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Reduction in Postoperative High-Density Lipoprotein Cholesterol Levels in Children Undergoing the Fontan Operation

Sinai C. Zyblewski,

Department of Pediatrics, Division of Pediatric Cardiology, Medical University of South Carolina, 165 Ashley Ave, MSC 915, Charleston, SC 29425, USA

W. Scott Argraves,

Department of Regenerative Medicine and Cell Biology, Medical University of South Carolina, 173 Ashley Avenue, Charleston, SC 29425, USA

Eric M. Graham,

Department of Pediatrics, Division of Pediatric Cardiology, Medical University of South Carolina, 165 Ashley Ave, MSC 915, Charleston, SC 29425, USA

Elizabeth H. Slate,

Department of Statistics, Florida State University, Tallahassee, FL 32306, USA

Andrew M. Atz,

Department of Pediatrics, Division of Pediatric Cardiology, Medical University of South Carolina, 165 Ashley Ave, MSC 915, Charleston, SC 29425, USA

Scott M. Bradley,

Department of Surgery, Division of Pediatric Cardiothoracic Surgery, Medical University of South Carolina, Charleston, SC 29425, USA

Tim C. McQuinn,

Department of Pediatrics, Division of Pediatric Cardiology, Seattle Children's Hospital, Seattle, WA 98105, USA

Brent A. Wilkerson,

Department of Regenerative Medicine and Cell Biology, Medical University of South Carolina, 173 Ashley Avenue, Charleston, SC 29425, USA

Shane B. Wing, and

Department of Regenerative Medicine and Cell Biology, Medical University of South Carolina, 173 Ashley Avenue, Charleston, SC 29425, USA

Kelley M. Argraves

Department of Regenerative Medicine and Cell Biology, Medical University of South Carolina, 173 Ashley Avenue, Charleston, SC 29425, USA

Sinai C. Zyblewski: chois@musc.edu

Abstract

Despite the emerging relevance of high-density lipoprotein (HDL) in the inflammatory cascade and vascular barrier integrity, HDL levels in children undergoing cardiac surgery are unexplored. As a measure of HDL levels, the HDL-cholesterol (HDL-C) in single-ventricle patients was quantified before and after the Fontan operation, and it was determined whether relationships existed between the duration and the type of postoperative pleural effusions. The study prospectively enrolled 12 children undergoing the Fontan operation. Plasma HDL-C levels were measured before and after cardiopulmonary bypass. The outcome variables of interest were the duration and type of chest tube drainage (chylous vs. nonchylous). The Kendall rank correlation coefficient and the Wilcoxon rank sum test were used. There were 11 complete observations. The median preoperative HDL-C level for all the subjects was 30 mg/dl (range, 24–53 mg/dl), and the median postcardiopulmonary bypass level was 21 mg/dl (range, 14–46 mg/dl) ($p = 0.004$). There was a tendency toward a moderate inverse correlation (-0.42) between the postcardiopulmonary bypass HDL-C level and the duration of chest tube drainage, but the result was not statistically significant ($p = 0.07$). In the chylous effusion group, the median postcardiopulmonary bypass HDL-C tended to be lower (16 vs. 23 mg/dl; $p = 0.09$). After the Fontan operation, the plasma HDL-C levels in children are significantly reduced. It is reasonable to conclude that the reduction in HDL-C reflects reduced plasma levels of HDL particles, which may have pertinent implications in postoperative pleural effusions given the antiinflammatory and endothelial barrier functions of HDL.

Keywords

Fontan; HDL-C; High-density lipoprotein-cholesterol

Since the original description of the Fontan operation by Fontan and Baudet [8] in 1971, the procedure has undergone significant improvements in both the surgical and medical managements. These modifications have allowed a broad cross-section of patients with single-ventricle physiology to undergo successful Fontan palliation with excellent survival rates [1, 13]. However, despite low mortality rates, patients who undergo the Fontan operation continue to remain at considerable risk for prolonged postoperative recovery complicated by persistent pleural effusions, ventricular dysfunction, arrhythmias, and protracted mechanical ventilation [18, 21].

