SURGERY FOR CONGENITAL HEART DISEASE

MODIFIED ULTRAFILTRATION VERSUS CONVENTIONAL ULTRAFILTRATION: A RANDOMIZED PROSPECTIVE STUDY IN NEONATAL PIGLETS

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Cardiopulmonary bypass in neonates generates large increases in inflammatory mediators, causing edema formation that may lead to multiple organ dysfunction. Clinical strategies aimed at removing inflammatory mediators, reducing edema formation, and improving organ function include conventional and modified ultrafiltration. *Objective:* This study examines the effectiveness of conventional and modified ultrafiltration in preventing weight gain, myocardial edema formation, and left ventricular dysfunction in neonatal piglets undergoing cardiopulmonary bypass. *Methods:* In this randomized prospective study, 18 1-week-old piglets were supported with cardiopulmonary bypass at $100 \text{ ml kg}^{-1} \cdot \text{min}^{-1}$, cooled to 25°C , exposed to 75 minutes of cardioplegic arrest, rewarmed to 37°C , and weaned from bypass. Left ventricular myocardial contractility was assessed by the preload-recrutable stroke work method, with the use of a sonomicrometric two-dimensional cylindrical model, before bypass and at 10, 60, and 120 minutes after separation from bypass. *Results:* Total body weight gain was significantly less in the modified ultrafiltration group than in either the conventional ultrafiltration group or the control group (no filtration). Myocardial wet/dry ratios were also improved with modified ultrafiltration, but not with conventional ultrafiltration, when compared with no filtration (control group). Hemodynamically, modified ultrafiltration was superior to conventional ultrafiltration and no filtration (control) in raising the mean arterial pressure and increasing the left ventricular preload-recrutable stroke work after bypass. *Conclusion:* Modified ultrafiltration is superior to conventional ultrafiltration and no filtration in reducing the total body weight gain, lessening myocardial edema, raising mean arterial pressure, and improving left ventricular contractility in neonatal piglets undergoing cardiopulmonary bypass and cardioplegic arrest. (J Thorac Cardiovasc Surg 1998;115:336-42)

Cardiopulmonary bypass (CPB) has become an effective and relatively safe procedure for adults undergoing cardiac operations. However, CPB is

still associated with a high morbidity and mortality in neonates.^{1,2} This increased mortality is partially due to the greater complexity of the procedures performed in neonates. However, neonates do not respond to CPB as well as older patients do, and some neonates undergo a dramatic inflammatory reaction, leaving them with tissue edema, pulmonary dysfunction, and poor cardiac performance.³

Experienced pediatric cardiac surgeons can now repair almost all cardiac malformations within a few days of life, but the neonate must still overcome the obstacle of recovery from CPB.^{4,5} Improved methods of CPB for neonates must be developed if the field of pediatric cardiac surgery is to progress to its full potential.

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Fig. 1. CPB circuit with filter. During CPB, tubing clamps are placed at 2 and 3 to exclude the filter. During modified ultrafiltration, tubing clamps are placed at 1 and blood is added from the reservoir through the filter as needed. During conventional ultrafiltration, all tubing clamps are removed.

The ideal CPB procedure would require no blood products for priming, cause no inflammation, yield no net water gain after CPB, and cause no organ dysfunction. One way to achieve some of these goals is the use of filtration as part of the CPB procedure.⁶ Ultrafiltration involves use of a semipermeable membrane, similar to those used in dialysis, to remove extra fluid and inflammatory mediators that result from exposure to the CPB circuit.⁶⁻⁸

Ultrafiltration in CPB seeks to (1) filter mediators of inflammation, (2) remove excess water, (3) improve post-CPB organ function, and (4) reduce the need for postoperative blood transfusion by providing hemoconcentration of blood from the CPB circuit.

Currently two distinct methods for ultrafiltration exist: ultrafiltration during CPB and ultrafiltration after CPB. With conventional ultrafiltration, a filter is connected in parallel with the CPB circuit, such that during rewarming circuit blood can be filtered.⁶ Modified ultrafiltration also uses a filter, but it is connected in series with the CPB circuit and is used only after the patient is weaned from CPB, allowing for both greater efficiency of filtration and greater concentration of red cells from the circuit.^{7,8}

Fig. 2. Left ventricle with four microcrystals and micro-transducer in place.

Early experience with the use of conventional ultrafiltration in neonates demonstrated that this method was not effective in achieving any of the aforementioned goals of ultrafiltration.⁷ Thus, an alternative method that used a more efficient filtration was developed.⁸ Modified ultrafiltration appears to lower the total body water gain and improve the hemodynamic performance in children undergoing CPB.⁷⁻⁹ However, the mechanisms of this improvement have not been elucidated. Furthermore, a direct comparison of modified ultrafiltration with conventional ultrafiltration has not been performed in a controlled laboratory environment.

