount of blood transfused and chest tube drainage were estimated by calculating the mean of all aprotinin arms. The random effects model of DerSimonian and Laird (15) was used to calculate the pooled RR for the proportion of children transfused, and the weighted mean difference (WMD) was calculated by pooling results of continuous variables (volume of transfused blood and volume of chest tube drainage), weighted by the inverse of the variance. We used Review Manager Version 4.2.3 (The Nordic Cochrane Centre, The Cochrane Collaboration 2003, Copenhagen, Denmark) for the analyses. Funnel plots were inspected for evidence of publication bias. We quantified the percentage of total variation across studies using the I^2 test for heterogeneity and defined a low, moderate, and high I^2 as 25%, 50%, and 75%, respectively (16). The *a priori* sources of heterogeneity we proposed were 1) study quality; 2)

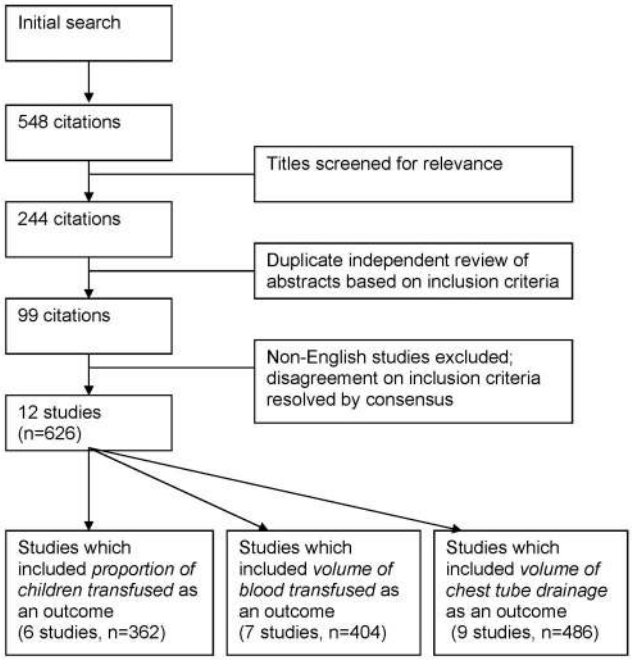

Figure 1. Results of article search and selection.

type of procedure (primary or redo sternotomies); 3) age or weight criteria; 4) cyanotic morphologies; and 5) aprotinin dose.

Results

Agreement between reviewers on study selection was moderate ($\kappa = 0.52$). Disagreement was often attributable to unspecified age criteria and/or surgical procedures in the abstracts of potentially eligible studies; however, disagreement was resolved by consensus in all cases. Initial agreement between reviewers on quality assessment was poor ($\kappa = 0.21$); however, this scale has been associated with considerable interrater variability (17). Disagreement was resolved by third-party adjudication in all cases.

We identified 548 citations representing 541 published articles and 7 abstracts by the comprehensive literature search. Titles were screened for relevance, leaving 244 citations, of which 11 full publications (12,13,18–26) and one abstract (27) were included in this review, enrolling a total of 626 children between the ages of <1 and 16 yr (Fig. 1). Of the 12 studies, 7 were 2-arm trials comparing aprotinin to either placebo or no therapy (12,13,19,22,23,25,27) and 4 included 3 intervention groups (large-dose aprotinin, small-dose aprotinin, and either placebo or no treatment) (5,18,21,24). There was no uniform definition of large- or small-dose aprotinin regimens among studies. All treatments were randomly allocated except for the large-dose aprotinin arm in the study by Miller et al. (24); therefore, this arm was not considered in the analysis. One study included 2 groups with active controls, ε-aminocarproic acid and the combination of ε-aminocarproic acid plus aprotinin, in addition to a standard control group (no aprotinin) (20). The active control arms that used other antifibrinolytic drugs were not included in this analysis. The number of adverse events in the treatment arms was reported in 6 trials (12,21–24,26); none were considered to be attributable to aprotinin.

Of the 578 surgical procedures reported in the 12 studies, the most frequent was Tetralogy of Fallot repair ($n = 140$), followed by atrial septal defect and and/or ventricular septal defect repair including complete atrio-ventricular septal defects ($n = 123$); repair of transposition of the great arteries ($n = 74$); repair of hypoplastic left heart syndrome including Fontan and modified Fontan procedures ($n = 71$); and valvular replacements or repairs ($n = 46$). The details of CPB were similar among studies; in most studies, core body temperature was decreased to 24.0°C–30.1°C, blood flow rates were maintained 2.4 $L/m^2/min$ and a cardiac membrane oxygenator was used. The cardiac bypass pump was generally primed with colloid and crystalloid solutions in addition to allogeneic RBCs or whole blood. Further characteristics of each study, including aprotinin dosages, patient age, and weight are summarized in Table 1.

Four of 12 studies were judged to be of good methodological quality (12,21–23). Two studies adequately described the method of randomization (20,22), and in only one (22) were those methods appropriate. Four studies used placebo as the control group (12,21–23), 2 of which were described as identical (12,23), and none of the other 8 studies were described as double-blind (13,18–20,24–27). One study described the method of allocation concealment (20), and none of the studies adequately reported the number or reasons for withdrawals and dropouts (Table 2).

Six studies representing 362 children reported the proportion of children requiring at least one allogeneic RBC or whole blood transfusion after surgery with and without aprotinin (12,19,21–24). The mean age of children in these studies was 3.3 yr (range, 3.6 mo to 14.5 yr) and the mean weight was 12.6 kg (range, <3.5 to 42.5 kg). Aprotinin reduced the proportion of children transfused by 33% (RR = 0.67; 95% CI, 0.51 −0.89) (Fig. 2). The percentage of total variation across studies attributable to heterogeneity was low ($I^2 = 15\%$). When only the 4 studies of good methodological quality (12,21–23) were pooled, the effect of aprotinin on the proportion of children transfused remained statistically significant (RR = 0.60; 95% CI, 0.38-0.95). Similarly, when only the 3 studies that used an objective transfusion protocol were pooled (21–23), the effect of aprotinin was significant (RR = 0.72; 95% CI, 0.58-0.89). Three

Table 1. Description of the Primary Studies Included in the Meta-analysis

Study	*N*	Control group	Aprotinin dose	Age (months)*	Weight (kg)*
Mossinger 2003 (12)	60	Placebo	30,000 KIU/kg + 50,000 KIU prime	4.8†	4.9†
Chauhan 2000 (20)	180	EACA Aprotinin + EACA No treatment	10,000 KIU/kg + 10,000 KIU/kg prime + 10,000 KIU/hr x 3hr post CPB	49.2 ± 14.4	6.2 ± 2.2
Miller 1998 (24)	30	No treatment	20,000 KIU/kg + 10,000 KIU/kg/hr until skin closure + 20,000 KIU/kg prime	52.8 ± 50.4	15.4 ± 7.9
Davies 1997 (22)	39	Placebo	**BSA <1.16m²**: 140,000 KIU/m^2 + 56,000 KIU/m^2/hr until skin closure+ 240,000 KIU/m^2 prime **BSA >1.16m²**: 250,000 KIU/m^2 + 70,000 KIU/m^2/hr until skin closure+ 280,000 KIU/m^2 prime	44.8 ± 16.3	13.0 ± 4.7
Seghaye 1996 (25)	25	No treatment	10,000 KIU/kg + 10,000 KIU prime	77 (9.5–151)	NR
D'Errico 1996 (21)	57	Placebo	**SD:** 120mg/m^2 + 28mg/m^2 continuous infusion+ 120mg/m^2 prime **LD:** 240mg/m^2 + 56mg/m^2 continuous infusion+ 240mg/m^2 prime	30.0† (3.6–153.6)	14.9 ± 9.3
Boldt 1994 (19)	30	No treatment	30,000 KIU/kg + 30,000 KIU/kg/hr during CPB+ 30,000 KIU/kg prime	33.6 ± 10.5	11.0 ± 7.5
Herynkopf 1994 (23)	30	Placebo	2.8mg/kg + 1.4mg/kg by continuous infusion during CPB+ 1.4mg/kg prime	8.0–132.0	16.4
Boldt 1993 (13)	48	No treatment	25,000 KIU/kg + 25,000 KIU/kg/hr during CPB+ 25,000 KIU/kg prime	21.1 ± 8.2	10.9 ± 1.6
Boldt 1993 (18)	42	No treatment	**LD:** 35,000 KIU/kg + 10,000 KIU/kg/min during surgery+ 35,000 KIU/kg prime **SD:** 20,000 KIU/kg + 20,000 KIU/kg/hr during CPB+ 20,000 KIU/kg prime	13.2 ± 7.6	12.3 ± 4.6
Dietrich 1993 (26)	60	No treatment	**LD:** 30,000 KIU/kg + 30,000 KIU/kg prime **SD:** 15,000 KIU/kg + 15,000 KIU/kg prime	9.1 ± 7.6	6.0 ± 2.1
Gomar 1995 (27)	25	Placebo	240 mg/m^2 + 50 mg/m^2/h until the end of surgery+ 50 mg KIU/m^2 prime	NR	>10kg

Prime = added to the cardiopulmonary bypass (CPB) circuit; *BSA* = body surface area; *EACA* = ε-aminocaproic acid; *LD* = large dose; *KIU* = kallikrein-inhibiting units; *SD* = small dose; *NR* = not reported.
* Mean ± SD or range (min–max), unless otherwise stated
† Median

(12,19,23) of the 6 studies enrolled patients undergoing primary sternotomy only; the proportion of children transfused was reduced by 56% in this group (RR = 0.44; 95% CI, 0.26–0.76). The average weight of children in 5 of the 6 studies was more than 10 kg (19,21–24) and the effect of aprotinin remained significant in these studies (RR = 0.73; 95% CI, 0.59–0.89). Even in the single trial (12) that exclusively enrolled children less than 10 kg, the effect of aprotinin was significant. None of the studies enrolled

Table 2. Design Features and Overall Assessment of Methodological Quality of the Primary Studies

Study	Method of Randomization	Funding source	Blinding	Allocation concealment	Withdrawals and dropouts	Objective transfusion protocol?	Methodological quality score†
Mossinger (12)	NR	NR	Placebo	NR	NR	No	3
Chauhan (20)	Unmarked envelopes	NR	NR	Unmarked envelopes	NR	No	0
Miller (24)	NR	NR	NR	NR	NR	No	1
Davies (22)	Computer generated tables	Industry	Placebo	NR	NR	Yes	3
Seghaye (25)	NR	NR	NR	NR	NR	No	1
D'Errico (21)	NR	Industry	Equal volume placebo	NR	NR	Yes	3
Boldt (19)	NR	NR	NR	NR	NR	Yes	1
Herynkopf (23)	NR	NR	Placebo	NR	NR	Yes	3
Boldt (13)	NR	NR	NR	NR	NR	Yes	0
Boldt (18)	NR	NR	NR	NR	NR	Yes	1
Gomar (27)	NR	NR	NR	NR	NR	No	1
Dietrich (26)	NR	NR	NR	NR	NR	No	1

NR = not reported
† Based on the methodological quality assessment scale of Jadad et al. (14) (maximum score is 5); a score of 2 or lower was considered "poor" methodological quality by this scale.

