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Invasive and noninvasive hemodynamic assessment in adults with Fontan palliation

Alexander C. Egbe [a,*], Heidi M. Connolly [a], Nathaniel W. Taggart [b], Mohamad Al-otaibi [a], Barry A. Borlaug [a]

[a] The Department of Cardiovascular Medicine, Mayo Clinic Rochester, MN 55906, United States
[b] Division of Pediatric Cardiology, Mayo Clinic Rochester, MN 55906, United States

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ABSTRACT

Background/objectives: Although echocardiographic-Doppler cardiac index (CI) assessment is widely used to guide heart failure management in patients with biventricular circulation, this application has not been studied in the Fontan population. The objective of this study was to: (1) determine the correlation between Doppler and cardiac catheterization CI calculation; (2) determine the association between Doppler CI and the occurrence of Fontan failure.

Methods: Retrospective review of adult Fontan patients followed at Mayo Clinic Adult Congenital Heart Disease program, 1994–2015. Inclusion criteria were: systemic left ventricle and echocardiogram and cardiac catheterization performed within the same week. Fontan failure was defined as a composite of all-cause mortality, heart transplantation listing, and palliative care.

Results: 59 patients (age 29 ± 6 years; men 32[54%]) underwent 97 studies. Of the 59, 41[69%] had atriopulmonary Fontan and 12 (20%) had cirrhosis. Compared to patients without cirrhosis, patients with cirrhosis had higher Doppler CI (3.6 ± 0.6 vs 2.8 ± 0.4 L/min $*$ m^2, $p = 0.039$); Fick CI (3.3 [2.5–3.7] vs 2.4 [1.6–3.1] L/min/m^2, $p = 0.028$); lower systemic vascular resistance (20 ± 3 vs 25 ± 4 WU $*$ m^2, $p = 0.04$).
There was a positive correlation between Doppler and Fick CI ($r = 0.52$; $p < 0.0001$). Fontan failure occurred in 13 patients (22%) within 7.5 ± 2.1 years. In patients without cirrhosis, Fick CI and Doppler CI <2.5 L/min/m^2 were associated with Fontan failure (odds ratio [OR] 1.58, $p = 0.046$) and (OR 1.43, $p = 0.051$) respectively.

Conclusions: Doppler CI assessment in feasible in a selected group of Fontan patients and it is predictive of clinical outcomes. The application of this concept in systemic right ventricles deserves further research.

1. Introduction

The Fontan physiology is characterized by low cardiac output (CO) and high central venous pressure because of the absence of an effective subpulmonary ventricle [1,2]. Low CO, common in Fontan physiology, plays an important role in the pathophysiology of Fontan associated diseases (FAD) [1,2]. Diastolic dysfunction is also common in Fontan physiology because of a chronic reduction in preload to the systemic ventricle resulting in ventricular remodeling, reduced compliance, and elevated ventricular filling pressures [1,2]. Elevated ventricular filling pressure leads to increased impedance to pulmonary blood flow, low CO and systemic venous hypertension, all contributing to FAD and Fontan failure [1,2].

CO reflects the efficiency of the Fontan circulation, and as a result meticulous serial monitoring of CO should be an integral part of routine clinical evaluation [1,2]. Currently cardiac catheterization is required for the assessment CO in Fontan physiology, and this is not ideal for routine longitudinal monitoring [3,4]. Echocardiography, on the other hand, is routinely used for CO assessment in patients with biventricular circulation, but not in Fontan physiology because of the absence of invasive validation and normative data [5]. To bridge this gap in knowledge we hypothesized that there was a correlation between Doppler derived CO and the gold standard invasive hemodynamics derived from cardiac catheterization, and that Doppler derived CO was predictive of clinical outcomes in patients with Fontan physiology.

2. Methods

2.1. Patient selection

This is a retrospective review of adult Fontan patients (>18 years) followed at the Mayo Clinic Adult Congenital Heart Disease program. The Mayo Clinic Institutional Review Board approved this study and waived informed consent. All patients who underwent both cardiac catheterization and transthoracic echocardiography within the same week

Abbreviations: CO, Cardiac output; CI, Cardiac index; FAD, Fontan associated diseases; PAWP, Pulmonary artery wedge pressure; LV, left ventricle; LVOT, left ventricular outflow tract; LVEDP, Left ventricular end-diastolic pressure; SVI, Stroke volume index; OR, odds ratio.

