Modified ultrafiltration improves global left ventricular systolic function after open-heart surgery in infants and children

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Received 26 October 1998; received in revised form 15 February 1999; accepted 11 March 1999

Abstract

Objectives: Modified ultrafiltration increases blood pressure and cardiac index following open-heart surgery in children, but it is unclear if this is secondary to an improvement in global left ventricular function. A previous report has suggested that left ventricular systolic function as assessed in a single chord is improved by ultrafiltration (Davies MJ, Nguyen K, Gaynor JW, Elliott MJ. Modified ultrafiltration improves left ventricular systolic function in infants after cardiopulmonary bypass. J Thorac Cardiovasc Surg 1998;115:361--370). The prominent vascular actions of modified ultrafiltration necessitate left ventricular assessment using load-independent indices of systolic and diastolic function.

Methods: In 22 consecutive infants and children undergoing open-heart surgery, left ventricular function was assessed following bypass and then 10 min later. Sixteen children (median weight 8.1 kg) underwent modified ultrafiltration during this period, the remainder (median weight 7.3 kg) were controls for spontaneous recovery without ultrafiltration. Real-time pressure-volume loops, with transient inferior caval vein snaring were generated from conductance and microtip pressure catheters inserted through the LV apex. From these, load-independent (slope of the end-systolic pressure-volume \( E_{es} \) and end-diastolic pressure-volume \( E_{ed} \) relationships) and load-dependent \( P_{max} \), end-diastolic LV pressure; \( P_{ed} \), maximum \( \frac{dP}{dt_{max}} \) and minimum \( \frac{dP}{dt_{min}} \) time derivatives of LV pressure; \( \tau \), time constant of isovolumic relaxation) indices of left ventricular function were measured.

Results: Haemoconcentration was achieved in all modified ultrafiltration patients, median increase in haematocrit 34% (interquartile range 21%, 42%), final haematocrit 0.40 (0.35, 0.41). \( E_{es} \) increased 58% (9, 159, \( P \approx 0.005 \)). The changes in \( E_{ed} \), \( P_{max} \), \( P_{ed} \), \( \frac{dP}{dt_{max}} \), \( \frac{dP}{dt_{min}} \) and \( \tau \) were not significantly different from the control group.

Conclusion: Modified ultrafiltration improves global left ventricular systolic function in infants and children following open-heart surgery. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Congenital heart disease; Cardiovascular surgery; Ventricular function

1. Introduction

Open-heart surgery in infants and children results in an increase in total body water that is mainly distributed to interstitial tissue [2]. This is primarily related to the use of cardiopulmonary bypass with haemodilution and the subsequent inflammatory response. Tissue oedema leads to fluid accumulation in body cavities and can have adverse effects on end organ function, especially of the lungs, heart and brain. Ultrafiltration during rewarming or after cardiopulmonary bypass is associated with a decrease in total body water [3,4], postoperative blood loss [3,5--8], alveolar–arterial oxygen gradient and duration of ventilation [5,6], frequency of pulmonary hypertensive episodes [9] and morbidity after cavopulmonary connections [7]. The haemodynamic effects of ultrafiltration are an elevation in arterial blood pressure [3,4,10,11], decrease in pulmonary vascular resistance and increase in cardiac index with an unchanged systemic vascular resistance [11]. However the effect of ultrafiltration on global left ventricular function has not been assessed, and in the presence of its prominent effect on loading conditions clearly requires evaluation by load-independent indices of systolic and diastolic function. A recent important report has described an improvement in minor-axis left ventricular systolic function using single-
chord indices analogous to global load-independent indices[1].

In infants and children undergoing modified ultrafiltration (MUF) following corrective open-heart surgery we report an improvement in global left ventricular function, assessed from the pressure–volume plane using a conductance and microtip pressure catheter.

2. Methods

2.1. Patients

The investigation was approved by the Royal Brompton Hospital Ethics Committee for Human Research. Informed consent was obtained for 22 children undergoing open-heart surgery (first 16 children had MUF, last six were controls). Diagnoses of the patients (numbers in brackets) were (a) MUF: primum atrial septal defect (1), secundum atrial septal defect (1), ventricular septal defect (2), secundum atrial septal defect and ventricular septal defect (2), atrioventricular septal defect (2), right ventricular outflow tract obstruction (1), tetralogy of Fallot (5), tetralogy of Fallot and atrioventricular septal defect (2); and (b) control: primum atrial septal defect (1), ventricular septal defect (3), tetralogy of Fallot (2). All patients were candidates for biventricular repair, were undergoing their first open-heart operation and there were no residual shunts following surgery. None of the patients had pre-existing fluid overload or renal impairment.