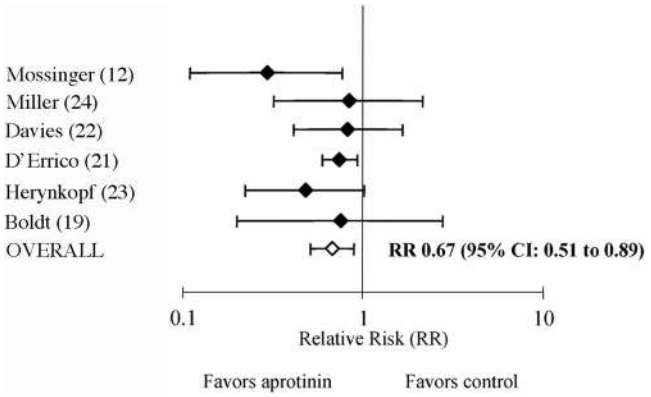

Figure 2. Pooled relative risk (RR) for the proportion of children who received red blood cells or whole blood transfusions after cardiac surgery with aprotinin. RR < 1 (dashed line) favors aprotinin, RR > 1 favors control. Diamonds represent point estimates; bars represent 95% confidence limits.

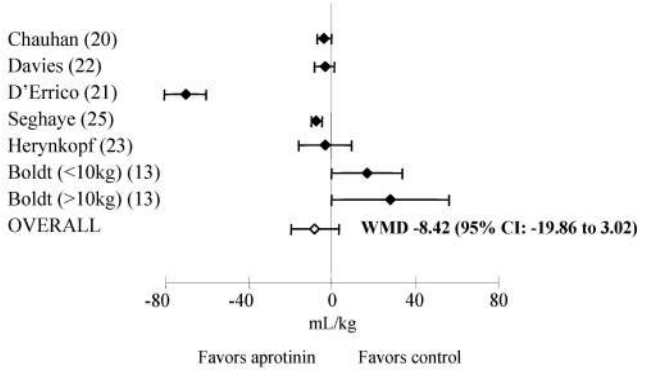

Figure 3. Weighted mean difference (WMD) in volume of blood transfused (mL/kg) to children after cardiac surgery. A reduction in the volume of blood transfused (negative WMD) favors aprotinin. Diamonds represent point estimates; bars represent 95% confidence limits.

children with cyanotic or noncyanotic CHD exclusively and each study used a different aprotinin dose regimen precluding analysis of these subgroups.

Seven studies enrolling 404 children reported the volume of blood transfused (13,20–23,25,27) and 10 studies enrolling 571 children reported the volume of chest tube drainage postoperatively with and without aprotinin (12,13,18–22,24,26,27). The effect of aprotinin on the volume of blood transfused (Fig. 3) and on the volume of chest tube drainage (Fig. 4) was not statistically significant (WMD = −8.42 mL/kg, 95% CI, −19.86 to 3.02; WMD = −0.97 mL/kg, 95%CI, −4.94 to 2.99, respectively). Heterogeneity across studies was high for these outcomes (I^2 = 96% for volume of blood transfused and 77% for volume of chest tube bleeding).

Discussion

In this meta-analysis of RCTs, aprotinin reduced the proportion of children who received RBCs or whole blood transfusions after cardiac surgery with CPB by 33%. The effect of aprotinin remained significant in the subgroup of children undergoing primary sternotomy, perhaps because primary procedures involve less anatomical disruption of wound scars and adhesions compared to redo operations. We also performed a sensitivity analysis based on weight, as smaller infants may be more prone to bleeding (29); the effect of aprotinin on the proportion of children transfused remained significant in the studies of children >10 kg and in the one study that enrolled children <10 kg exclusively. Although the proportion of children transfused was reduced, there was no difference in the volume of blood transfused or on the

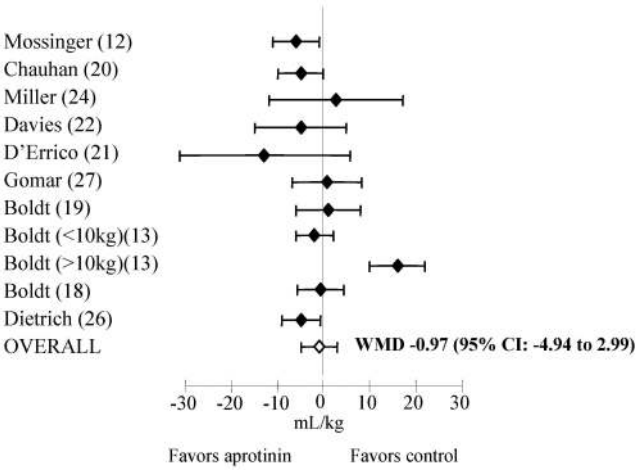

Figure 4. Weighted mean difference (WMD) in volume of postoperative chest tube drainage (mL/kg) for children after cardiac surgery. A reduction in chest tube drainage (negative WMD) favors aprotinin. Diamonds represent point estimates; bars represent 95% confidence limits.

amount of chest tube drainage, suggesting that there is no sustained benefit for aprotinin with respect to reducing blood loss. Conversely, the measurement of volume of blood transfused and chest tube drainage may be more prone to bias than the measurement of the number of children transfused, especially if blinding was not strictly maintained in those studies (30).

With current methods of blood donor testing, allogeneic blood transfusion is extremely safe. Thus, the requirement for blood transfusion may be less clinically important than other "hard" outcomes such as reoperation rates resulting from bleeding, in-hospital morbidity, and death. Moreover, although the proportion of patients transfused may be reduced with the use of aprotinin, the number of overall donor exposures may not be similarly reduced, as most CPB circuits were primed with allogeneic blood.

The methodological quality of most studies included in this review was poor. Although all 12 studies were randomized, none provided an adequate description of withdrawals or dropouts, only 1 adequately described allocation concealment, and only half used an objective transfusion protocol. Our comprehensive search of the literature uncovered a subgroup report of children enrolled in an industry-sponsored compassionate use trial (28). The methods used in this study were not described, and substantially different numbers of patients were allocated to each of the 4 study arms. Moreover, the author stated that "we did not do hands-on monitoring of the trial, so the data may not be quite as clean as data from a more formal trial" (28). Therefore, this study was excluded from our review. In addition, 2 of the 12 trials in this review were industry-sponsored, a feature that has been associated with inflated estimates of benefit (31). This review also uncovered certain inconsistencies in reporting between aprotinin trials; each study used a different dose regimen (Table 1), and transfusion outcomes were occasionally reported as "blood transfusion" or "blood product" transfusions without specifying whether whole blood, RBCs, platelets, or plasma was transfused.

Any transfusion-sparing effect of aprotinin must be weighed against its associated complications and cost. Venous thrombosis and stroke are major causes of early and late morbidity and mortality after Fontan surgery, the definitive palliative surgical treatment for most congenital univentricular heart lesions; however, these complications have also been reported with other cardiac procedures (32). Seven of the 12 studies included in this review reported the frequency of complications and/or adverse events. No thrombotic or allergic complications of aprotinin were observed, and the frequency of adverse events were similar between groups in all studies, except one (22) where 5 early and 9 delayed adverse events were observed in the aprotinin group, compared with 2 early and 6 delayed adverse events in the placebo group (no test of significance was provided). Rare events, such as the thrombotic complications of aprotinin, are poorly captured in RCTs; even meta-analyses are usually underpowered to detect important effects because so few events are included in the original studies. The additional risk of thrombosis attributable to aprotinin in children undergoing corrective or palliative cardiac surgery remains unclear but must be considered for high-risk procedures. In addition, the cost of aprotinin is substantial; the average cost of aprotinin for a 10-kg child undergoing a 3-hour procedure using the large-dose regimen outlined in the Boldt et al. study (18) would be approximately $470 US.

In summary, pooling results of RCTs, aprotinin reduced the proportion of children who received allogeneic blood transfusions during cardiac surgery with CPB. However, aprotinin had no significant effect on the volume of blood transfused or on the amount of chest tube drainage. Among trials examining the effect of aprotinin in children, there is a need for consistency in reporting dosing regimens and transfusion requirements using objective transfusion protocols (30). Before the routine use of aprotinin in children undergoing cardiac surgery can be recommended, further independent RCTs are needed to carefully examine clinically important outcomes including bleeding, reoperation rates, and death in addition to the need for perioperative transfusion.

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CHD

Modified and conventional ultrafiltration during pediatric cardiac surgery: Clinical outcomes compared

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Objective: This prospective study compared clinical outcomes after heart surgery between three groups of infants with congenital heart disease. One group received dilutional conventional ultrafiltration (group D), another received modified ultrafiltration (group M), and a third group received both dilutional conventional and modified ultrafiltration (group B). We hypothesized that group B patients would have the best clinical outcome.