* Corresponding author at: Mayo Clinic and Foundation, 200 First Street SW, Rochester, MN 55905, United States.
E-mail address: egbe.alexander@mayo.edu (A.C. Egbe).

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from January 1, 1994 through December 31, 2015 were identified. Patients were included in the study if they met the following criteria: (1) single systemic left ventricle (LV) with ventricular-arterial concordance, (2) no prior surgical intervention to the aortic valve or left ventricular outflow tract (LVOT), (3) mild or absent aortic or mitral regurgitation; and (4) absence of atrial arrhythmia at the time of echocardiography and cardiac catheterization.

2.2. Invasive and noninvasive data acquisition

2.2.1. Cardiac catheterization

All cardiac catheterizations were performed for clinical indications. The techniques for performing cardiac catheterization in patients with Fontan physiology have been described [6]. In this cohort, cardiac index (CI) was calculated based on the Fick principle using assumed oxygen consumption [7,8]. Ventricular filling pressure was assessed by measuring pulmonary artery wedge pressure (PAWP) in all patients, and by measuring both PAWP and left ventricular end-diastolic pressure (LVEDP) in the patients that had both right and left heart catheterizations. Systemic vascular resistance index was calculated as (mean systemic arterial pressure – Fontan pressure)/CI. Plasma volume at the time of catheterization was estimated by: (1-hematocrit) (a ± [b weight in kg]), where $a = 1530$ in men and 864 in women, and $b = 41.1$ in men and 47.9 in women [9].

2.2.2. Echocardiography

The technique for the assessment of stroke volume index (SVI) and CI in patients with Fontan palliation using Doppler echocardiography has been described [5]. We reviewed all digital echocardiography images and verified the accuracy of the following 2-dimensional and Doppler indices: LVOT diameter (measured in the parasternal long-axis view), LVOT time velocity integral (TVI; measured in the apical view), 2D LV end-diastolic and end-systolic dimensions, and LV end-diastolic and end-systolic volumes. For patients with sub-optimal 2D and Doppler measurements, these indices were remeasured offline, following the recommendation of the American Society of Echocardiography [5].

Stroke volume assessment by Doppler echocardiography is based on the hydraulic orifice formula (flow rate = cross-sectional area × flow velocity). All measurements and calculations were performed as stipulated by the American Society of Echocardiography guidelines. Stroke volume was calculated as $0.785 \times (\text{LVOT diameter})^2 \times \text{LVOT TVI}$ [5]. CO was calculated as stroke volume × heart rate. SVI and CI were calculated by dividing the stroke volume and CO by the body surface area. The monoplane Simpson method was used for the calculation of LV ejection [5]. Estimated LV ejection fraction data were collected from the echocardiographic report, as documented by the interpreting cardiologist.

2.3. Endpoint definitions

The primary endpoint was to determine the correlation of noninvasive CI with the gold standard of direct cardiac catheterization. The secondary endpoint was to determine the association Doppler-derived CI with the occurrence of Fontan failure.

Fontan failure was defined as a composite of all-cause mortality, listing for heart transplantation, and initiation of palliative care. Palliative care was defined as being declined for heart transplant listing because of prohibitive surgical risk. Only one event was counted per patient for the composite endpoint of Fontan failure. The definition of FAD used in the current study was similar to prior studies [10,11]. Liver cirrhosis was defined as liver stiffness >5.0 kPa by magnetic resonance elastography or stage 4 fibrosis on histology.

2.4. Statistical analysis

Analyses were performed with JMP software (version 10.0; SAS Institute Inc) and STATA 14 (StataCorp). Categorical variables were reported as percentages, and continuous variables were reported as mean (±standard deviation) or as median (interquartile range) for skewed data. Categorical variables were compared using the χ^2 test or Fisher exact test, and continuous variables were compared with a 2-sided, unpaired *t*-test or Wilcoxon rank sum test, as appropriate.