Heart catheterization and echocardiographic evaluations are routinely performed before the Fontan operation in efforts to predict how the lungs and heart will interact. Yet, despite this practice, predicting the early postoperative course remains difficult, and it is becoming increasingly evident that catheterization hemodynamic data are not consistently associated with early postoperative outcomes [5, 16]. This suggests the existence of other unexplored variables that place Fontan patients at risk for prolonged postoperative recovery despite acceptable hemodynamic criteria.

In recent years, reductions in high-density lipoprotein (HDL) levels have been reported in acute inflammatory conditions such as sepsis and in adults undergoing cardiac surgery with cardiopulmonary bypass (CPB) [6, 11, 22]. Findings have shown that HDL mediates

enhancement of the endothelial barrier function, thus reducing vascular permeability [4] and eliciting antiinflammatory effects [3]. Despite the emerging relevance of HDL in the inflammatory cascade and vascular barrier integrity, HDL levels in children undergoing cardiac surgery are unexplored. This study aimed to assess HDL levels as a function of HDL-cholesterol (HDL-C) in single-ventricle patients before and after the Fontan operation and to determine whether relationships exist with early postoperative outcomes, specifically the duration and type of chest tube drainage.

Methods

Study Design

This single-institution, prospective, observational cohort study was approved by the Institutional Review Board at the Medical University of South Carolina. Informed written consent was obtained from the parents of all the participants before their enrollment. Children were prospectively enrolled between May 2008 and July 2009. All operations were performed by a single surgeon (S.M.B.). The inclusion criteria specified male and female children ages of 2–7 years with single-ventricle physiology undergoing the Fontan operation. The exclusion criteria ruled out patients with a previous Fontan or Kawashima operation.

Clinical Data Collection

Demographic information, pre-Fontan catheterization hemodynamic data, and cardiac anatomic details were collected at enrollment in the study. The intraoperative data consisted of operative technique, duration of aortic cross clamp, deep hypothermic cardiac arrest, and total duration of CPB. The postoperative data included cardiac intensive care unit (CICU) hemodynamic measurements and peak inotropic score on the first postoperative day, duration of mechanical ventilation, duration of pleural effusions, presence or absence of chylous effusions, duration of CICU stay, and total hospitalization time.

The first postoperative day (POD 0) represented the period including transfer from the operating room to the CICU through 7:00 a.m. on the morning after surgery. The mean Fontan pathway pressure was measured from an internal jugular catheter, and the mean left atrial pressure was measured by an intracardiac common atrial catheter. Aninotropic score for POD0 was calculated with a previously described formula [dopamine + dobutamine + (milrinone $\times$ 10) + (epinephrine $\times$ 100)] using peak infusion rates measured in $\mu\text{g/kg/min}$ [7].

Blood Collection and HDL-C Analysis

All the study participants had a baseline whole-blood sample (2 ml) collected in a chilled ethylenediaminetetraacetic acid (EDTA)-containing tube. The samples were collected in the operating room after the induction of general anesthesia and before skin incision, then 24 h after separation from CPB. Plasma was isolated by centrifugation, decanted into aliquots, and stored at -80°C until processed for analysis. The Cholestech LDX Lipid System (Hayward, CA) was used to measure HDL-C in 35- μl aliquots of plasma samples.