Methods: Children younger than 1 year undergoing heart surgery for biventricular repair by the same surgeon were randomly allocated to one of the three study groups. Patient management was standardized, and intensive care staff were blinded to group allocation. Primary outcome measure was duration of postoperative mechanical ventilation. Other outcome measures recorded included total blood products transfused, duration of chest tube in situ, chest tube output, and stays in intensive care and in the hospital.

Results: Sixty infants completed study protocol. Mean age and weight were as follows: group D (n = 19), 61 days, 4.3 kg; group M (n = 20), 64 days, 4.5 kg; and group B (n = 21), 86 days, 4.4 kg. Preoperative and intraoperative characteristics were similar between groups. Ultrafiltrate volumes obtained were 196 ± 93 mL/kg in group D, 105 ± 33 mL/kg in group M, and 261 ± 113 mL/kg in group B. There were no significant differences between groups for any outcome variable. Technical difficulties prevented completion of modified ultrafiltration in 2 of 41 infants.

Conclusion: There was no clinical advantage in combining conventional and modified ultrafiltration. Because clinical outcomes were similar across groups, relative risks of the ultrafiltration strategies may influence choice.

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During cardiopulmonary bypass (CPB) for cardiac surgery, children are subjected to anticoagulation, hemodilution, hypothermia, nonpulsatile blood flow, and exposure of blood to nonendothelialized surfaces. In response to these nonphysiologic conditions, patients initiate a systemic inflammatory response syndrome (SIRS) that increases total body water and may result in multi-organ dysfunction. SIRS is considered a major contributor to the increased morbidity and mortality associated with CPB in children.[1,2]

Ultrafiltration can ameliorate the effects of CPB by removing free water and some inflammatory mediators.[3,4] Conventional ultrafiltration (CUF) is performed during CPB.[5] If fluid is added to the CPB circuit during CUF to increase the volume of ultrafiltrate, the process is dilutional ultrafiltration (DCUF). Modified ultrafiltration (MUF) is conducted after CPB.[6] Ultrafiltration of the prime (PUF) before the onset of CPB is sometimes performed if the CPB circuit is primed with packed red

Abbreviations and Acronyms

ANOVA = analysis of variance
CPB = cardiopulmonary bypass
CUF = conventional ultrafiltration
DCUF = dilutional ultrafiltration
DHCA = deep hypothermic circulatory arrest
ICU = intensive care unit
MUF = modified ultrafiltration
PRBCs = packed red blood cells
PUF = ultrafiltration of prime before onset of CPB
SIRS = systemic inflammatory response syndrome

blood cells (PRBCs).[7] All these ultrafiltration methods for cardiac operations have been found clinically beneficial relative to unfiltered control CPB[4-6,8-10] and can be used separately or combined in the same patient to provide potentially additive positive effects.[11]

Differences between DCUF and MUF merit consideration. Technically, DCUF demands little of the surgeon's attention, whereas MUF increases the complexity of the immediate post-CPB period. DCUF enables removal of inflammatory mediators throughout CPB and does not prolong the duration of CPB, but it can only achieve moderate hemoconcentration. MUF provides more effective hemoconcentration,[12,13] but it extends the duration of patient exposure to nonendothelial surfaces[14] and does not reduce plasma concentrations of inflammatory mediators in children.[15] Both techniques are considered safe.

Controversy remains regarding the optimal ultrafiltration strategy.[5,8,13,16-21] Surrogate outcome measures, such as cytokine levels, have not been helpful in guiding the choice of ultrafiltration in children, because the relationships between plasma concentrations of proinflammatory and anti-inflammatory cytokines and patient outcome are poorly defined.[12,13,15] Gaynor[12] stated, "Further studies are necessary to identify patients most likely to benefit from ultrafiltration, and to define standard protocols for use of ultrafiltration in infants and neonates undergoing CPB."

The aim of our prospective study was to compare clinical outcome after cardiac operations between three groups of infants. One group of patients received DCUF only, another group received MUF only, and the third group received both DCUF and MUF. On the premise that ultrafiltration is beneficial, the protocol was designed to optimize each ultrafiltration strategy. Study hypothesis was that the infants who underwent both DCUF and MUF would have a better clinical outcome than the other groups.

Materials and Methods

The study protocol was approved by the institutional review board, and informed parental consent was obtained before patient enrollment.

Study Population

Infants younger than 1 year were enrolled in this prospective, randomized study. With a random numbers table, patients were allocated to receive DCUF (group D), MUF (group M), or both DCUF and MUF (group B).

Inclusion criteria were gestational age greater than 37 weeks, postnatal age younger than 12 months, and scheduling for cardiac operations performed by V.M.R. Exclusion criteria were as follows: active noncardiac disease that was expected to compromise the patient's postoperative recovery; previous sternotomy, which may influence blood loss, an outcome variable; weight greater than 9 kg, because of the need for a CPB oxygenator of greater flow capacity (to reduce CPB variables, the oxygenator was limited to one model); and single-ventricle palliation (surgeon's preference).

Anesthesia, Surgery, and CPB

Anesthesia was induced with sevoflurane or ketamine (1-2 mg/kg) and maintained with fentanyl (30-100 μg/kg), midazolam (0.1-0.4 mg/kg), and rocuronium bromide, supplemented with isoflurane. Preoperative steroids were not administered.

Anticoagulation was established with an initial bovine heparin dose of 400 U/kg, and additional heparin was administered during CPB to maintain Celite-based activated clotting time greater than 480 seconds. The dose and adequacy of anticoagulation reversal by protamine were guided by heparin-protamine titration. Nonpulsatile CPB was performed with a hollow-fiber membrane oxygenator (Terumo Capiox RX05; Terumo Cardiovascular Systems, Ann Arbor, Mich) and nonocclusive roller pump. CPB circuit components, setup, and prime were standardized. The circuit was primed with normal saline solution, 25% albumin, mannitol, sodium bicarbonate, calcium chloride, methylprednisolone (30 mg/kg), and heparin. Banked PRBCs and fresh-frozen plasma were added to achieve a hematocrit of about 30% during initiation of CPB. Hypothermia was induced in all patients, and blood gases were regulated according to the alpha-stat regimen unless deep hypothermia was required, in which case a pH-stat regimen was used during cooling. Myocardial preservation was achieved with cold crystalloid cardioplegia. Transfusion therapy in the operating room and intensive care unit (ICU) was standardized to established protocols. Target post-CPB hematocrit varied from 35% to 50%, depending on the patient's cardiac and respiratory status. Antifibrinolytics were not administered.

Whenever possible, the surgeon attempted to standardize the conduct of surgery, CPB, and ultrafiltration. Toward the end of CPB, the usual time to initiate preparations for MUF, the perfusionist divulged the patient's study group allocation to the surgeon and anesthesiologist.

Ultrafiltration

The polysulfone hemofilter used (Minntech HPH 400; Minntech Corporation, Minneapolis, Minn) uses hollow-fiber technology and is rated to have a filtration cutoff to particles greater than

TABLE 1. Demographics of the patient population

Variable	Group D	Group M	Group B	*P* value
No.	19	20	21	
Age (d, mean ± SD)	61.21 ± 63.82	64.30 ± 73.89	86.10 ± 104.00	.58
Weight (kg, mean ± SD)	4.27 ± 1.29	4.52 ± 1.23	4.35 ± 1.51	.84
Male sex (No.)	9/19 (47%)	10/20 (50%)	13/21 (62%)	.62

65,000 d molecular weight. A transmembrane pressure gradient of at least 200 mm Hg was applied during ultrafiltration.

After the addition of blood products, hemofiltration of the CPB circuit prime was performed before CPB to adjust pH and electrolyte concentrations and to remove inflammatory mediators.[22] Filtrate volume from PUF ranged from 100 to 200 mL.

DCUF was performed throughout CPB to achieve a filtrate volume of at least 120 mL/kg. Fluids (crystalloid, PRBCs, or plasma) were added when necessary to provide sufficient volume in the CPB circuit to permit ultrafiltration.

Arteriovenous MUF was initiated after separation from CPB by standard technique. Blood from the aortic cannula and from the CPB circuit venous reservoir was pumped through the hemofilter and then warmed by a coiled heat exchanger (Medtronic MYOtherm XP cardioplegia delivery system; Medtronic Inc, Minneapolis, Minn) and returned through the cardioplegia circuit to the patient's venous cannulas. Infusion rates were adjusted to maintain appropriate central venous or left atrial pressure. MUF was terminated when red cell salvage of circuit contents was judged by the perfusionist to be complete.

Postoperative Care

The ICU staff participating in postoperative patient management were blinded to study group assignment. Goals for mechanical ventilator support depended on the patient's cardiorespiratory status. Weaning from ventilator support was initiated after the patient had exhibited clinical stability. When the child demonstrated the ability to sustain adequate spontaneous respiratory effort and required minimal supplemental oxygen, as assessed by arterial blood gas analysis, the child's trachea was extubated.

Data Collection

The primary patient outcome measure was duration of postoperative mechanical ventilation of the lungs. Secondary outcome measures were total volume and units of blood products transfused by weight of infant, duration of chest tube in situ, and ICU and hospital stays.

Data were recorded regarding patient demographics, preoperative clinical status, and the ultrafiltration methods used. Aspects of the intraoperative and postoperative courses were recorded for the first 5 days of ICU care or until discharge from the ICU, whichever was earlier. Details included transfusion therapy, cardiorespiratory function and support, fluid balance, nutrition, drug therapy, laboratory tests, perioperative adverse events, and the period from termination of CPB to end of surgery.

Power Analysis

With standard sample size calculation for a power of 0.80, $P = .05$, equal variance and effect size similar to that reported for postoperative duration of lung ventilation,[5] the sample size required was 51 (n = 17 per group). Sample size calculations indicated that a sample of 51 would also be appropriate for the secondary outcome variables.

Data Analyses

Data were analyzed to ascertain whether groups D, M, and B were similar and could be compared. Clinical outcome was compared between all three groups of patients. Analysis of variance (ANOVA) was used to compare group means between the three types of ultrafiltration methods for continuous outcome measures. The Pearson χ^2 was used to analyze categoric variables. Longitudinal continuous data was analyzed with mixed effects analysis. When data were not normally distributed, nonparametric statistical analyses (Kruskall-Wallis) were used. Computations were performed with SAS 9.1 (SAS Institute, Inc, Cary, NC).