2.2. Cardiopulmonary bypass and myocardial protection

All patients received a standardized protocol of isoflurane gaseous induction, pancuronium, fentanyl and isoflurane maintenance. They underwent bicaval and ascending aorta cannulation, and subsequently core cooling was begun on bypass to 20–25°C. The priming solution was a mixture of whole blood and Hartmann’s solution in a ratio calculated to achieve a haemoglobin concentration of 8–9 g/dl. Each patient received cold crystalloid cardioplegia (St. Thomas’ solution 1, 20 ml/kg) delivered by the perfusionist into the aortic root at 40 mmHg, after aortic cross-clamping. Cardiopulmonary bypass flow was 150 ml/kg per min (weight < 10 kg) or 2.4 l/m² per min (weight > 10 kg). At the end of the procedure the cross-clamp was removed and rewarming begun on bypass. Ionized calcium was maintained at 1.0 mmol/l, boluses of calcium were given no closer than 20 min prior to the first set of post-cpb measurements and no calcium was given between measurements. All patients were in sinus rhythm and each patient remained on the same dose of dopamine (5–10 mg/kg per min) post-bypass and throughout the study period.

2.3. Modified ultrafiltration

Modified ultrafiltration was performed for 10 min within 5–10 min of cessation of bypass using the Great Ormond Street Hospital protocol [3] with a paediatric haemofilter (Paediatric Filtral 66, Gambro, Engstrom, Sweden). Flow through the filter was maintained at 200 ml/min by an inlet roller pump and outlet resistance varied to maintain a filtration rate of 100–150 ml/min. The previously optimized left atrial pressure was maintained during filtration by transfusion from the venous reservoir through the filter. Filtration was performed for 10 min aiming to achieve a haemoglobin concentration of 12 g/dl. Blood was taken for measurement of haemoglobin concentration and haematocrit immediately before and after ultrafiltration.

2.4. Assessment of left ventricular function

The conductance catheter has been extensively validated for left ventricular volume measurement and details of the theory [12] and our customized conductance catheter system are presented elsewhere [13,14]. Left ventricular function was assessed with the chest and pericardium widely open and ventilation stopped at end-expiration, initially 5–10 min after coming off cardiopulmonary bypass and then repeated after a further 10 min with or without (controls) an intervening period of modified ultrafiltration. Real-time left ventricular pressure–volume loops were generated using conductance catheter and microtip pressure catheter (2F, Millar) inserted through the left ventricular apex and secured with a pledget and purse-string suture. The conductance catheters were custom built (NuMed Inc., Hopkinton, NY) single-field 3F (interelectrode distance 0.36–0.50 cm) or 5F (interelectrode distance 0.71 cm) catheters with eight platinum ring electrodes. Conductance catheters of the appropriate size were selected based on the measured left ventricular long axis from the parasternal long-axis view of the pre-operative echocardiogram. The conductance catheter was manipulated until all five segmental volumes were in-phase and a counter-clockwise rotating pressure–volume loop was formed demonstrating that the conductance catheter was not in the left atrium or aorta, and therefore must lie within the long-axis of the left ventricle. Preload was varied by transient (10 s) snaring of the inferior caval vein. All volume measurements were corrected for blood resistivity and parallel conductance, and each was determined before and after ultrafiltration. Parallel conductance was determined by the hypertonic saline method [12] using an injection of 0.5–2.5 ml of 20% NaCl into the pulmonary artery. Once a stable position with good quality pressure–volume loops was found there was no further catheter manipulation, and the dimensionless gain constant alpha was assumed to be unity and unchanged during the study period.

The conductance catheter signal encoding volume and ECG data were fed to a stimulator/processor unit (Sigma - 5-DF, Cardidynamics) and then to a committed microcomputer, where it was integrated with the amplified pressure
the time constant of isovolumic relaxation; d

(d state microtip pressure recordings: peak systolic pressure

Load-dependent indices were also obtained from steady-

dation was calculated for each patient (pre-MUF compared to

Importantly there was a highly significant increase in $E_{es}$ (median increase 57.8%) in the MUF group as compared to the controls ($P = 0.005$). Changes in indices of diastolic function ($E_{es}$, $dP/dt_{max}$, $\tau$) for the MUF group were not significantly different from controls (Fig. 1).

### 4. Discussion

In this study 10 min of modified ultrafiltration cleared signals (Fylde Isotransducer Amplifier) in custom designed software.

