Original Article

Hematological Effects of a Low-Prime Neonatal Cardiopulmonary Bypass Circuit Utilizing Vacuum-Assisted Venous Return in the Porcine Model

Kevin Ahlberg, BS, CCP; Joseph J. Sistino, MPA, CCP; Shintaro Nemoto, MD

Medical University of South Carolina, Department of Extracorporeal Circulation Technology, Charleston, South Carolina

Keywords: cardiopulmonary bypass, VAVD, low prime, hemodilution, neonatal, coagulation

Presented at the AmSECT 37th International Conference, April 8–12, 1999, New Orleans, Louisiana

ABSTRACT

Limiting hemodilution in neonates is difficult when extracorporeal circuits require priming volumes that are 2 to 3 times the blood volume of the newborn patient. This extreme hemodilution contributes to the development of significant postbypass coagulation disturbances. The purpose of this project was to design a low-prime neonatal bypass circuit and evaluate the coagulation status after reduced hemodilution. The null hypothesis stated there is no significant difference in the measured coagulation parameters between the low-prime circuit and the standard high-prime circuit.

Four neonatal piglets (2–4 kg) were divided into two groups and placed on cardiopulmonary bypass using either a low- (200 ml) or high-prime (500 ml) circuit. Both groups were cooled to 20°C, and, following cardioplegic arrest, underwent circulatory arrest for 20 minutes. The low-prime circuit used vacuum-assisted venous drainage, which permitted the circuit to be at the patient level. The high-prime circuit required fresh washed donor red blood cells to maintain the hematocrit in the desired range of 15–20%.

The platelet count on bypass decreased by 60 ± 1.0% in the low-prime group versus 79.6 ± 0.1% in the high-prime group. Following bypass, the platelet count was reduced by 38.3 ± 14.3% in the low-prime versus 60.2 ± 2.6% in the high-prime group. During rewarming, the mean heparinase activated clotting time (ACT) increased 5.1% above baseline in the low-prime group and 53.5% above baseline in the high-prime group. Mean plasma-free hemoglobin levels increased 40.4 mg/dl in the low-prime group versus 62.1 mg/dl in the high-prime group during bypass. This laboratory evaluation of a low-prime neonatal circuit demonstrates that coagulation disturbances often present in neonates can be reduced with the use of a low-prime circuit.

Address correspondence to:
Kevin Ahlberg, BS, CCP
Sarasota Memorial Hospital
Perfusion Department
1700 S. Tamiami Trail
Sarasota, FL 34239

INTRODUCTION

Neonates, infants, and children undergoing surgical repair of congenital heart defects are exposed to the more extreme conditions of cardiopulmonary bypass (CPB), including deep hypothermia and extreme hemodilution. Hemodilution, via asanguineous priming solutions in the extracorporeal circuit (ECC) during CPB, has long been known to provide many benefits by opposing the effects of hypothermia on blood flow, oxygen delivery, and renal function (1–3). The modest reductions in coagulation factor activity levels from routine CPB are usually not great enough to result in a bleeding diathesis in most adults. However, in the neonatal patient, the small patient blood volume is diluted excessively by the large volume of priming solution in the ECC currently used in most institutions (4, 5). This is further exacerbated by the fact that in neonates, hepatic maturation continues for the first 2–3 weeks of life, resulting in coagulation factor concentrations, antithrombin III levels, and fibrinogen levels being less than 50% of concentration levels in adults (6, 7). In neonates under the age of 30 days, it has been found that an ECC primed with a total of 750 ml including whole blood to achieve a hematocrit of 20% resulted in global coagulation deficits by reducing coagulation factor levels by 50% and platelet counts by 70% (8). Neither cooling to deep hypothermic temperatures or prolonged exposure to the ECC has been shown to result in demonstrable changes in platelet numbers, coagulation factor levels, or antithrombin III levels (8).