Results

Sixty-two infants were enrolled in the study. Two subjects were excluded from data analysis for protocol violations. Of the remaining 60 patients, 19 received DCUF only (group D), 20 received MUF only (group M) and 21 received both DCUF and MUF (group B).

Demographic characteristics of the three groups were similar and are presented in Table 1. Operations performed included repair of ventricular septal defect (n = 13), repair of tetralogy of Fallot (n = 12), repair of atrioventricular septal defect (n = 12), repair of transposition of the great arteries (n = 9), repair of total anomalous pulmonary venous return (n = 3), complex repair of double-outlet right ventricle (n = 3), repair of multiple level obstruction of left heart (n = 2), repair of anomalous origin of coronary artery from pulmonary artery (n = 1), resection of cardiac tumor (n = 1), repair of congenitally corrected transposition (n = 1), repair of cor triatriatum (n = 1), repair of truncus arteriosus (n = 1), and repair of biventricular outflow obstruction (n = 1). The operative procedure included valve repair in 5 cases (excluding tetralogy of Fallot and atrioventricular septal defect repairs) and aortic reconstruction in 14 cases.

TABLE 2. Intraoperative characteristics of the patient population

Characteristic	Group D	Group M	Group B	*P* value
Complex surgery (No.)	7/19 (37%)	9/20 (45%)	9/21 (43%)	.87
CPB prime (mL, mean ± SD)	459 ± 43	471 ± 52	476 ± 47	.51
CPB duration (min, mean ± SD)	123 ± 52	142 ± 57	146 ± 57	.40
Aortic crossclamp time (min, mean ± SD)	94 ± 104	86 ± 33	86 ± 44	.90
Minimum core temperature (°C, mean ± SD)	26.6 ± 5.4	25.1 ± 5.3	25.1 ± 4.8	.56
Total heparin (units, mean ± SD)	5442 ± 1111	4935 ± 1952	5200 ± 1072	.55

CPB, cardiopulmonary bypass.

There were no significant differences in the prevalence of preoperative medication use or the need for preoperative mechanical ventilation. Study groups also did not differ significantly with respect to preoperative hematocrit, white blood cell count, electrolyte levels, and renal and coagulation laboratory test values. Selected intraoperative characteristics of patients are presented in Table 2. There were no significant differences between groups for duration of CPB, duration of crossclamping, minimum core temperature during CPB, or total heparin dose. The distributions of individual anesthesiologists and perfusionists caring for these patients were not significantly different between groups. Groups did not differ significantly in the complexity of cardiac operations performed. None of the patients were subjected to deep hypothermic circulatory arrest (DHCA). Total volumes of ultrafiltrate obtained were 196 ± 93 mL/kg (group D), 105 ± 33 mL/kg (group M), and 261 ± 113 mL/kg (group B).

MUF increased hematocrit values in group M from 39% ± 6% to 47% ± 6% ($P < .0001$) and in group B from 39% ± 7% to 47% ± 8% ($P < .0001$). In addition, MUF increased arterial blood pressures in group M from 57 to 84 mm Hg systolic ($P < .0001$) and from 34 to 51 mm Hg diastolic ($P < .0001$) and in group B from 58 to 76 mm Hg systolic ($P < .0001$) and from 35 to 48 mm Hg diastolic ($P < .0001$). Hematocrit and arterial blood pressure at equivalent time points did not change significantly for group D patients.

The primary and secondary outcome measures are shown in Table 3. There was no difference between groups in the duration of postoperative mechanical ventilation of the lungs, duration of chest tube placement, or ICU and hospital stays. Total blood product use, measured by volume per kilogram of body weight and by units per kilogram of body weight, also did not differ between groups. Blood products transfused during surgery and in the first 24 postoperative

TABLE 3. Principal outcome measures

Outcome	Group D	Group M	Group B	*P* value
Duration of mechanical ventilation (h)*				.57
25%	27.75	40.71	25.66	
50%	48.75	69.92	66.66	
75%	76.16	128.75	112.83	
Duration of chest tube in situ (h)*				.20
25%	62.50	48.38	47.58	
50%	71.00	88.79	94.16	
75%	86.00	162.71	115.83	
Total volume of transfused blood products (mL/kg)†	237.8 ± 87.5	223.9 ± 91.0	262.7 ± 138	.54
Stay in ICU (h)*				.82
25%	98.18	101.76	118.98	
50%	150.41	212.41	164.56	
75%	352.73	332.32	256.33	
Duration in hospital (d)*				.49
25%	7	7	6	
50%	10	15	11	
75%	18	25	21	

ICU, intensive care unit. *Data are presented as median and 25% and 75% quartiles, and Kruskal-Wallis test was computed. †Data are presented as mean ± SD, and ANOVA was computed.

hours were 1.87 ± 0.79 units/kg (group D), 1.72 ± 0.68 units/kg (group M), and 1.99 ± 0.96 units/kg (group B) for all products combined and did not differ between groups ($P = .57$, ANOVA). Likewise there were no differences in use (units per kilogram) of PRBCs ($P = .55$), plasma ($P = .39$), platelets ($P = .65$), or cryoprecipitate ($P = .76$). Hematocrit values measured at 48 postoperative hours did not differ significantly between groups (mean ± SD group D 44% ± 5%, group M 44% ± 6%, and group B 43% ± 5%, $P = .49$).

Additional clinical outcome parameters were then analyzed. There were no differences between groups for the following (data not presented): pulmonary compliance and resistance at 24 postoperative hours ($P = .55$ and $P = .10$, respectively, ANOVA); alveolar-arterial oxygen gradient at 24 postoperative hours ($P = .71$, Kruskal-Wallis); systolic blood pressure preincision, at the end of operation, and at 24 postoperative hours ($P = .64$, $P = .41$, and $P = .69$, respectively, ANOVA), doses of inotropes used during the first 5 days in the ICU (dopamine $P = .11$, milrinone $P = .31$, random coefficient analysis); duration that a central venous catheter was in situ ($P = .24$, Kruskal-Wallis); interval between administration of protamine and termination of surgery ($P = .71$, Kruskal-Wallis); chest tube output at 24 postoperative hours ($P = .77$, Kruskal-Wallis); and values of blood urea nitrogen and serum creatinine at 48 postoperative hours ($P = .38$ and $P = .30$, respectively, ANOVA).

Post hoc power analysis was based on a 2-sample *t*-test to resolve a 50% change in group B with actual observed variance and assuming an α of 0.05. The powers to resolve 50% change in outcome variables were 92% for duration of postoperative ventilation, 99% for duration of chest tube, and 99% for total volume of blood products transfused.

Of the 60 patients that completed study protocol, 2 died. Both were in study group M and were late deaths (postoperative days 29 and 95) that were unlikely to be related to the ultrafiltration technique used. Two patients (weight 3.9 kg and 1.8 kg) allocated to group B were excluded from data analysis because the study protocol was not followed. In both cases, the patients had received DCUF but MUF was terminated prematurely because of systemic hypotension.

Discussion

We hypothesized that an ultrafiltration strategy that used DCUF to facilitate early modification of SIRS and MUF to maximize hemoconcentration would provide optimal outcome for infants undergoing cardiac operations. Our study found that the combination of MUF and DCUF afforded no additional benefit in terms of patient outcome relative to either MUF or DCUF alone. Technical complications were twice encountered during MUF.

Evidence has accumulated that ultrafiltration reduces postoperative morbidity after pediatric cardiac operations. Ultrafiltration has been shown to decrease total body water accumulation, decrease postoperative blood loss and blood product use, increase arterial blood pressure and improve left ventricular systolic function, improve the alveolar–arterial oxygen gradient and pulmonary compliance, decrease the frequency of pulmonary hypertensive episodes and the duration of postoperative ventilation, and decrease the incidence of pleural effusions after superior cavopulmonary connection and the Fontan procedure.[12] Although the mechanisms by which ultrafiltration produces beneficial effects remain unclear, surmises include reduction of tissue edema, hemoconcentration, and removal of inflammatory mediators.

MUF was introduced in 1991 because CUF inadequately limited the postoperative accumulation of total body water in children.[6] The introduction of zero balance ultrafiltration[8] and DCUF[5,23] permitted removal of large volumes of ultrafiltrate during CBP and prompted debate about the relative merits of MUF, DCUF, and a combination of the two techniques.[6,8,16]

Two recent reviews of ultrafiltration during cardiac operations concur that the results of published studies are conflicting and that further investigations are necessary to better define ultrafiltration strategies in the pediatric population.[12,15] Pediatric studies that have compared ultrafiltration during CPB and MUF are listed in Table 4. A major problem that complicates interpretation of study findings is the lack of standardization in the performance of ultrafiltration. Factors that may influence study results include type of ultrafiltration during CPB (CUF, DCUF), type of MUF (arteriovenous, venovenous), duration of ultrafiltration during CPB, volume of ultrafiltrate obtained, end point chosen for termination of MUF, the type of hemofilter, use of PUF, concomitant anti-inflammatory therapies (such as aprotinin or corticosteroids), patient characteristics (eg, young age, presence of pulmonary hypertension[23]), CPB variables (eg, prime volume and type), and complexity of cardiac surgery (eg, use of DHCA[24]). Additionally, several reports of ultrafiltration were retrospective or included historical control subjects.

Our single-institution, prospective, randomized study was designed to reduce confounding variables by blinding the ICU caregivers, standardizing intraoperative and postoperative care, and limiting the study population to infants. Also, it was hoped that by selecting this age group, detection of differences in outcome would be enhanced, because the benefits of ultrafiltration are more pronounced in infants undergoing complex cardiac operations.[24] Twenty-nine of the study patients (48%) were neonates.