Outcome Variable

The postoperative outcome variable of interest was chest tube drainage given its ability to be objectively measured and its potential relationship to vascular permeability. Additionally, chest tube drainage has been well documented as a complication after the Fontan operation that prolongs postoperative recovery, extends the hospital length of stay, and contributes to morbidity [13, 18]. Duration of chest tube drainage was defined as the number of days until the last remaining pleural chest tube was removed. Chest tubes were removed when the drainage from that specific tube totaled less than 2 ml/kg/day for a 24-h period. Because chest tube removal often was not complete during the CICU stay, the duration of chest tube drainage was inclusive of both CICU and ward days. The chest tube drainage outcome also was dichotomized into chylous effusion and nonchylous effusion groups. Chylous effusion was diagnosed by milky appearance and/or laboratory testing that confirmed a triglyceride content of more than 100 mg/dl and/or lymphocytes exceeding 85 % by cell count in a nonfasting state.

Statistical Analysis

Baseline data were summarized as proportions or medians and ranges. Preoperative, intraoperative, and CICU data were compared between the chylous and nonchylous effusion groups using the Wilcoxon rank sum test. The Kendall rank correlation coefficient was used to examine relationships between HDL-C levels and duration of postoperative chest tube drainage and total hospital length of stay. To ensure a conservative comparison with preoperative levels, the value of 14 mg/dl was used for two postoperative HDL-C measurements censored below at 14 mg/dl (i.e., known to be 14 mg/dl at most). All statistical tests were two-sided, and exact *p* values are reported. Statistical analysis was computed in R version 2.9.0 (Vienna, Austria).

Results

Study Population

The inclusion criteria were met by 12 subjects, and they were successfully enrolled in the study between May 2008 and July 2009. All the subjects underwent a hemodynamic catheterization before their Fontan operation and had a superior cavopulmonary anastomosis as their pre-Fontan anatomy. The preferred surgical technique was the extracardiac conduit Fontan with a fenestration ($n = 9$, 75 %). Concomitant secondary surgical procedures included pulmonary artery augmentation ($n = 4$, 33 %) and atrial septectomy ($n = 2$, 17 %). All the subjects received modified ultrafiltration.

The demographic and operative characteristics of the subjects are shown in Table 1. Hospital survival was 100 %. None of the subjects required Fontan takedown. Pre-, intra-, and postoperative characteristics are shown in Table 2.

The pre-Fontan catheterization data did not differ significantly between the chylous and nonchylous effusion groups. The subjects in the chylous effusion group had a significantly longer cardiopulmonary bypass time, with a median of 118 min (range, 112–204 min) versus a median of 103 min (range, 88–113) in the nonchylous effusion group ($p = 0.01$). The

chylous effusion group also had a longer chest tube drainage, with a median of 12 days (range, 10–24 days) versus a median of 9 days (range, 8–14 days) for the nonchylous effusion group ($p = 0.05$) (Table 2). Three of the four patients in the chylous effusion group had drainage longer than 10 days.

HDL-C Reduction in Postoperative Plasma

The levels of HDL-C were measured in plasma samples from 12 patients, and there were 11 complete observations. The one incomplete observation occurred because the baseline blood sample of one subject was inadvertently discarded. The median baseline preoperative HDL-C level was 30 mg/dl (range, 24–53 mg/dl), and the median 24-h post-CPB HDL-C level was 21 mg/dl (range, 14–46 mg/dl). The HDL-C level was significantly reduced between the baseline preoperative and the 24-h post-CPB levels (Fig. 1), with a median reduction of 38 % ($p = 0.004$). The baseline preoperative HDL-C levels and their percentages of reduction did not correlate with the durations of chest tube drainage or the hospital stays. There was a tendency toward a moderate inverse correlation (-0.42) between the 24-h post-CPB level of HDL-C and the total duration of chest tube drainage, but the association was not statistically significant ($p = 0.07$). The baseline preoperative HDL-C levels and the 24-h post-CPB levels trended lower in the chylous effusion group (Fig. 2), but the difference did not reach statistical significance. The median baseline preoperative HDL-C level was 26 mg/dl (range, 24–33 mg/dl) in the chylous effusion group and 41 mg/dl (range, 25–53 mg/dl) in the nonchylous effusion group ($p = 0.11$). The median 24-h post-CPB level of HDL-C was 16 mg/dl (range, 14–21 mg/dl) in the chylous effusion group and 23 mg/dl (range, 14–46 mg/dl) in the nonchylous effusion group ($p = 0.09$) (Fig. 2).