Literature review has shown that extreme hemodilution is directly, or in part, responsible for:

- Reduced concentrations of magnesium, calcium, and albumin that persist for days after the end of bypass (9).
- Crystalloid hemodilution to a hematocrit of 18% in the canine model resulted in significant myocardial edema, depressed LV performance, and decreased LV compliance. These effects were not negated with the addition of packed red blood cells (to a hematocrit of 35%) nor by raising osmolarity with the hypertonic mannitol (10).
- A hyperdynamic state after weaning from CPB with elevated cardiac output, decreased vascular resistance, and excessive fluid requirements (11).
- Dilution of plasma proteins resulting in a substantial drop in buffering capacity (12).
- Abnormal hemostasis before the compromise of global tissue oxygenation (13).
- Clotting factor dilution in neonates prolongs the ACT test, which may result in inadequate heparinization, resulting in an increase in coagulation activity resulting in increased bleeding diathesis post-CPB (14).
- Exacerbates capillary leak phenomena in the neonate, resulting in tissue edema and organ dysfunction, and increasing pulmonary, cardiac, and central nervous system morbidity (15).

To compensate for the effects of excessive hemodilution in the neonatal patient, it is often necessary to introduce whole blood or packed red blood cells into the ECC priming solution and infuse platelets, fresh frozen plasma, and cryoprecipitate after termination of CPB (8, 16). This results in exposure to multiple blood donors and potential blood-borne diseases along with the complication that stored blood additives are poorly tolerated by neonates (17). Other methods of ameliorating the effects of extreme hemodilution include modified ultrafiltration (MUF) and, to some degree, conventional ultrafiltration. Both techniques have been successful in increasing concentrations of fibrinogen, hematocrit, total plasma proteins, and other coagulation factors, along with decreasing postoperative bleeding and transfusion requirements (18–20). Recent studies in neonatal piglets that had undergone CPB with hemodilution and deep hypothermia found that MUF, in particular, reduced edema, improved normally depressed cerebral oxygen consumption, increased cerebral blood flow, and increased myocardial contractility (21, 22).

Tailoring the ECC specifically for the neonatal patient to minimize hemodilution in an effort to prevent or reduce some of the morbid effects of hemodilution has long been described in the literature (23–28). Most previous designs of microsize circuits that are clinically viable have had priming volumes of approximately 250–350 milliliters. With the incorporation of vacuum-assisted venous drainage (VAVD) and new ECC components specifically tailored for the neonatal patient, it would be ideal to have an ECC that includes all necessary components to perform CPB but yet compact enough not to hemodilute the neonatal patient excessively.

The purpose of this project was to design a low-prime neonatal bypass circuit and compare the coagulation status to a standard neonate circuit in the porcine model. In addition, the efficacy and practicality of departing from the traditional pump console and moving the ECC up to the patient level along with the extensive use of vacuum devices was examined. The null hypothesis stated there is no significant difference in the measured coagulation parameters between the low-prime circuit and the standard high-prime circuit.

MATERIALS AND METHODS

PREPARATION OF PIGLETS

Four 1-week-old piglets weighing 3–5 kg were studied with approval of the institution's animal care and use committee and in compliance with the "Guide for the Care and Use of Laboratory Animals" (29). The animals were premedicated with a ventilation mixture of 5% isoflurane. Animals were intubated, and their lungs were ventilated with a pressure-controlled ventilator.[a] After a dose of pancuronium ($0.1mg \times kg^{-1}$), anesthesia was maintained with a continuous ventilation mixture of 2

a Ohmeda Anesthesia Systems, Madison, WI 53707

to 4% isoflurane. A carotid artery catheter was placed for measurement of mean arterial pressure and arterial blood sampling. A median sternotomy was performed, and the heart and great vessels were exposed by opening the pericardium.