Some of the beneficial effects of ultrafiltration may be transient and have minimal positive effect on clinical out-

TABLE 4. Studies comparing MUF and conventional CUF in children undergoing cardiac surgery

First author	Group	Age* (mo)	n	Ultrafiltrate (mL/kg)	Hct† (%)	Clinical outcome
Wang[18]	MUF	62	24	—‡	18	No difference in inotrope use, diuresis, duration of ventilation, ICU stay
	CUF	44	26	—‡	18	
Thompson[16]	MUF	13	43	95	28-30	No difference in blood product transfusions, hemodynamics, left ventricle shortening, duration of ventilation, ICU stay
	CUF	9	67	68	28-30	
Maluf[19]	MUF + CUF	9	20	39	25	No difference in inotrope use, transfusions, duration of ventilation, ICU stay, hospital stay
	CUF	15	21	20	25	
Sever[20]	MUF + CUF	9	13	—‡	>20	MUF + CUF: better hemodynamics, less bleeding and transfusions, shorter duration of ventilation, shorter ICU stay
	CUF	13	14	—‡	>20	
Bando[5]	MUF + DCUF	17	50	155	14-18	MUF + DCUF: high-risk patients§ had less transfusions, better oxygenation, shorter duration of ventilation, shorter ICU stay
	CUF	30	50	29	14-18	
Journois[8]	MUF + DCUF	13	10	>200	—‡	MUF + DCUF: less blood loss, better alveolar-arterial oxygen gradient, shorter duration of ventilation
	MUF	6	10	30	—‡	
Hiramatsu[21]	MUF + DCUF	67	11	186	18-28	MUF + DCUF: lower pulmonary vascular resistance (Fontan procedure)
	CUF	74	11	25	18-28	

MUF, modified ultrafiltration; *CUF*, conventional ultrafiltration; *ICU*, intensive care unit; *DCUF*, dilutional ultrafiltration. *Mean or median age of patients. †Target hematocrit during cardiopulmonary bypass. ‡Value not published. §High risk factors were neonatal age, pulmonary hypertension, and CBP duration longer than 120 minutes.

come. Keenan and colleagues[25] reported that MUF, relative to nonultrafiltered control CPB, resulted in a significant improvement in lung compliance immediately after CPB but not at the end of surgery or 24 postoperative hours. There were no differences between groups in duration of mechanical ventilation or ICU stay. With this in mind, we chose outcome variables that were of clinical relevance and likely to influence our future choice of ultrafiltration strat-l egies (Table 3). None of these principal outcome measures differed significantly between groups. Other more subtle and perhaps transient outcome parameters were then compared between groups, but no significant differences were found. Parameters included postoperative measures of pulmonary function (compliance, resistance, alveolar–arterial oxygen gradient), cardiac function (arterial blood pressure, inotrope requirements, duration that central venous catheter was in situ), hemostasis (duration of intraoperative post-CPB period, chest tube output), and renal function (blood urea nitrogen, creatinine).

Review of the publications listed in Table 4 suggests that differences in outcome between study groups are more likely when the groups being compared differ greatly in the volumes of ultrafiltrate obtained. This is not surprising, because the positive benefits of ultrafiltration correlate with the volume of filtrate removed.[26] Total ultrafiltrate volumes for our study exceeded those reported in the studies summarized in Table 4. A recent publication[27] that demonstrated efficacy of MUF in neonates obtained a mean ultrafiltrate volume of 104 mL/kg; our MUF ultrafiltrate volume was 105 mL/kg. The significant increases in hematocrit and arterial blood pressure during MUF provide additional evidence that MUF was adequately performed.[3,26,27]

For all our study patients, banked PRBCs were added to the CPB circuit prime and PUF was performed. PUF is reported to lower plasma concentrations of bradykinin and high–molecular weight kininogen and, relative to control procedures, result in less tissue edema, improved cardiorespiratory status, and reduced durations of mechanical ventilation and ICU stay.[7,22,28] None of the studies listed in Table 4 ultrafiltered the heme prime before initiation of CPB. It is uncertain what influence PUF had on the outcome of our patients, but it may be that large ultrafiltrate volumes and early initiation of ultrafiltration are both important for improving clinical outcome.

There are other factors to consider. None of our study patients were submitted to DHCA; infants undergoing DHCA particularly benefited from MUF.[24,27] With the exception of the study by Thompson and associates,[16] the target hematocrit during CPB in our study was considerably higher than those of other studies (Table 4). Addition of methylprednisolone to the CPB prime may have modified the outcome of our patients. Unlike the other studies listed in Table 4, all our patients were infants and were operated on by the same surgeon.

Although ultrafiltration during and after CPB in children is considered safe,[12] consideration of risk is warranted.[25] Hemofiltration carries the potential for human and equipment error and increases plasma heparin concentration.

Compared with DCUF, MUF has some additional risks. The aortic cannula may entrain air. Removal of blood from the systemic circulation may result in hemodynamic instability or impair aortopulmonary shunt flow. High flow rates through the ultrafilter decrease cerebral blood flow velocities and cerebral mixed venous oxygen saturation.[29] In small infants, the aortic cannula may be obstructive, and its early removal may limit or prevent use of arteriovenous MUF. MUF extends the period of patient exposure to nonendothelialized surfaces. Cooling of the patient will occur if the ultrafiltered blood is inadequately warmed.

Two patients assigned to study group B did not receive MUF because of hemodynamic issues during the immediate post-CPB period. After assessing our data, we have opted not to provide MUF to infants undergoing cardiac operations, because MUF and DCUF were similarly beneficial but the incidence of complications, although uncommon, was greater for MUF than for DCUF. We combine PUF and DCUF.

Selection of ultrafiltration strategies appears linked to the conduct of CPB. Gaynor and coworkers[27] retrospectively reviewed 99 neonates who underwent the first stage of Norwood reconstruction and noted that MUF was successfully and safely used in all cases. DHCA was universally used (mean duration 45 minutes), and the mean duration of CPB support was 100 minutes. In such instances, MUF seems a logical option because duration (and perhaps benefit) of DCUF would be limited if there is no blood flow for nearly half of the CPB period. At our institution, DHCA is seldom used for the first stage of Norwood reconstruction.

The conclusions of this study of infants may not be applicable to older children. MUF may be desirable for hemoconcentration in bigger children, in whom avoidance of exposure to donor blood products is feasible. Study weaknesses should be noted. It was impossible to completely blind intraoperative care providers to the method of ultrafiltration. Most of the outcome measures pertained to the patient's postoperative clinical course, however, and ICU caregivers were blinded. It is possible that the study had insufficient power to detect differences between groups, although post hoc power analysis indicates that this is unlikely.

In summary, this prospective, randomized study of 60 infants found no difference in clinical outcome between patients who received DCUF only, patients who received MUF only, and patients who received both DCUF and MUF.

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PEDIATRIC AND CONGENITAL HEART DISEASE

Original Studies

Transcatheter Closure of Perimembranous Ventricular Septal Defects Using the Amplatzer Membranous VSD Occluder: Immediate and Midterm Results of an International Registry

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Objective: To report the immediate and midterm results of transcatheter closure of perimembranous ventricular septal defect (PmVSD) using the Amplatzer membranous VSD occluder (AMVSD). Methods: Between April 2002 and August 2004, 100 patients underwent an attempt of percutaneous device closure of PmVSD using the AMVSD in 24 international centers. The median age was 9.0 years (0.7–58 years) and the median weight was 27.5 kg (7–121 kg). Results: A device was successfully deployed in 93/100 (93%) patients. Reasons for procedural failure were an increased gradient across the left ventricle outflow tract in one patient, aortic regurgitation in 2 patients, and inability to securely position the device in 4 patients. The median VSD size by TEE was 7.0 mm (1.5–13 mm), median device size 10 mm (4–16 mm) and median fluoroscopy time 22.1 min (8.9–96.0 min). Weight below 10 kg ($P = 0.0392$), inlet extension of the VSD ($P = 0.0139$) and aortic cusp prolapse into the VSD ($P = 0.0084$) were significantly associated with a lower procedural success. Patients have been followed up for a median of 182 days (1–763 days). There were no procedure-related deaths. Complications were encountered in 29/100 (29%) patients, including rhythm or conduction anomalies in 13 patients (two with complete heart block requiring permanent pacemaker implantation), new or increased aortic (9 patients) or tricuspid (9 patients) regurgitation, most of which were classified as trivial or mild. Patients with a weight below 10 kg had a significantly higher incidence of adverse events than patients with a weight above 10 kg (58.3% versus 25.0%, $P = 0.0285$). Immediately after device release complete closure of the defect was present in 54/93 (58.1%) patients, increasing to 46/55 (83.6%) patients at 6-months follow-up ($P = 0.0012$). Left ventricle end-diastolic diameter decreased from a median of 44 mm prior to device closure to a median of 39 mm at 6-months postprocedure ($P = 0.0015$). Conclusion: Closure of PmVSDs using the AMVSD occluder is safe and effective. However, longer follow-up period is warranted prior to the wide spread use of this device.

Key words: perimembranous ventricular septal defect; catheterization; interventional

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INTRODUCTION

To prevent long-term complications such as pulmonary hypertension, arrhythmias, aortic regurgitation, double chambered right ventricle, or endocarditis [1,2], closure of ventricular septal defects (VSDs) beyond infancy is recommended in asymptomatic older children and adults with a restrictive VSD but a hemodynamically significant left-to-right shunt (Qp:Qs $\geq$ 1.5:1). In the past this has been considered a clear indication for surgical intervention, and results of percutaneous device closure were unsatisfactory [3]. However, since the introduction of the Amplatzer membranous VSD device, results of transcatheter closure have significantly improved [4–8]. This series reports the largest cohort of an international registry of patients with perimembranous VSD (PmVSD) who underwent device closure using the Amplatzer membranous VSD device.

METHODS

Study Population

Between April 2002 and August 2004, 100 patients from 24 US and international tertiary referral centers were included in this study (see Appendix), which was conducted as a prospective, nonrandomized, interventional registry. The clinical indication for VSD closure was assessed by the principal investigator at each participating institution. Patients were considered on a case by case basis and inclusion criteria were the presence of a hemodynamically significant PmVSD as documented by echocardiography or cardiac catheterization (LVEDD above the upper limit of normal for age, Qp/Qs $\geq$ 1.5) and patients with a small PmVSD and history of infective endocarditis or for employment reasons.