Discussion

The etiology of pleural effusions in patients undergoing the Fontan operation likely is multifactorial, and many studies indicate that the inflammatory response contributes to this process [10, 14, 15]. Findings have identified HDL as an important antiinflammatory mediator [2]. The described antiinflammatory functions of HDL include limiting lipid peroxidation, inhibiting expression of proinflammatory cytokines, interfering with proinflammatory transcription factors, and modulating recruitment and adhesion of monocytes at the cellular and molecular levels [2, 17]. It is reasonable to conclude that a reduction in HDL-C reflects reduced plasma levels of HDL particles.

The low baseline HDL-C levels identified in this study raise the possibility that a subset of single-ventricle patients exist in a chronic inflammatory state, even before the Fontan operation. Adults with unrepaired congenital heart disease and chronic cyanosis have been shown to have hypocholesterolemia [9], and it is worth noting that the median baseline preoperative HDL-C level for the chylous effusion group was below the 5th percentile (30 mg/dl) for U.S. children between the ages of 4 and 5 years [12]. The concept of chronic inflammation in the single-ventricle population deserves further investigation given the significant but enigmatic morbidities in the single-ventricle population, specifically protein-losing enteropathy, collateral vessel formation, and lymphatic disease.

High-density lipoprotein is a major plasma carrier of sphingosine 1-phosphate (S1P), a sphingolipid that interacts with G protein–coupled receptors on endothelial cells, enhances endothelial barrier function, and reduces vascular permeability [4]. Therefore, HDL levels may reduce the amount of bioavailable S1P, thus impairing the process of endothelial barrier recovery after the inflammatory injury of CPB.

In a murine model of endotoxin lipopolysaccharide-induced lung injury, mice genetically deficient in their capacity to synthesize S1P, and thus having reduced plasma S1P levels, display increased pulmonary edema [20]. Additionally, in a canine model of lipopolysaccharide-induced acute lung injury, “rescue” administration of S1P reduced pulmonary shunt formation, attenuated alveolar protein accumulation, and decreased alveolar edema formation [19]. Therefore, we hypothesize that an acute or sustained decrease in HDL-S1P may lead to pathologic vascular leakage in pediatric cardiac patients undergoing CPB.

Limitations of the Study

This study had important limitations. The sample size was very small, thereby prohibiting definitive conclusions regarding HDL-C and its impact on postoperative recovery after the Fontan. The chylous effusion group had a significantly longer total CPB time than the nonchylous effusion group, and this finding potentially confounds the relationship between HDL-C and chest tube drainage.

Liver function was not assessed in the patients before surgery. A comprehensive lipoprotein profile was not performed, and qualitative HDL function was not assessed. Additionally, the HDL-C levels at hospital discharge were not analyzed, so it is unknown whether the levels normalized or remained low.

Conclusions

In summary, the plasma HDL-C levels are significantly reduced in children after the Fontan operation. Future research needs to include a larger sample and should further investigate the inflammatory state of children before and after the Fontan operation, the qualitative HDL function in children with single-ventricle physiology, the measurement of HDL-C levels at multiple postoperative time points, and the correlation with short- and long-term outcomes after the Fontan operation. Additional investigation of plasma HDL-S1P in children undergoing cardiopulmonary bypass also deserves research, especially given that therapies targeting S1P-mediated vascular endothelial barrier function may reduce vascular permeability and subsequently improve capillary leak, tissue edema, and the postoperative recovery after cardiac surgery.