LOW PRIME CPB CIRCUIT (FIGURE 1)

The prime composition in the low-prime CPB circuit consisted of 200 ml Plasmalyte-A[b], 500 IU heparin, and 5-mEq sodium bicarbonate. A Cobe Micro[c] hollow-fiber oxygenator/heat exchanger and venous reservoir were used with 3/16-in arterial and venous tubing, along with a pediatric arterial filter.[d] Monitoring devices included an in-line arterial blood gas/temperature probe,[e] in-line venous blood oxygen saturation probe,[f] and a venous blood temperature probe. A renal dialysis roller pump[g] was used for the arterial pump along with a small roller pump[h] for cardioplegia delivery. The cardioplegia system delivered a 1:1 blood to cardioplegic solution via 1/8-in lines and heat exchanger.[i] The entire circuit, including all monitoring devices, was mounted on a pole stand with the venous reservoir at the same height as the operating table. Venous drainage from the patient and suction for the two 3/16-in cardiotomy suction lines connected to the reservoir was achieved by applying high-volume vacuum to the venous reservoir, which was controlled by a valve placed in the vacuum supply line. The valve allowed for the maintenance of stable negative pressure, (−15 to −30 mm Hg was adequate for both cases) in the venous reservoir even with varying degrees of cardiotomy suction line occlusion. Safety devices included an arterial line high-pressure pump shut-off[j] and an air detection device[k] placed at the outlet of the venous reservoir, which automatically shut the arterial pump off and clamped the arterial line if the venous reservoir was emptied.

HIGH-PRIME CPB CIRCUIT

The prime composition in the high-prime CPB circuit consisted of 5-mEq sodium bicarbonate, 500 IU heparin, and enough packed red blood cells to achieve a calculated postdilutional hematocrit of 20% with the addition of a sufficient amount of Plasmalyte-A[b] to achieve a total priming volume of 500 ml. The CPB circuit components were identical to those in the low-prime circuit, with the following exceptions.

- A conventional blood roller pump[l] was used for arterial blood and cardioplegia delivery.
- Cardiotomy suction was via roller pump, rather then vacuum.
- The circuit was mounted on a conventional CPB roller pump base stand with the venous reservoir near the floor to allow for conventional gravity venous drainage.
- A ¼-in arterial and venous tubing was used.

CONDUCT OF CPB

After administering heparin (1200 IU × kg^{-1}), CPB was initiated with the insertion of an 8F arterial cannula in the ascending aorta and a single 16F venous cannula in the right atrial appendage. After 3 min of normothermic CPB at 150 ml × kg^{-1} × min^{-1}, the animals were then cooled to a core temperature of 20°C over 20 min. An aortic cross clamp was placed on the ascending aorta, and cardioplegic solution was injected into the root of the aorta (20 ml × kg^{-1}) over 3 min. After 20 min of circulatory arrest, the animals were rewarmed to 37°C over 20 min and weaned from CPB. Protamine was administered (0.6 mg/100 IU of total heparin given), and the animal was supported by positive pressure ventilation for 15 min, then euthanized.

DATA COLLECTION

Blood samples were collected and data recorded at the following times:

- Baseline (after establishing arterial access).
- 1 min after CPB initiation.
- After reaching 20°C.
- After reaching 37°C.
- 15 min post protamine.

The following studies were performed on the specimens drawn:

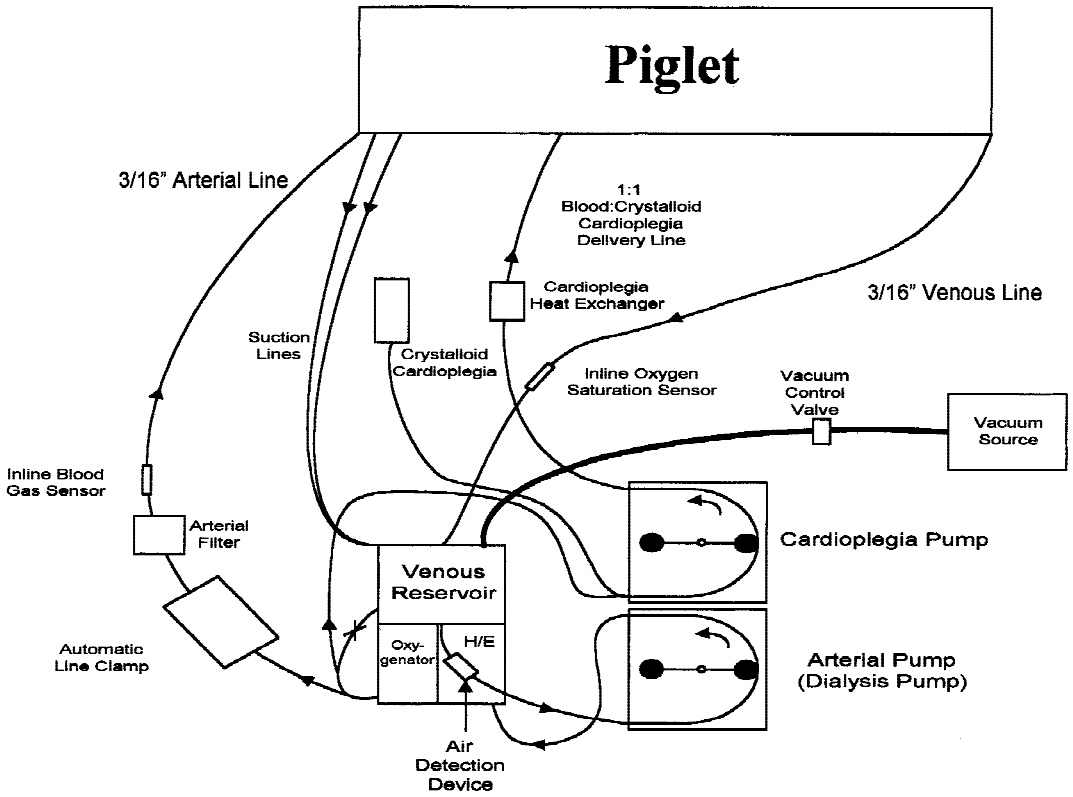
- Platelet count (baseline, 1 min after CPB initiation, 15 min post protamine).
- Plasma-free hemoglobin (baseline, 1 min after CPB initiation, 15 min post protamine).
- Activated clotting time (ACT)[m].
- Heparinase ACT[m].
- Hematocrit.[n]

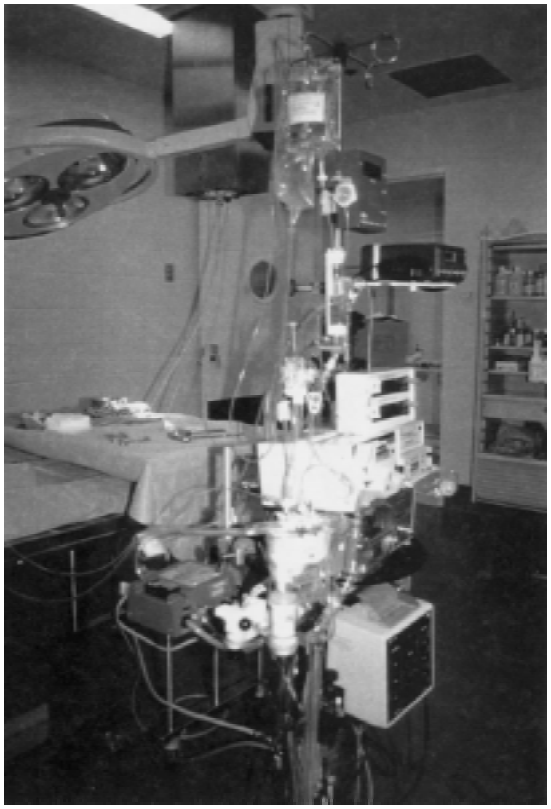
RESULTS

PLATELET COUNT (FIGURE 2)