#### 2.5. Data analysis

The end-systolic and end-diastolic pressure–volume relationships were derived from left ventricular pressure–volume loops generated under varying preload. Since the pericardium was widely opened and preload was varied over only a limited range, the end-diastolic pressure–volume relationship was fitted with a straight line. Linear regression estimations of the end-systolic and end-diastolic pressure–volume relationships were excluded if $R^2 < 0.5$. Load-dependent indices were also obtained from steady-state microtip pressure recordings: peak systolic pressure ($P_{max}$), left ventricular end-diastolic pressure ($P_{ed}$), tau ($\tau$), the time constant of isovolumic relaxation; $dP/dt_{max}$ and $dP/dt_{min}$, maximum and minimum values of the time derivative of LV pressure; $\tau$, time constant of isovolumic relaxation.

| Abbreviations: $E_{es}$ and $E_{ed}$, slopes of end-systolic and end-diastolic pressure–volume relationship; $P_{max}$, peak LV pressure; $P_{ed}$, LV end-diastolic pressure; $dP/dt_{max}$ and $dP/dt_{min}$, maximum and minimum values of the time derivative of LV pressure; $\tau$, time constant of isovolumic relaxation. | Abbreviations: $E_{es}$ and $E_{ed}$, slopes of end-systolic and end-diastolic pressure–volume relationship; $P_{max}$, peak LV pressure; $P_{ed}$, LV end-diastolic pressure; $dP/dt_{max}$ and $dP/dt_{min}$, maximum and minimum values of the time derivative of LV pressure; $\tau$, time constant of isovolumic relaxation. |

| Weight (kg) | 7.3 [4.0, 8.2] | 8.1 [4.7, 13.2] |
| Bypass time (min) | 68 [59, 76] | 74 [69, 101] |
| Cross-clamp time (min) | 40 [37, 45] | 49 [39, 83] |
| ICU stay (days) | 1 [1, 4] | 2 [1, 4] |
| $E_{es}$ (% change) | $-24$ [ $-39$, 11] | 58 [9, 159] |
| $E_{ed}$ (% change) | 44 [ $-41$, 170] | 27 [$-13$, 194] |
| $P_{max}$ (% change) | $-7$ [ $-15$, 1] | 15 [$-11$, 27] |
| $P_{ed}$ (% change) | $-19$ [ $-35$, 3] | $-4$ [$-13$, 27] |
| $dP/dt_{max}$ (% change) | $-5$ [ $-26$, 3] | 8 [$-14$, 70] |
| $dP/dt_{min}$ (% change) | $-10$ [ $-27$, 4] | 8 [$-14$, 64] |
| $\tau$ (% change) | $2$ [ $-10$, 24] | $0$ [$-21$, 3] |

| Table 1 Comparison of control and modified ultrafiltration groups (median[interquartile range]) |

There was no significant difference between the control and MUF groups in weight, bypass duration, cross-clamp time and intensive care unit stay. There were two deaths in the MUF group (patients 15 and 16 who died 0.3 and 3 days post-operatively) secondary to pulmonary hypertensive crises. Technically adequate end-diastolic pressure–volume regression lines with $R^2 > 0.5$ could not be obtained at either of the two time points in seven subjects (five in the MUF group, two in the control group), and hence $E_{ed}$ values are based on 15 patients. All other reported indices used all 22 patients. Linear regression determinations of the end-systolic and end-diastolic pressure–volume relationships had a mean $R^2 = 0.78$ and 0.67, respectively. Haemoco

| $P_{max}$ (% change) | 15, 1] | 15 [$-11$, 27] |
| $P_{ed}$ (% change) | 13, 194] | 27 [$-13$, 194] |
| $dP/dt_{max}$ (% change) | $-10$ [ $-27$, 4] | 8 [$-14$, 64] |
| $dP/dt_{min}$ (% change) | $-10$ [ $-27$, 4] | 8 [$-14$, 64] |
| $\tau$ (% change) | $2$ [ $-10$, 24] | $0$ [$-21$, 3] |

4. Discussion

In this study 10 min of modified ultrafiltration cleared...
sufficient plasma to achieve haemoconcentration, and was associated with improved LV systolic function as assessed by a load-independent index (median increase \( E_{es} = 58\% \)). The weak relationship in this study between change in haematocrit and \( E_{es} \) implies that plasma clearance is important, but does not discriminate between free water or cytokine clearance. Modified ultrafiltration did not alter diastolic function in this study. The failure to detect a consistent decrease in \( E_{es} \) with ultrafiltration could be related to the study conditions (open-chest, open-pericardium) which allowed a truer assessment of myocardial performance, but removed the normal effects of pericardial restraint on chamber diastolic function. Alternatively, modified ultrafiltration genuinely may not improve clearance of excess myocardial tissue water. This is unlikely as in a neonatal pig model of cardiopulmonary bypass with ischaemic arrest, modified ultrafiltration decreased cardiac wet weight and increased the preload recruitable stroke work, but diastolic indices were not reported [4]. Although myocardial oedema is associated with increased myocardial stiffness [15], the converse, of oedema clearance by ultrafiltration increasing compliance and by implication improving diastolic function, has not been shown.