In this randomized prospective study in neonatal piglets, we compared the effectiveness of modified ultrafiltration, conventional ultrafiltration, and no filtration (control group) on total body weight gain, myocardial edema formation, left ventricular contractility, and hemodynamic performance after CPB.

Materials and methods

Preparation of piglets. All animals were studied with the approval of the institution's animal care and use committee and in compliance with the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources and published by the National Institutes of Health (NIH publication No. 85-23, revised 1985). Eighteen 7-day-old piglets were premedicated with intramuscular ketamine ($20 \text{ mg} \cdot \text{kg}^{-1}$) and methylprednisolone ($40 \text{ mg} \cdot \text{kg}^{-1}$). Animals were intubated and their lungs ventilated with a pressure-controlled infant ventilator (Sechrist Industries, Anaheim, Calif.). After a dose of fentanyl ($50 \text{ } \mu\text{g} \cdot \text{kg}^{-1}$) and pancuronium ($0.1 \text{ mg} \cdot \text{kg}^{-1}$), anesthesia was maintained with a continuous intravenous infusion of fentanyl ($50 \text{ } \mu\text{g} \cdot$

Fig. 3. Total body weight gain after CPB and 120 minutes of recovery. * $p < 0.05$, MUF versus CUF group and MUF versus control group.

$\text{kg}^{-1} \cdot \text{hr}^{-1}$). A median sternotomy was performed and the heart and great vessels were exposed by opening the pericardium. Epicardial microcrystals were placed along the minor and major axis of the left ventricle, and vessel loops were placed around the superior and inferior venae cavae. A 2.5 mm microtransducer was placed in the left ventricle.

CPB circuit. A Minimax Plus hollow-fiber infant oxygenator (Medtronic, Inc., Anaheim, Calif.) was used with standard tubing. The circuit was primed with whole blood from a donor swine 15 minutes before the start of CPB. A hematocrit value of 24% was achieved by dilution with lactated Ringer's solution. The reservoir prime volume was 400 ml and the total prime volume was 650 ml in all cases. An infant roller pump (Medtronic) was used and the circuit was warmed to 37° C before the initiation of CPB.

Conduct of CPB. CPB was instituted with the insertion of an 8F arterial cannula in the ascending aorta and a single 18F venous cannula in the right atrial appendage. After 5 minutes of normothermic CPB at $100 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, the animals were then cooled to 25° C over 15 minutes. CPB was maintained at 25° C for 5 minutes while the left atrium was vented. An aortic crossclamp was placed on the ascending aorta and cardioplegic solution (St. Thomas' Hospital solution) was injected into the root of the aorta ($10 \text{ ml} \cdot \text{kg}^{-1}$) over 90 seconds. The total ischemic time was 75 minutes in all groups. After the cross-clamp was removed, the animals were randomized to the modified ultrafiltration group (MUF group), conventional ultrafiltration group (CUF group), or no filtration group (control group). Piglets were kept at 25° C for 2 minutes, rewarmed to 37° C, and weaned from CPB without inotropic support.

Ultrafiltration. Animals in the control group received no filtration. Animals in the CUF group were subjected to continuous filtration during rewarming, removed volume being replaced with lactated Ringer's solution. Animals in the MUF group were subjected to filtration for 15 minutes, 10 minutes after separation from CPB. A Cobe ultrafilter (Cobe Laboratories, Houston, Tex.) was used in both conventional and modified ultrafiltration. In both the MUF and CUF groups, suction was applied to the filter to maintain a continuous negative pressure across the membrane (−125 mm Hg). During continuous and modified ultrafiltration, the flow rate through the filter was kept at

Fig. 4. Left ventricular wet/dry mass ratios. * $p < 0.05$, MUF versus CUF group and MUF versus control group.

$10 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ by means of a second roller pump (Fig. 1).

Determination of contractility. Contractility was determined by means of the preload-recrutable stroke work (PRSW) method as described by Glower and associates.¹⁰ A cylindrical model, which has been previously validated in this laboratory,¹¹ was used with microcrystals on the posterior and anterior left ventricle for the minor axis and on the apex and the left atrioventricular groove for the left ventricular major axis (Fig. 2). PRSW determinations were made immediately before CPB, 10 minutes after CPB, and at 60 and 120 minutes after CPB. Three consecutive vena caval occlusions were used for each data point, and results reflect data averaging of these points. The data were acquired at 200 Hz, and individual beat points were analyzed with the use of a VAX data analysis system (Digital Laboratories, Milpitas, Calif.).