The platelet count on bypass decreased from baseline levels by 60 ± 1.0% in the low-prime group versus 79.6 ± 0.1% in the

b Baxter Healthcare Inc., Irvine, CA 92714
c Cobe Micro Neonatal Oxygenating System, Cobe Cardiovascular, Inc. Arvada, CO 80004
d Pall Biomedical, Inc., Fajardo, PR 00738
e CDI 400, 3M Health Care, St. Paul, MN 55144
f Optical Transmission Cell-0250, Bentley Puerto Rico Inc., Anasco, PR 00610
g Minipump RS-7800, Minntech Corporation, Minneapolis, MN 55441
h Cole Palmer Pumps, Denver, CO 56342
i BCD Vanguard, Sorin Biomedical Inc., Irvine CA 92614.
j MinniAlert Pressure Monitoring System, Minntech Corporation, Minneapolis, MN 55441
k Sonalarm Air Detection System, Minntech Corporation, Minneapolis, MN 55441
l Shiley Laboratories, Inc., Irvine CA 92714
m ACT II, Medtronic Hemotec, Inc., Englewood, CO
n Micro-Capillary Centrifuge, Model MB, International Equipment Company, Boston, MA





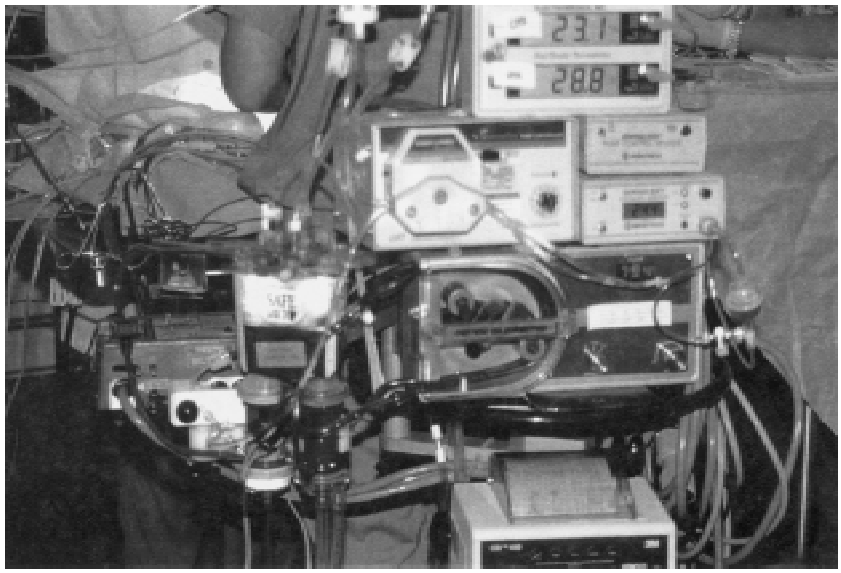


Figure 1: Low-prime circuit

high-prime group. Following bypass, the platelet count was reduced from baseline levels by 38.3 ± 14.3% in the low-prime versus 60.2 ± 2.6% in the high-prime group.

ACTIVATED CLOTTING TIME (FIGURE 3)

During bypass, the mean ACT in the high-prime group exceeded 1000 sec, and the mean ACT in the low-prime group remained in the normal bypass range of 408.5 sec.

ACTIVATED CLOTTING TIME WITH HEPARINASE (FIGURE 4)

During rewarming, the mean heparinase ACT increased 5.1% above baseline in the low-prime group and 53.5% above baseline in the high-prime group.

HEMATOCRIT (FIGURE 5)

Mean hematocrit levels in both the high-prime and low-prime group during and after bypass were between 16 and 20%. The high-prime group required the addition of packed red blood cells to the ECC prime to achieve the desired levels.

PLASMA-FREE HEMOGLOBIN (FIGURE 6)

Mean plasma-free hemoglobin levels in the low-prime group decreased by 53 ± 7.1% during bypass and increased by 65 ± 61.2% postbypass. In the high-prime group, levels decreased by 30 ± 6.9% during bypass and increased by 187 ± 3.1% postbypass.