Exclusion criteria were patients with a weight below 5 kg, irreversible pulmonary vascular disease with a pulmonary vascular resistance index (PVRi) above 7 Woods unit, sepsis, or contraindications to antiplatelet therapy.

Patients or the guardian of patients who met the enrolment criteria were informed about all available treatment options, including an alternative surgical approach. The ultimate decision to participate in the study was made by the patient or guardian.

Data Collection

Data was collected prospectively at the time of the procedure as well as during the follow-up period at each participating institution and submitted to a central database held by the principal investigator. The data included the following:

1. *Demographics:* Date of procedure, age, sex, weight, height.
2. *Clinical data:* Symptoms, indication(s) for VSD closure.
3. *Electrocardiography:* Right/left/biventricular hypertrophy (RVH, LVH, BVH), atrioventricular (AV) block, right or left bundle branch block (RBBB, LBBB), and other intraventricular conduction delay, other abnormal findings.
4. *VSD size:* Where available, VSD size by transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), intracardiac echocardiography (ICE), and angiography.
5. *Echocardiography:* Left ventricular end-diastolic diameter (LVEDD), presence and quantification of aortic regurgitation (AR) or tricuspid regurgitation (TR), presence and quantification of residual shunt(s), and VSD morphology (presence of aneurysmal septum, aortic cusp prolapse, VSD inlet extension).
6. *Hemodynamics:* Qp:Qs, mean pulmonary artery pressure, and PVRi.
7. *Procedure details:* Fluoroscopy time, device size, sheath sizes, other devices used, incidence of device pulling through VSD, and additional interventions performed.
8. *Adverse events:* Details and outcome of any adverse event during the procedure or follow up period.

Excel spreadsheets were distributed via e-mail among all participating institutions to standardize the collected follow-up data as well as supplementing original clinical and demographic patient data, using a detailed instruction sheet and predefined drop-down menus. Where data was inconclusive or raised additional questions the local investigator was directly contacted and asked for clarification.

The median follow-up so far has been 182 days (1–763 days). At least limited follow-up data beyond day 1 postprocedure was available for 77/93 (82.8%) patients. However, follow-up data was not received for 16 patients from 9 centers for variable reasons. Out of 93 patients (successful procedures only), 82 (88.2%) patients completed 1-day follow-up, 57 (61.3%) patients completed 1 month follow-up, 55 (59.1%) patients completed 6 month follow-up, 17 (18.3%) patients completed 12 month follow-up, and only 8 (8.6%) patients completed 24 month follow-up. Preoperative morphological, echo and procedural data was available for all patients. In contrast, detailed clinical data (indication, symptoms) was available for analysis in 77/100 (77%) patients and electrophysiological data in 73/100 (73%) patients.

Local experienced pediatric echocardiographers at each participating institution interpreted all echocardiographic data in a nonblinded fashion.

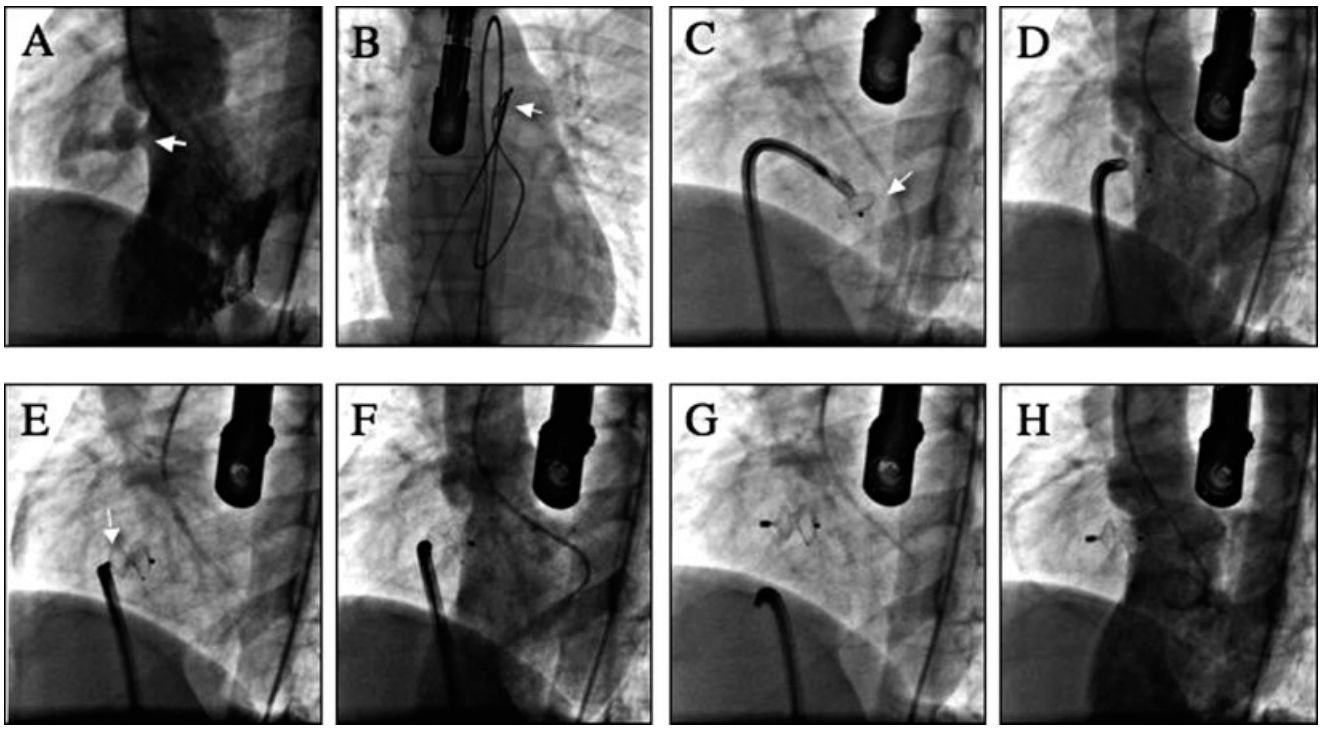

Fig. 1. A: LV angiogram in the LAO view in an 11 year old child with 7 mm perimembranous VSD (arrow). B: cine image in the frontal projection during snaring the Noodle wire (arrow) from the main pulmonary artery. C: cine image during deployment of the left ventricle disk (arrow) of an 8-mm Amplatzer Membranous VSD device in the left ventricle. D: angiogram in the LV after the LV disc has been pulled towards the defect indicating good position. E: cine image immediately after the RV disc has been deployed (arrow). F: angiogram after the device has been deployed indicating good device position. G: cine image after the device has been released. H: final angiogram in the LV indicating good device position and no residual shunt.

Measured Outcome Parameters

The main outcome parameters were procedural success as defined by device release in appropriate position without embolization, complete closure or quantification of a residual shunt, symptomatic improvement as well as occurrence of procedure or device related complications, including new or increased aortic or tricuspid regurgitation, and other adverse events during the follow-up period.

Residual shunts were evaluated using color Doppler echocardiography and classified as trivial (<1 mm), small (1–2 mm), moderate (2–4 mm), or large (≥ 4 mm), depending on the width of the color jet as it exited through the ventricular septum, similar to the technique used to describe atrial level shunts after device closure [9].

Device

The Amplatzer membranous VSD occluder [AMVSD] (AGA Medical Corporation, Golden Valley, MN) is self-expandable and made of Nitinol wire. The device and the specialized delivery system (7–9 French) have been described in a previous report [10].

Closure Protocol

The procedures were performed routinely under general anesthesia unless intracardiac echocardiography (ICE) was used to guide the procedure. The protocol we used for transcatheter closure of PmVSD has been described in details in previous reports [4,8]. Figure 1 demonstrates the fluoroscopic steps of the closure. All patients had a chest X-ray, TTE, and ECG within 24 hr following the procedure. The follow-up protocol included assessments at least once within the first 6 months following the procedure. All visits included routine physical examination as well as ECG and TTE. Patients were routinely maintained on Aspirin or equivalent antiplatelet therapy for the duration of 6 months following the procedure.

Statistical Analysis

Descriptive statistical reports including mean, median, standard deviation, and range were evaluated for each parameter using StatsDirect software (StatsDirect

Ltd, Sale, Cheshire, United Kingdom). We used nonparametric tests to compare interval patient variables such as VSD size with outcome parameters such as procedural success or occurrence of adverse events or residual shunts (Mann–Whitney test).

We also compared other demographic data such as weight above or below 10 kg as well as morphometric VSD details, such as presence of an aneurysmal septum, aortic cusp prolapse, or VSD inlet extension with outcome parameters such as procedural success, presence of new or increased aortic or tricuspid regurgitation and occurrence of adverse events, using an exact Fisher's test. All tests were performed at $\alpha = 5\%$.

TABLE I. Morphological and Procedural Data of Percutaneous VSD Closure (n = 100 procedures)

VSD size by TTE (mm)	7.0 (1.5–13)
VSD size by TEE (mm)	7.0 (1.5–13)
VSD size by angiography	8.0 (1.5–14)
Aortic cusp prolapse	7/93 (7.5)[a]
Aneurysmal septum	28/93 (30.1)
Inlet extension of VSD	8/92 (8.7)
Procedural success	93/100 (93)
Device used (mm)	10 (4–16)
Fluoroscopy time (min)	22.1 (8.9–96)
Repeated attempts at deployment	23/95 (24.2)
Unsuccessful use of smaller device	12/95 (12.6)

[a]Values in parentheses (except where a range is indicated) are in percentages.