Statistics. Data were analyzed with statistical software (Microsoft Corporation, Redmond, Wash.) with the use of Student's *t* test to compare results between groups at single time points and an analysis of variance test to compare the results between groups at multiple time points. All results are expressed as the mean $\pm$ the standard error of the mean. Differences between groups were considered significant at the $p < 0.05$ level.

Results

Total body weight gain. After induction of anesthesia all animals were weighed for determination of pre-CPB mass. At the completion of the study, piglets were weighed on the same scale while all body fluids remained in situ. The mass gain was $496.7 \pm 61.4 \text{ gm}$ in control animals, $584.2 \pm 51.6 \text{ gm}$ in the CUF group, and $284.2 \pm 82.4 \text{ gm}$ in the MUF group ($p = 0.001$, MUF vs CUF; $p = 0.018$, MUF vs controls; Fig. 3).

Myocardial edema. The left ventricle, including the septum, was isolated and weighed immediately after the animal was euthanized. The specimens were then placed into a drying oven for 1 week and reweighed. The wet/dry ratio was determined by dividing the wet mass by the dry mass as an index of

Fig. 5. Hematocrit value of piglets during the study period. Only modified ultrafiltration was capable of raising the hematocrit value and maintaining it significantly higher after CPB.

myocardial water content. Myocardial wet/dry ratios were 4.81 ± 0.11 in controls, 4.92 ± 0.04 in the CUF group, and 4.44 ± 0.08 in the MUF group ($p = 0.0048$, MUF vs CUF; $p = 0.05$, MUF vs controls; Fig. 4).

Hematocrit. The baseline hematocrit values were $32\% \pm 1\%$ in controls, $31\% \pm 1\%$ in the CUF group, and $29\% \pm 2\%$ in the MUF group. Ten minutes after CPB, the hematocrit value was $29\% \pm 1\%$ in controls, $30\% \pm 1\%$ in the CUF group, and $28\% \pm 3\%$ in the MUF group. Fifteen minutes of MUF raised the hematocrit value such that it was significantly greater than in both the control group and the CUF group at 60 and 120 minutes after CPB (Fig. 5).

Hemodynamics. The heart rates were not significantly different between the groups at any time point (Fig. 6). As shown in Fig. 7, the mean arterial pressures at baseline and 10 minutes after CPB were also similar among all groups. At 60 minutes after CPB, mean arterial pressures were 64.7 ± 8.9 mm Hg in the control group, 66.0 ± 15.0 mm Hg in the CUF group, and 93.5 ± 9.4 mm Hg in the MUF group. At 120 minutes after CPB, the mean arterial pressures were 66.7 ± 11.3 mm Hg in the control group, 55.5 ± 3.4 mm Hg in the CUF group, and 84.7 ± 8.9 mm Hg in the MUF group ($p = 0.02$, MUF vs CUF; $p = 0.04$, MUF vs controls; analysis of variance).

Contractility. As shown in Fig. 8, the left ventricular contractility determinations were similar in all groups before CPB. At 10 minutes after CPB and before modified ultrafiltration, the control and

Fig. 6. Heart rates of piglets during the study as determined by electrocardiographic tracings.

Fig. 7. Mean arterial pressure as determined by a femoral catheter. * $p < 0.01$, MUF versus CUF group and MUF versus control group.

MUF groups had a higher contractility than did the CUF group. Contractility improved in the MUF group at 60 minutes, continuing to increase at 120 minutes after CPB while remaining decreased after CPB in both the control and CUF groups ($p = 0.008$, MUF vs CUF; $p = 0.02$, MUF vs controls; analysis of variance).

Discussion

This study demonstrates that exposure to moderate hypothermic CPB with a clinically relevant period of protected myocardial ischemia results in considerable cardiac dysfunction with associated weight gain and an increase in the myocardial water content. The decreased cardiac function was manifest as a decreased mean arterial pressure and an impaired left ventricular myocardial contractility. Modified ultrafiltration alone was effective in reducing weight gain, lessening myocardial edema, and improving left ventricular contractility.