DISCUSSION

This study suggests that coagulation disturbances often present in neonates undergoing CPB can be reduced with the use of a low-prime circuit. The higher platelet counts and the normal heparinase ACTs suggest improved coagulation status both during and after CPB. The maintenance of clinically acceptable hematocrit levels during bypass without the use of blood products is an additional bonus.

Although the statistical analysis of the results is limited by the small sample size, the objective of designing a reduced prime circuit was achieved. This complete circuit includes an arterial filter, cardioplegia delivery system, and all the safety components required for CPB. This circuit is a prototype using

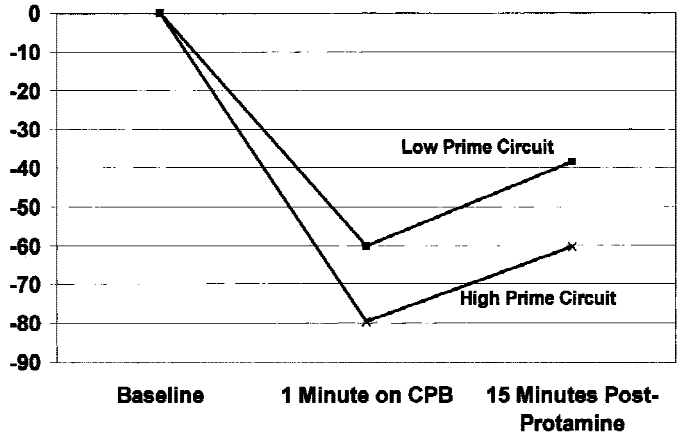


Figure 2: Mean percentage change of platelet levels from baseline (*m* = 4)

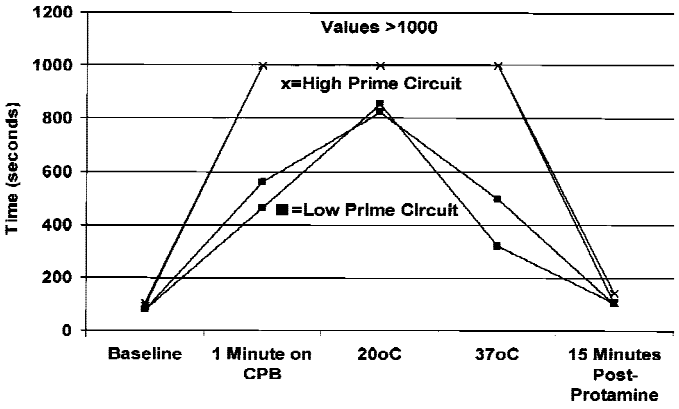


Figure 3: Low-prime circuit vs. high-prime circuit activated clotting times

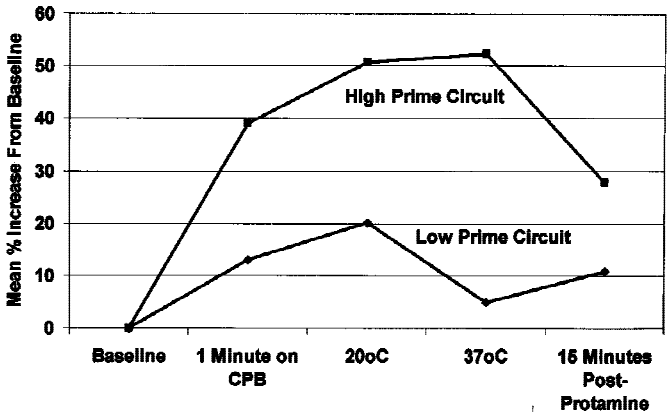


Figure 4: Low-prime circuit vs. high-prime circuit mean percentage of baseline ACT times with heparinase (*m* = 4)