RESULTS

Demographics and Clinical Data

100 patients were enrolled in the study with a median age of 9.0 years (0.7–58 years) and a median weight of 27.5 kg (7–121 kg). 41/100 (41%) patients were female and 40/77 (51.9%) patients had clinical symptoms related to the presence of the VSD such as shortness of breath or exertional dyspnoea in 26/76 (34.2%), failure to thrive in 16/75 (21.3%), palpitations in 4/74 (5.4%), or overt congestive cardiac failure in 7/74 (9.5%). Indications for VSD closure were the presence of a hemodynamically significant shunt in 76/88 (90.5%) patients, clinical symptoms in 39/79 (49.4%) patients, pulmonary hypertension in 11/89 (12.4%) patients, a history of bacterial endocarditis in 4/91 (4.4%) patients, employment reasons in 1/84 (1.2%) patients, and other reasons in 5/84 (5.9%) patients—many patients having more than one category listed as an indication for VSD closure. There were 6/93 (6.5%) patients who in hindsight had a questionable indication for VSD closure. 42/73 (57.5%) patients had an abnormal ECG prior to the procedure, including LVH/RVH/BVH in 26/73 (35.6%) patients, RBBB in 10/73 (14.2%) patients, and other abnormalities in 12/73 (16.4%) patients. One patient had preexisting heart block and was sequentially paced.

VSD Morphology, Echocardiography, and Cardiac Catheterization (Table I)

The VSD extended into the inlet portion of the septum in 8/92 (8.7%) patients. In 28/93 (30.1%) patients the VSDs were associated with an aneurysmal septum and in 7/93 (7.5%) patients there was at least a mild degree of prolapse of the noncoronary cusp of the aortic valve into the VSD. 2 patients had a Gerbodi-type VSD and 1 patient had a small doubly-committed (supracristal) VSD.

The median size of the VSD by TTE was 7.0 mm (1.5–13 mm), by TEE 7.0 mm (1.5–13 mm), and by angiography 8.0 mm (1.5–14 mm). ICE was used during the procedure in 9 patients (exclusively in 2 patients) with a median size of 6.0 mm (4.0–9.0 mm).

Aortic regurgitation was present prior to VSD closure in 18/88 (20.5%) patients, all classified as mild degree or less. Tricuspid regurgitation was present prior to VSD closure in 36/89 (40.4%) patients, in 3 classified as mild-to-moderate or more. In 59/93 (63.4%) patients, the LVEDD exceeded the upper limit of normal for age with a median LVEDD prior to VSD closure of 44 mm (24–69 mm).

Hemodynamic evaluation revealed a Qp/Qs of 1.5:1 or higher in 64/93 (68.8%) patients, a median mean pulmonary artery pressure of 20 mmHg (10–62 mmHg) and a median PVRi of 1.6 Woods units (0.9–10.0 iU/m^2).

Procedural Data (Table I)

A device was successfully delivered in 93/100 (93%) patients. Reasons for procedural failure were new or increased aortic regurgitation in 2 patients, a gradient across the left ventricular outflow tract (LVOT) in 1 patient or inability to securely place a device in 4 patients. At least mild aortic cusp prolapse into the VSD was present in three of the unsuccessful procedures. The device had to be deployed in the ascending aorta in 5 patients, 4 of which due to unavailability of a noodle wire and 1 due to technical difficulties.

The median device size used was 10 mm (4–16 mm). 4 patients had more than one VSD, and in 1 patient multiple residual VSDs after attempted surgical closure were closed in 2 procedures, using 2 different sized membranous VSD occluders. Additional interventional procedures performed at the same setting included closure of a secundum ASD in 3 patients, PDA occlusion in 1 patient, pulmonary balloon valvuloplasty in 1 patient, and occlusion of venous collateral in 1 patient. The median fluoroscopy time was 22.1 min (8.9–96.0 min), and median sheath size used for device delivery was 8 Fr (6–11 Fr). In 23/95 (24.2%) patients, more than 1 attempt at device delivery was necessary (device pulling through

the VSD), and in 12/95 (12.6%) patients at least one device-size was unsuccessfully used (need to change to a larger size).

Technical difficulties were encountered in 11/100 (11%) procedures. In 5 patients both disks of the device were deployed but not released in the left ventricle with successful recapture in all. In one patient the device was released with both disks within the left ventricle, and in another patient the device embolized after release to the left pulmonary artery—with successful snare and recapture in both patients. In 2 patients the right or left ventricular disks did not configure in the usual fashion, being associated with a small residual shunt in one patient. The delivery sheath had to be upsized from 7 Fr to 8 Fr because of kinking in one patient and the device had to be removed because of clot formation on the device (despite anticoagulation) in another.

Adverse Events and Follow-Up (Tables II and III)

Procedure or device-related complications or adverse events were encountered in 29/100 (29%) patients. All patients have survived and most encountered complications resolved completely. The median follow-up has been 182 days (1–763 days).

The most commonly observed adverse events were tricuspid or aortic regurgitation, usually of trivial or mild degree. New or increased aortic regurgitation postprocedure was observed in 9/97 (9.2%) patients. At the most recent follow up, this had resolved in 4 patients, or was classified as trivial or mild in 4 patients, and mild-to-moderate in only 1 patient. New or increased tricuspid regurgitation postprocedure in excess of trivial/physiologic was observed in 9/97 (9.2%) patients and at the most recent follow up this had resolved in 3 patients, or was classified as trivial or mild in 5 patients, and mild-to-moderate in 1 patient.

Rhythm or conduction anomalies were seen in 13/100 (13%) of patients. These included transient 1st degree heart block in 1, transient 2nd degree heart block in 2, transient complete heart block in 2 patients within four days from the procedure (reference being published in CCI), and complete heart block requiring insertion of a permanent pacemaker in 2 patients. One of the patients requiring implantation of a permanent pacemaker subsequently had an almost complete recovery of the AV conduction, requiring the use of the permanent pacemaker in less then 1% of the time. In the other patient, heart block developed only several hours after an uneventful procedure. Permanent RBBB was seen in 4 patients and transient RBBB in 1 patient. Transient LBBB was observed in 1 patient and 3 patients had transient episodes of junctional rhythm. However, overall the incidence of normal 12-lead ECG recordings increased significantly from 31/73 (42.5%) prior to the procedure to 28/42 (66.7%) at 6-months follow-up ($P = 0.0136$).

TABLE II. Adverse Events After Device Closure of Perimembranous VSDs (n = 100 procedures)

Procedure related complications	29/100 (29)[a]
■ Mortality	0/100 (0)
■ Arrhythmia/conduction anomalies	13/100 (13)
○ CHB requiring pacemaker	2/100 (2)
○ Transient CHB	1/100 (1)
○ Transient 1st DG HB	1/100 (1)
○ Transient 2nd DG HB	2/100 (2)
○ Transient LBBB	2/100 (2)
○ Transient junctional rhythm	3/100 (3)
○ RBBB	5/100 (5)
■ New/Increased AR	9/97 (9.2)
○ AR at last F/U > mild	1 Patient
■ New/Increased TR	9/97 (9.2)
○ TR at last F/U > mild	1 Patient
■ Tricuspid stenosis	1/100 (1)
■ Device embolization	2/100 (2)
■ Bradycardia/hypotension	3/100 (3)
■ Hemolysis	2/100 (2)
■ Mitral regurgitation	2/100 (2)
■ Other complications	2/100 (2)

[a]Values in parentheses are in percentages.

Other complications infrequently encountered included intravascular hemolysis in two patients with a trivial residual shunt, tricuspid stenosis in a patient who subsequently underwent PFO device closure to reduce a secondary atrial-level right-to-left shunt, mild or trivial mitral regurgitation in two patients, hypotension/bradycardia in three patients, vascular complications in one patient, right lung atelectasis in one patient, and device embolization with successful snare and recapture in two patients.

The percentage of patients who were clinically asymptomatic increased significantly from 38/77 (49.4%) prior to the procedure to 48/51 (94.1%) at the most recent follow-up ($P < 0.0001$).

Residual Shunts and LVEDD (Table III)

Immediately after the procedure the VSD was completely closed in 54/93 (58.1%) patients. A trivial residual shunt was present in 28/93 (30.1%), a small residual shunt in 10/93 (10.7%) patients and a moderate residual shunt in 1/93 (1.1%) patient. The percentage of complete closure increased from 54/93 (58.1%) immediately postprocedure to 59/82 (71.9%) at day 1 postprocedure, 45/57 (78.9%) at 1-month postprocedure, and 46/55 (83.6%) at 6 months follow-up ($P = 0.0012$). Out of a subgroup of 46 patients who had complete closure at 6-months follow up, 14 patients originally had a residual shunt immediately postprocedure. 1 patient with multiple VSDs required an additional percutaneous procedure to close a residual shunt; but no patient so far required a surgical intervention.

TABLE III. Follow Up After Device Closure of Perimembranous VSDs[a]

	Pre-Implant	Post-Implant	Day 1	1 Mo	6 Mo
Perimembranous VSD follow-up					
Asymptomatic	38/77 (49.4)[b]	–	–	48/57 (84.2)[b]	48/51 (94.1)[b]
Median LVEDD	44	–	42	41	39
Residual shunts					
Shunt on ECHO					
■ Closed		54/93 (58.1)[b]	59/82 (71.9)	45/57 (78.9)[b]	46/55 (83.6)[b]
■ Trivial		28/93 (30.1)	12/82 (14.6)	4/57 (7.0)	4/55 (7.2)
■ Small		10/93 (10.8)	10/82 (12.2)	7/57 (12.3)	4/55 (7.2)
■ Moderate		1/93 (1.1)	1/82 (1.2)	1/57 (1.8)	1/55 (1.8)
■ Large		0/93 (0.0)	0/82 (0.0)	0/57 (0.0)	0/46 (0.0)

[a]Median follow-up was 182 days (1–763 days).
[b]Values in parentheses are in percentages.

The LVEDD) decreased significantly from a median of 44 mm (24–69 mm) prior to device closure to a median of 42 mm (21.8–64 mm) at day one postprocedure, a median of 41 mm (30–64 mm) at 1-month follow-up and a median of 39 mm (20–64 mm) at 6-months follow-up ($P = 0.0015$).