The exact reasons for differences in the effectiveness between modified and conventional ultrafiltra-

Fig. 8. PRSW determinations of the left ventricle. $p < 0.05$, MUF versus CUF group and MUF versus control group.

tion have not been fully elucidated. However, several differences between the two methods deserve consideration. First, modified ultrafiltration is performed after the cessation of CPB, which offers the advantage of more efficient filtration. Because the volume to be filtered in the piglet is approximately 200 ml and the volume of the entire circuit including the piglet is approximately 850 ml, modified ultrafiltration is at least four times as efficient as conventional ultrafiltration. Second, modified ultrafiltration allows the concentration of hematocrit and other blood components, because the reservoir may be completely drained during this process, whereas conventional ultrafiltration requires that the reservoir volume be maintained while CPB is being conducted. Last, modified ultrafiltration is performed while blood is at body temperature and circulating normally through the heart and lungs, whereas conventional ultrafiltration is undertaken as the blood is being heated above body temperature (38° to 39° C) and being “bypassed” from the lungs. This may be of importance inasmuch as the lungs are known to absorb activated leukocytes,¹² which have been shown to contribute to the inflammatory process in the heart and other organs.¹²

Although conventional ultrafiltration was found to be ineffective in this model of neonatal swine undergoing CPB, this method of ultrafiltration has been found efficacious in adult patients undergoing similar procedures.¹³ Although studies comparing modified and conventional ultrafiltration in adult swine and neonatal swine have not been done, it was the relative lack of effectiveness of conventional ultrafiltration in neonatal patients that actually led to the development of modified ultrafiltration.⁷ The discrepancy between adults and neonates may be related to the tendency of neonates to have a greater inflammatory response from CPB,³ necessitating a

more efficient filtration process and a greater degree of removal of excess water and inflammatory mediators. Furthermore, adults have a higher glomerular filtration rate than neonates, which suggests that adults may be capable of achieving the same efficient filtration with their own kidneys, obviating the need for modified ultrafiltration.

It is not known, nor has it been determined in this study, whether the beneficial effects of modified ultrafiltration are due to the removal of “free water” or to the removal of mediators of inflammation. Several studies have clearly demonstrated that ultrafiltration lowers the serum levels of several factors known to contribute to postoperative organ dysfunction.^{14,15} Furthermore, “free water” and inflammatory factors are interrelated, because it is inflammation that allows free water to leak from capillaries and cause the tissue edema which leads to organ dysfunction. In a recent clinical study, “short duration” modified ultrafiltration alone was compared with modified ultrafiltration and high-volume, zero-balanced ultrafiltration.¹⁶ In this article, the authors conclude that the combination of these techniques resulted in a lower alveolar-arterial oxygen gradient and afforded lower plasma levels of tumor necrosis factor, interleukin-10, myeloperoxidase, C3a, interleukin-1, and interleukin-6. This study suggests that the “free water” removal of modified ultrafiltration is more effective at improving pulmonary function when the plasma levels of inflammatory cytokines have been lowered. Although cytokines were not measured in our study, in preliminary investigations we observed an immediate decrease in the PRSW when small amounts (10 ml) of the modified ultrafiltrate were reinfused. This decrease in PRSW indicates that substances that act as potent myocardial depressants are removed by modified ultrafiltration. Further investigations directed at the interaction of individual cytokines with specific organs are warranted to delineate the mechanisms and prevent cardiopulmonary dysfunction in systemic inflammatory reactions.

In our institution, modified ultrafiltration is used routinely in pediatric patients undergoing CPB. The clinical benefits of modified ultrafiltration have been reported previously.⁷⁻⁹ This large animal study concurs with the clinical data and adds to our understanding of the benefits of modified ultrafiltration by demonstrating its effects on myocardial function. In summary, this study confirms that CPB causes an increase in weight, myocardial edema, and depressed cardiac function. Modified ultrafiltration

was effective in lessening weight gain, reducing myocardial edema formation, and improving cardiac function, whereas conventional ultrafiltration was not.

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Discussion

Dr. J. Nilas Young (*Berkeley, Calif.*). Dr. Daggett and his colleagues at Duke have provided important information regarding some of the significant physiologic effects of an intraoperative intervention, namely ultrafiltration, in a neonatal animal model. They have used sophisticated data acquisition protocols that they helped to popularize.

The authors have demonstrated experimentally that conventional ultrafiltration (i.e., dialysis on CPB) is not beneficial in neonates and may in fact be detrimental, but that modified ultrafiltration (i.e., dialysis after CPB) is beneficial with regard to hematocrit levels, total body weight gain, myocardial edema formation, and ventricular contractility. Their experimental data and conclusions appear to be validly obtained and statistically justified, and their experimental data seem to corroborate the findings of several other published, limited clinical studies.

It is interesting that mean arterial blood pressures after modified ultrafiltration were markedly increased to hypertensive levels for a neonate. Dr. Daggett, what do you think was the cause of this arterial hypertension? Other investigators have noted similar increases in systemic blood pressure without an increase in peripheral vascular resistance after modified ultrafiltration. In fact, some have noted decreased pulmonary vascular resistance and improved cardiac output. Do you have vascular resistance data to share with us?