The agreement between CI by Doppler echocardiography and cardiac catheterization were evaluated via Pearson correlation analysis and Bland-Altman analysis. Logistic regression analysis was used to determine the association between invasive and noninvasive hemodynamics and the occurrence of Fontan failure. The strength of association for each variable was expressed as an odds ratio (OR) and 95% confidence Limit. For the construction of the logistic regression model, we dichotomized all variables using cut points that have been shown in previous studies to be clinically significant [12–14]. For the patients that had more than one set echocardiographic or invasive assessments, we used the hemodynamic indices from the first echocardiogram and cardiac catheterization for the analysis of the association with Fontan failure. For all statistical analyses, a p value <0.05 was considered statistically significant.

3. Results

There were 59 patients who underwent 97 sets of cardiac catheterization and echocardiography studies. The mean age at the time of these studies was 29 ± 6 years, 32 (54%) were men and 41 (69%) had atriopulmonary Fontan connection (Table 1). The structural diagnoses were tricuspid atresia ($n = 44$ [75%]), pulmonary atresia ($n = 13$ [22%]), and double-inlet LV ($n = 2$ [3%]). Of the 59 patients in this study, 12 (20%) had a diagnosis of cirrhosis at baseline.

3.1. Cardiac output assessment

Of the 97 echocardiograms analyzed, image quality was sufficient for ejection fraction calculation in 86 (89%). There was no difference in the estimated and calculated ejection fractions for the patients that had both assessments reported (45 ± 5% vs 43 ± 9%, $p = 0.51$). Mean SVI and CI were 43 ± 15 mL/m^2 and 3.1 ± 0.9 L/min/m^2. Both right and left heart catheterizations were performed in 76 (78%) of cases, while right heart catheterization alone was performed in 21 (22%). The indications for cardiac catheterization are shown in Table 1. The median CI by Fick was 2.8 (1.8–3.5) L/min/m^2.

Table 1
Baseline Clinical Characteristics*($N = 59$).

Age at time catheterization, years	29 ± 6
Age at Fontan operation, years	8 ± 3
Male	32 (54%)
Body surface area, m^2	1.9 ± 0.4
Estimated plasma volume, mL	3086 ± 527
Prior shunt palliation	54 (92%)
CHD diagnosis	
Tricuspid atresia	44 (75%)
Double inlet left ventricle	2 (3%)
Pulmonary atresia	13 (22%)
Fontan connection	
Atriopulmonary Fontan	41 (69%)
LTF/IAC	14 (24%)
Extracardiac Fontan	4 (7%)
*Indication for cardiac catheterization***	
Heart failure/arrhythmia	22 (37%)
Preop cardiac surgery	14 (24%)
Liver disease	8 (14%)
Protein losing enteropathy	4 (7%)
Cyanosis	21 (26%)
Laboratories	
Hemoglobin, g/dl	13.4 ± 1.1
Platelet, ×10^9/L	144 ± 38
Creatinine, mg/dl	1.2 ± 0.5
Albumin, g/dl	4.1 ± 0.4
Aspartate aminotransferase, U/L	37 ± 5
Alanine aminotransferase, U/L	42 ± 6
NT-proBNP, pg/mL	378 ± 91
Comorbidities	
Protein-losing enteropathy	5 (9%)
Thromboembolism	11 (19%)
Cirrhosis	12 (20%)
Atrial arrhythmia	26 (44%)
Heart failure hospitalization	7 (12%)
Creatinine clearance <60 mL/min	11 (19%)
Hyperlipidemia	19 (32%)
Hypertension	2 (3%)
Diabetes mellitus	6 (10%)
Obesity	11 (19%)
Sleep apnea	10 (17%)
Therapies	
Paced rhythm	11 (19%)
BB or CCB therapy	9 (15%)
RAAS antagonist	13 (22%)
Warfarin	15 (25%)
Diuretics	17 (29%)

LTF: lateral tunnel Fontan; IAC: intra-atrial conduit; preop: preoperative; BB: beta blocker; CCB: calcium channel blocker; RAAS: renin angiotensin aldosterone system;
Baseline Clinical Characteristics*: at the time of initial cardiac catheterization; Indication for cardiac catheterization**: some patients had more than one indication for cardiac catheterization; U/L: unit per liter; pg/mL: picogram per milliliter; NT-proBNP: N-terminal pro b-type natriuretic peptide.

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