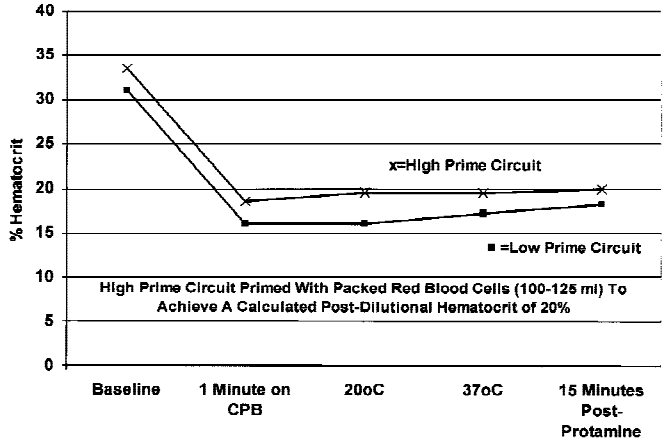


Figure 5: Low-prime circuit vs. high-prime circuit mean percentage hematocrit (*m* = 4)

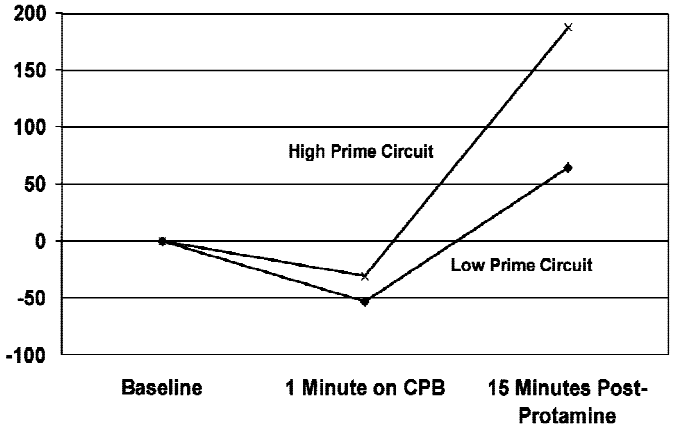


Figure 6: Mean percentage change in plasma-free hemoglobin levels from baseline (*m* = 4)

pumps designed for dialysis and using components not specifically approved for CPB. Further testing of this design is mandatory before clinical use can be recommended.

Other factors pertaining to the safety of vacuum-assisted venous drainage have recently been addressed. During in vitro testing, Rider et al. has reported the increased transmission of gaseous microemboli distal to the arterial filter when air was entrained into the venous line during vacuum-assisted venous drainage (30). Our study was designed to evaluate the hematological effects of a low-prime circuit and did not test for gaseous microemboli. The air detector used in our study at the outlet of the venous reservoir was not designed to and did not detect any microemboli. Only macroair attributable to an empty venous reservoir would stop the arterial pump. It is possible that the increased GME may be amplified in a miniature circuit because of low venous reservoir volume and reduced defoamer residence times.

The use of negative pressure in the venous reservoir to power the cardiotomy suction return may also increase gaseous microemboli and needs further evaluation. Integrated cardiotomy reservoirs designed for conventional roller pump suction and gravity venous return may not have the capacity to handle the increased air associated with this circuit. We look forward to manufacturers' improvements in the design of reservoirs to enhance air removal.

Further challenges with miniaturized VAVD systems have been identified by Darling et al. (31) and include:

- Increased shunt flows.
- Inadequate reservoir venting resulting in overpressurization of the reservoir during sucker pump use.
- Underocclusion of the arterial roller pump, exposing the oxygenator to vacuum pressure, causing air to be drawn across the membrane fibers.
- Diminished reaction time because of the small circuit components and line lengths.

Thorough examination of all these issues was beyond the scope of this study. However, the experience gained with this circuit allowed us to demonstrate its technical feasibility and show that some of the major hematological disturbances that occur during conventional neonatal CPB can be reduced with the use of a low-prime circuit.

ACKNOWLEDGMENTS

The authors acknowledge Cobe Cardiovascular Inc. and Minntech Inc. for their financial support of this project.

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