Dr. Daggett. Previous studies of CPB have demonstrated that the viscosity of the blood is directly related to the hematocrit value and that it is this increase in hematocrit value which increases the viscosity of the blood, causing hypertension. However, on examining the relationship of the cardiac output and cardiac index, we found that no statistically significant difference between the two groups. I have no data on the systemic vascular resistance, so I cannot directly comment on that.

Dr. Young. If part of the benefit of ultrafiltration is removal of inflammatory mediators, why do you think that conventional ultrafiltration might not be just as beneficial, since these mediators could be removed presumably just as well during CPB as after CPB? Were any measurements made of inflammatory mediators? You mentioned that reinfusion of the ultrafiltrate after modified ultrafiltration was associated with hemodynamic decompensation. Is this also true if the ultrafiltrate from conventional ultrafiltration is reinfused?

Dr. Daggett. With regard to your first question, modified ultrafiltration is much more efficient than conventional ultrafiltration; one of the fundamental problems with conventional ultrafiltration is that the blood is being filtered during CPB. Thus the inflammatory mediators can never be removed, because they are being continuously created during CPB. We did not specifically measure inflammatory mediators in this study, although several groups have demonstrated that both tumor necrosis factor and interleukin-8 are decreased by this technique.

We did not study infusion in either of these groups. In preliminary studies, however, the hemodynamic compromise consisted mainly of pulmonary hypertension and cardiovascular collapse with decreased cardiac output. The acute nature and the small amount of volume that was infused from both conventional ultrafiltrate and modified ultrafil-

trate would suggest that the mediators of this hemodynamic compromise were likely to be anaphylotoxins or other acute mediators of inflammation, having a direct effect on myocardial performance and pulmonary vascular resistance.

Dr. Young. Last, from a clinical standpoint, sometimes a neonate who has just been weaned from CPB is not in totally stable condition. What percentage of neonates undergoing congenital heart surgery with CPB at Duke receive modified ultrafiltration, and in those patients receiving modified ultrafiltration, are the results similar to those found in your piglet model?

Dr. Daggett. The vast majority of patients at Duke undergo modified ultrafiltration. There are criteria for exclusion, such as the need to be placed back on CPB or immediate return to the intensive care unit. I would emphasize that modified ultrafiltration is a very effective clinical technique. These results were the same as those in our neonatal clinical studies.

Dr. Edward D. Verrier (*Seattle, Wash.*). I think this issue needs to be put into some context, and then I have a question. There are as many studies in the literature stating that no beneficial effect is derived from ultrafiltration as there are those that show the benefit. It is very seductive to institute ultrafiltration at the end of CPB, get a little bottle of water in front of you, and think: "this is goodness." There must be "bad things" that happen with blood going through the artificial circuit, and now these "bad things" end up in the bucket. What is in the filtered fluid that is so bad, and why do you believe you saw such a benefit? Ultrafiltration has not attracted much attention in the adult literature, yet the same principles ought to be applied. Adults have a bigger body surface area, so one might argue there are more reasons to generate inflammatory mediators.

The question I have with your study, Dr. Daggett, is that it is not randomized or blinded. During ultrafiltration, how do you maintain fluid balance and how does that relationship influence edema formation? Did you have to add large amounts of saline solution to maintain hemodynamics? Does the lack of randomness prejudice the study results a priori?

Dr. Daggett. Thank you, Dr. Verrier. The reason modified ultrafiltration was developed initially was the failure of conventional ultrafiltration. One of the reasons for this failure is that the glomerular filtration rate in neonates and infants is significantly less than it is in adults. Adults may be able to accomplish the same thing using their own kidneys with diuretics given at the time of CPB, whereas neonates often have a decrease in kidney function after CPB. That is one of the likely reasons for the difference between pediatric patients and adults.

To answer your question regarding randomization: The animals were randomized just before being rewarmed. The study was not blinded, of course, but the circuit was constructed in an identical fashion in every case, with the ultrafilter in place, so that the priming volume and other parameters were identical. It was only after cardiac arrest and before rewarming that we randomized to prevent bias.

As far as returning fluid from the circuit to the animal, during modified ultrafiltration enough was added to keep the left atrial pressures the same in every group at the end of CPB. That was our criterion for returning blood from the cardiopulmonary reservoir. During conventional ultrafiltration, lactated Ringer's solution was added to replace losses, such that the volume in the reservoir was the same as when we started CPB.