Factors Impacting Procedural Success, Residual Shunts or Incidence of Adverse Events

Procedural failure was significantly related to patient weight below 10 kg ($P = 0.0392$), the presence of aortic cusp prolapse ($P = 0.0084$), or inlet extension of the VSD ($P = 0.0139$). 3/12 (25.0%) of procedures were unsuccessful in patients with a weight below 10 kg, compared with 4/88 (4.6%) of procedures in patients with a weight above 10 kg. In 3/7 (42.8%) patients with presence of aortic cusp prolapse into the VSD, the operators were unable to successfully deploy a device. There was no correlation between procedural failure and size of the VSD ($P = 0.4769$) or presence of an aneurysmal septum ($P = 0.4276$).

Patients with a weight below 10 kg had a significantly higher incidence of procedure-or device related adverse events (7/12, 58.3%) than patients with a weight above 10 kg (22/88 25.0%) ($P = 0.0285$). The size of the VSD ($P = 0.2064$) or device used ($P = 0.4915$) was not related to the occurrence of procedure-or device related complications.

The presence of aortic cusp prolapse ($P > 0.6576$) was not associated with an increased incidence of new or increased aortic regurgitation. However, interestingly all 9 cases of new or increased aortic regurgitation occurred in patients without the presence of an aneurysmal septum ($P = 0.0332$). There was no correlation between the presence of inlet extension of the VSD and the incidence of new or increased tricuspid regurgitation ($P = 0.2928$).

There was a suggestion of early residual shunts being more commonly seen with an aneurysmal septum, even though the numbers were not statistically significant (13/25 versus 19/61, $P = 0.0794$) or the presence of inlet extension of the VSD (5/5 versus 29/80, $P = 0.0085$). However, the incidence of residual shunts was unrelated to patient weight below 10 kg at the time of the procedure ($P = 0.9117$). The median VSD size in patients with early complete closure was 6.5 mm, compared to 8.0 mm in patients with an early residual shunt ($P = 0.0103$).

Slightly longer fluoroscopy times were observed in patients with a weight below 10 kg (26.6 vs. 20.0 min, $P = 0.0498$) or presence of inlet extension of the VSD (33.3 vs. 19.8 min, $P = 0.0356$). Other characteristics such as presence of an aneurysmal septum ($P = 0.8964$), or the presence of aortic cusp prolapse ($P = 0.1002$) were not associated with significantly longer fluoroscopy times. The presence of an aneurysmal septum was not significantly correlated with an increased incidence of repeated device deployments because of device pulling through VSD ($P = 0.2934$).

DISCUSSION

Our study reports the largest cohort of patients with PmVSDs who underwent device closure using the AMVSD occluder.

Adequate patient selection is of fundamental importance when considering percutaneous VSD device closure. Most patients included in this study would have equally qualified for surgical VSD closure. Natural history studies suggest that there is no need for VSD closure in asymptomatic patients with normal distal pulmonary artery pressures and a Qp:Qs < 1.5:1 [2,11,12], although other studies have documented that even small VSDs are associated with significant morbidity and even mortality [13]. However, at the present stage, we would not recommend percutaneous closure of small, hemodynamically insignificant, PmVSD. Whether the results of percutaneous device closure and incidence of adverse events will improve to a degree that would allow considering closure in these patients remains to be seen. Patients selected for VSD device closure should therefore have evidence of a hemodynamically significant left-to-

right shunt, preferably based on transthoracic echocardiography (LVEDD exceeding the upper limit of normal for age) as well as hemodynamic evaluation (Qp:Qs $\geq$ 1.5:1). Other indications such as a history of endocarditis or employment issues should be considered on a case-by-case basis. Our data suggests that the presence of aortic cusp prolapse should probably be regarded as a contraindication for percutaneous device closure and the percutaneous approach needs to be carefully considered in patients with a lower weight because of the increased incidence of procedure or device related complications.

The rate of complete closure has been very good, being 83.6% at 6 months. A further increase in the rate of complete closure is likely to be observed at subsequent follow up, this is similar to device closure of muscular VSDs, where rates of complete closure increased from 69.6% at 6-months to and 92.3% at 12 months follow up [14]. These excellent closure rates have been confirmed by other reports. Thanopoulos and colleagues reported complete closure in 9 out of 10 patients where a PmVSD was closed using the AMVSD device [7]. In one patient a trivial shunt resolved by 3 months postprocedure. Bass and colleagues reported complete occlusion in 23/25 (92%) patients within 1 week of device implantation [4]. Surgical results are not dissimilar. The incidence of residual VSDs after surgical closure has been reported to be as high as 28% [15]. Meijboom and colleagues reported a long-term incidence of residual VSDs after a mean follow-up of 14.5 years of about 6% [16]. However, similar to residual VSDs after percutaneous device closure, most residual VSDs after surgical closure are hemodynamically insignificant and very rarely require any form of surgical or percutaneous re-intervention.

The success of the procedure is also reflected in the decrease of the LVEDD postprocedure, as well as the improvement of clinical symptoms in those patients with symptoms related to the presence of the VSD prior to percutaneous closure.

The most frequently observed adverse events were related to conduction anomalies or new or increased aortic or tricuspid regurgitation. A total of four patients experienced heart block; however, two of the patients were treated with steroids and aspirin and the heart block resolved completely [17]. Therefore, the incidence of complete heart block requiring implantation of a permanent pacemaker was 2%; this is probably slightly higher than what has been observed after surgical closure of similar patient population. In one patient, the pacemaker has not been in use, indicating that the heart block that was sustained was transient. When heart block is to occur, perhaps one should not rush to implanting a permanent pacemaker, but rather to treat for few days with anti-inflammatory medications including steroids and high dose aspirin.

Conduction anomalies are usually seen directly as a result of the tension of the arteriovenous loop or delivery sheath on the conduction system in close proximity to the VSD. However, in the four cases that sustained the complete heart block, the procedures were totally uncomplicated.

Overall, the incidence of rhythm and conduction anomalies compares well to surgical series. Postoperative right bundle branch block remains common after surgical VSD closure and more recently reported incidences ranges somewhere between 6.3 and 64% [15,18]. However, postoperative complete heart block is a rarity today—the reported incidence in the literature ranging somewhere between 0 and 2% [18–21].

Very important device related complications are those affecting the function of aortic and tricuspid valve. The most sensitive tool to evaluate valvar obstruction or regurgitation is continuous monitoring using TEE or ICE, which should be performed in great detail prior to the release of the device. In our series this technique identified a significantly increased gradient across the LVOT in one patient, leading to recapture and removal of the device and termination of the procedure. The overall incidence of new or increased aortic or tricuspid regurgitation in our series was low. Our data suggests that the presence of a septal aneurysm may be associated with a reduced incidence of aortic regurgitation, which is likely related to the device being incorporated within the aneurysm and as such associated with a slightly larger distance to the aortic valve cusps.

In one patient the device caused a degree of tricuspid stenosis, which emphasizes again the need to carefully evaluate both semilunar and atrioventricular valves prior to device release. However, not all device-related valvar complications can be detected prior to release, due to the reconfiguration of the device once the tension of the delivery cable has been released. In most patients of this series, there was only a trivial or mild degree of new or increased tricuspid or aortic regurgitation, resolving completely in almost 40% of these patients over the follow-up period. These findings are not uncommon even after surgical interventions, especially after procedures that utilize detachment of the tricuspid valve leaflet to access the VSD [19]. One of our patients had a small doubly-committed VSD and device closure did not lead to an increased degree of aortic or pulmonary regurgitation. However, although this defect was very small and successfully closed, we would, in general, now not recommend undertaking device closure in these types of

VSDs because of deficient margins to both, aortic and pulmonary valves.

One of the most challenging technical aspects of the procedure is to place the VSD device in appropriate position, which is reflected in 6 procedures where both disks were deployed in the left ventricle. Accurate TEE and or ICE guidance is mandatory for successful accomplishment of this step and an appropriate deployment is usually much more readily achievable from a position within the left ventricular apex rather than the ascending aorta. Positioning the delivery sheath in the left ventricular apex can be difficult, not infrequently complicated by kinking of the delivery sheath or accidental pull back into the right ventricle. At PICS-VII, Amin and colleagues presented a modification of the delivery system that included a female screw at the center of the left ventricular disk. This could be attached to a male screw placed at the tip of the noodle wire [22], allowing more controlled positioning of the device and thereby facilitating the device deployment. The presence of ventricular septal aneurysms can be challenging and the operator has to be prepared to potentially use larger device sizes as initially estimated based on echocardiographic imaging.

Closing PmVSD using the AMVSD device is a fairly new technique and as such each operator will have a learning curve in using this device. This is likely to lead to further reduction in the incidence of procedure or device related complications as well as an increase in the procedural success rate.

Limitations

Our study has some limitations. Patients were not prospectively randomized between surgical or percutaneous closure and as such comparison between the two approaches may be biased. Our data collection as well as follow-up data is incomplete and long-term conclusions cannot be drawn. The percutaneous approach to closure of PmVSDs requires significant technical operator skills that may only be obtained and maintained by performing large number of complex interventional procedures.

In conclusion, our study has demonstrated good closure rates and a low morbidity using the AMVSD occluder to close PmVSDs. The incidence of permanent morbidity after this procedure is low and compares well to surgical procedures. The incidence of conduction anomalies and specifically complete heart block requires further long-term evaluation. Patient selection and an experienced operator are very important for procedural success and the suitability of the percutaneous approach has to be carefully considered in patients with a lower weight. Morphological characteristics such as the presence of aortic cusp prolapse, septal aneurysms, or inlet extension of the VSD have to be taken into consideration when judging the suitability of the percutaneous approach. Device closure using the AMVSD device should be considered an important alternative to the surgical approach in treating suitable cases of perimembranous ventricular septal defects beyond infancy. Furthermore, longer term follow-up is clearly needed to specifically evaluate the function of the aortic valve in the presence of this device and to monitor the long-term effects of this device on the conduction system before the widespread use of this device.

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APPENDIX: THE AMPLATZER MEMBRANOUS VSD INVESTIGATORS ACCORDING TO DATE OF PROCEDURE

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