A recent study in 21 infants suggested MUF improved left ventricular function based on changes in pressure–dimension loops i.e. global left ventricular function was inferred from changes in a single minor-axis chord [1]. Extrapolating global chamber changes from the behaviour of a single chord is potentially misleading, but is particularly problematic in the immediate post-bypass period when incoordinate wall motion is frequently encountered. Indeed our group has previously demonstrated that M-mode derived indices of ventricular function are critically dependent on the axis examined [16]. The small decrease in end-diastolic pressure, wall thickness, wall area and increase in minor axis length were interpreted as reflecting an increase in compliance. Standard indices of diastolic function such as time constant of isovolumic relaxation, \( dP/dt_{min} \) and the end-diastolic pressure–volume relationship were not reported and hence assessment of diastolic function was indirect.

4.1. Effect of ultrafiltration on cytokines

Ultrafiltration can potentially ameliorate increased total body water and inflammation following open-heart surgery. Although increased free water clearance whilst avoiding a hypercoagulable state seems worthwhile for overall post-operative management, most attention has focused on the effects of ultrafiltration on the inflammatory cascade.

Our group [16] and others [5,6,17–19] have demonstrated ultrafiltration induced attenuation of the rise in cytokines (tumour necrosis factor \( \alpha \); interleukins 1, 6, 8 and 10), complement (C3a, C5a) and neutrophil degranulation in children undergoing open-heart surgery. The method of ultrafiltration (MUF versus conventional) only improved the clearance of tumour necrosis factor in one clinical study [19]. However, in a randomized study of conventional versus modified ultrafiltration in neonatal pigs, MUF was superior in terms of decreasing total body and cardiac weight gain, increasing systemic blood pressure and improving LV function as demonstrated by an increase in preload recruitable stroke work, although cytokine levels were not measured [4].

High-volume haemofiltration (median 4.97 l/m²) with no net fluid removal during rewarming, leads to lower cytokine levels immediately after haemofiltration and 24 h later, and reductions in postoperative blood loss, alveolar–arterial oxygen gradient, time to extubation compared to controls [6]. Immediately after haemofiltration tumour necrosis factor \( \alpha \), interleukin 10, C3a and myeloperoxidase were lower than controls whereas 24 h later interleukin 1, 6, 8 and myeloperoxidase were lower. The authors suggested that haemofiltration during rewarming, when cytokine levels usually rise, may have attenuated the inflammatory response. This study clearly shows that some effects of massive ultrafiltration are independent of free water clearance. However both the haemofiltration group and control group received modified ultrafiltration post-bypass, and so the effects of free water clearance could not be assessed.

Only one negative study of the effects of intraoperative haemofiltration has been published, and this was in a group of older children with median weight 17 kg [20]. Saatvedt et al. [20] reported 18 children with half randomized to receive ultrafiltration. Although 25 ml/kg fluid was removed there was no difference between the two groups in terms of haemodynamics, inflammatory mediator levels and post-operative course. The overall fluid balance for the first 24 h was no different between the two groups, largely because the ultrafiltration group required more colloid replacement as compared to controls in the intensive care unit, i.e. post-operatively they were forced to replace most of the fluid that had been removed by ultrafiltration intra-operatively. We have observed a similar high colloid requirement post-operatively, in some but not all patients that have undergone modified ultrafiltration.

The increase in \( E_{es} \) produced by modified ultrafiltration represents a moderate improvement in LV systolic function, approximately comparable to the effects of 4–5 mg/kg per min dopamine in a non-cardiopulmonary bypass animal model [21]. Although our results have added improvement in systolic LV function to the list of benefits of modified ultrafiltration, we caution against unequivocal acceptance of cytokine network manipulation by this technique prior to a large randomized trial. The more extensive experience of immunomodulatory therapies in sepsis has been disappointing, often initially encouraging at the small trial stage but when extended to larger populations have either failed or increased morbidity and mortality [22,23].

4.2. Conclusion

A significant increase in global left ventricular systolic
function has been found in children undergoing modified ultrafiltration following open-heart surgery. This supports a previous analysis of the effects of ultrafiltration on left ventricular minor-axis function [1].

Acknowledgements

Many thanks to the perfusionists that performed the modified ultrafiltration in these children: Stanley Brown, Judith Hall and Victor Aston. This study was supported by the Scott Rhodes Research Fund and by the Royal Brompton Hospital Clinical Research Committee.

References