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Fig. 1. Reduction in high-density lipoprotein-cholesterol (HDL-C) levels after the Fontan operation. The pre- and postoperative plasma HDL-C levels measured in the patients undergoing the Fontan operation ($n = 11$) can be seen. Data are presented in box-and-whisker diagrams. The boxes correspond to the interquartile range (IQR). The horizontal bar within the box indicates the group median HDL-C level. The whiskers extend $1.5 \times$ IQR. The colored lines connect pre- and postoperative measurements for individual subjects, and the X indicates the two postoperative measurements known to be 14 mg/dl or less

Fig. 2.

Comparison of high-density lipoprotein-cholesterol (HDL-C) levels in the nonchylous and chylous effusion groups. The chylous effusion group had a tendency toward lower pre- and postoperative HDL-C levels compared with the nonchylous group. The pre- and postoperative plasma HDL-C levels measured in the patients undergoing the Fontan operation and grouped according to their effusion type (chylous vs. nonchylous) can be seen. Data are presented in box-and-whisker diagrams. The box corresponds to the IQR. The *horizontal bar* within the box indicates the median, and the whiskers extend $1.5 \times$ IQR

Table 1

Demographic and operative characteristics

Variable	Study subjects (<i>n</i> = 12) <i>n</i> (%)
Male gender	9 (75)
Age: years (range)	4.2 (3.2–5.5)
Weight: kg (range)	14.2 (13.2–21.5)
Systemic RV	7 (58)
Heterotaxy	1 (9)
Perfusion strategy	
CPB + AXC	2 (17)
CPB + AXC + DHCA	4 (33)
Fontan type	
Extracardiac	9 (75)
Lateral tunnel	3 (25)
Fenestration	11 (92)
Secondary surgical procedure	6 (50)

RV right ventricle, *CPB* cardiopulmonary bypass, *AXC* aortic cross clamp, *DHCA* deep hypothermic circulatory arrest

Data are presented as medians (with ranges) and proportions

Table 2

Pre-, intra-, and postoperative characteristics

Variable	All (<i>n</i> = 12) <i>n</i> (range)	Nonchylous (<i>n</i> = 8) <i>n</i> (range)	Chylous (<i>n</i> = 4) <i>n</i> (range)	<i>p</i> value
Preop TPG (mmHg)	4 (3–7)	4 (3–7)	4 (3–7)	0.86
PA (mmHg)	11 (7–15)	11 (7–15)	12 (8–13)	0.61
EDP (mmHg)	6 (4–12)	6 (4–12)	7 (5–10)	0.80
PVR (U m ²)	1.5 (0.8–2.3)	1.5 (1.0–3.0)	1.4 (0.8–2.3)	0.68
CPB (min)	110 (88–204)	103 (88–113)	118 (112–204)	0.01
Mechanical ventilation (h)	10 (5–23)	10 (5–23)	12 (5–17)	0.86
Peak inotropic score	15 (7–21)	14 (7–15)	15 (12–21)	0.24
CVP (mmHg)	13 (10–15)	13 (10–15)	13 (12–14)	0.93
LAp (mmHg)	6 (4–9)	7 (4–9)	5 (4–9)	0.54
Chest tube drainage (days)	10 (8–24)	9 (8–14)	12 (10–24)	0.05
CICU stay (days)	2.5 (2.5–12.0)	2.5 (2.5–3.5)	3 (2.5–12.0)	0.18
Total hospital stay (days)	10 (8–26)	10 (8–16)	14 (10–26)	0.08
Preop HDL-C (mg/dl)	30 (24–53)	41 (25–53)	26 (24–33)	0.11
Postop HDL-C (mg/dl)	21 (14–46)	23 (14–46)	16 (14–21)	0.09

TPG transpulmonary gradient, PA pulmonary artery, EDP ventricular end-diastolic pressure, PVR pulmonary vascular resistance, CPB cardiopulmonary bypass time, CVP central venous pressure, LAp left atrial pressure, CICU cardiac intensive care unit, HDL-C high-density lipoprotein cholesterol

All results are expressed as medians (with ranges)