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ORIGINAL ARTICLE

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Renal dysfunction is associated with higher central venous pressures in patients with Fontan circulation

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Abstract

Purpose: Elevated central venous pressure (CVP) has deleterious effects on several organ systems in patients with Fontan circulation. However, the relationship between CVP and estimated glomerular filtration rate (eGFR) has not been assessed in patients with Fontan circulation.

Methods: Patients with Fontan circulation whose hemodynamics were assessed by catheterization between 1987 and 2015 and had a serum creatinine measured within 72 hours prior to the procedure were included for analysis. Patients with primary kidney disease were excluded. Renal function was calculated by "bedside Schwartz" equation in children (< 18 years) and Modification of Diet in Renal Disease equation in adults. Renal dysfunction (RD) was defined by eGFR < 90 mL/min/1.73 m^2. Fontan patients with and without RD were compared based on demographics, comorbidities, medication use, echocardiographic findings, hemodynamics assessed at time of catheterization, and laboratory testing values.

Results: Sixty-seven patients with Fontan circulation met inclusion criteria and 15 patients (22%) had RD; eGFR (mL/min/1.73 m^2) was 60-89 in 13 (87%), 45-59 in 1 (7%), and 30-45 in 1 (7%). Compared to patients with eGFR equal to or greater than 90, patients with RD had higher CVP (18.0 [15.0-21.0] mm Hg vs 13.5 [12.3-16.0] mm Hg ($P = 0.001$), lower pulmonary blood flow 2.2 [1.9-2.6] L/min/m^2 vs 2.8 [2.3-3.7] L/min/m^2, higher ventricular end-diastolic pressure 10.5 [7.0-17.3] mm Hg vs 8.0 [6.0-10.0] mm Hg ($P = 0.050$), were more likely to have worse atrioventricular valve regurgitation ($P = 0.02$) and were more likely to be African American ($P = 0.009$). After multivariant analysis of relevant hemodynamic parameters, only CVP remained associated with RD ($P = 0.035$).

Conclusions: In this study population, renal dysfunction in patients with Fontan circulation is associated with increased CVP and factors that affect CVP. African Americans with Fontan circulation may be at particular risk for renal dysfunction. Continued investigation of the effects of venous congestion on kidneys and other factors associated with renal dysfunction in patients with Fontan circulation is warranted.

KEYWORDS

central venous pressure, Fontan circulation, glomerular filtration rate, kidney dysfunction, renal function, venous congestion

1 | INTRODUCTION

The Fontan operation is commonly employed to palliate patients with single ventricle lesions.[1] Although survival in patients with Fontan circulation has improved,[2–4] many organ systems are progressively affected by venous congestion and low cardiac output (CO), features intrinsic to the Fontan circulation.[5,6]

By necessity, central venous pressure (CVP) is elevated to drive pulmonary blood flow in Fontan circulation and is thought to deleteriously impact upstream organs. Chronically elevated CVP and hepatic

congestion are thought to lead to cellular transdifferentiation which causes progressive hepatic fibrosis.[6,7] Likewise, elevated CVP and venous congestion are implicated in the etiology of protein losing enteropathy (PLE) in patients with Fontan circulation.[8] Renal function is significantly dependent on a favorable preglomerular and postglomerular pressure gradient, and therefore, may be affected in patients with Fontan circulation. Indeed, there is a growing body of evidence supporting the hypothesis that the hemodynamic effects of the Fontan circulation may adversely affect kidney health.[9–11] In this study, we sought to evaluate relationship of CVP and estimated glomerular filtration rate (eGFR) in the patients with Fontan circulation.

2 | METHODS

This study was approved by the Baylor College of Medicine Institutional Review Board. We performed a retrospective study of all patients with Fontan circulation at Texas Children's Hospital between 1987 and 2015 whose hemodynamics were assessed by cardiac catheterization and had a serum creatinine within the previous 72 hours of the procedure. Except for one case performed under monitored anesthesia care, catheterizations were conducted under general anesthesia with positive pressure ventilation. eGFR was calculated by "bedside Schwartz" equation in children (< 18 years)[12] and Modification of Diet in Renal Disease (MDRD) equation in adults.[13] Renal dysfunction (RD) was defined as eGFR < 90.0 mL/min/1.73 m^2. Calculated eGFR between 60.0 and 89.9 mL/min/1.73 m^2 was defined as "mild dysfunction"; 45.0–59.9 mL/min/1.73 m^2 was defined as "mild-to-moderate dysfunction"; and 30.0–44.9 mL/min/m^2 was defined as "moderate-to-severe dysfunction." Patients with eGFR > 150.0 mL/min/m^2 were not considered to have RD. Patients with primary kidney disease were excluded from the study. Demographic data included age, height, sex, race, systemic ventricle morphology, presence of a patent fenestration, age at Fontan completion, age at catheterization. Variables collected included hemodynamic data from cardiac catheterization. Ventricular end-diastolic pressure (EDP) was assessed either by direct measurement or pulmonary capillary wedge pressure (PCWP). The most consistent pressure within the cavopulmonary circuit was used as the "Fontan pressure." Vascular resistance and flows were calculated using Fick equation; VO_2 was assumed based on the patient's sex, age, and heart rate. Data from transthoracic echocardiograms (TTE) such as systolic ventricular function, atrioventricular valve and semilunar valve regurgitation were included if these studies were performed within 3 months of cardiac catheterization. A clinical diagnosis was necessary for inclusion of medical conditions such as plastic bronchitis (PB), protein losing enteropathy (PLE), heart failure (HF), thrombosis, and/or arrhythmia. Statistical analyses were performed with SAS 9.4 (SAS Institute Inc., Cary, NC) software. Data were reported as frequency (n) with proportion (%), or median with interquartile range (IQR, 25th-75th percentile). Continuous variables were compared using Student's *t*-test for normally distributed data or Wilcoxon Rank-Sum for data with non-normal distribution. Proportions for categorical variables were compared using Chi-square test. Binary-logistic regression with Hosmer–Lemeshow goodness-of-fit was used to perform multivariant analysis. Statistical significance was defined as P value ≤ 0.05.

TABLE 1 Estimated glomerular filtration rate by kidney function

Renal Function (eGFR L/min/1.73 m^2)	n	eGFR (L/min/1.73 m^2)
Normal (90.0+)	52	121.5 [106.2–140.6]
Mild dysfunction (60–89.9)	13	78.6 [74.6–84.4]
Mild-to-moderate dysfunction (60.0–89.9)	1	52.0
Moderate-to-severe dysfunction (30.0–44.9)	1	42.5

3 | RESULTS

Sixty-seven patients with Fontan circulation met inclusion criteria, including 22 (33%) females and 11 (16%) adults. Forty-seven (70%) patients were White, 7 (10%) were African American, 8 (12%) were Hispanic, and 2 (3%) were Asian. The dominant ventricular morphology was right ventricle in 27 (40%), left ventricle in 29 (43%), and indeterminate in 11 (16%). Heterotaxy syndrome was present in 20 (30%) patients. Forty-six (69%) patients had an extracardiac conduit, 18 (27%) had a lateral tunnel, and 2 (3%) had an atriopulmonary Fontan connection. A patent fenestration was present in 30 (47%) patients.

Co-morbidities at time of catheterization included: PB in 5 (7%), PLE in 20 (30%), HF in 6 (9%), arrhythmia in 17 (25%), and thrombosis in 11 (16%) patients. Medications taken at time of or just before catheterization included: loop diuretics in 50 (75%), thiazide diuretics in 12 (18%), other diuretic (principally spironolactone) in 28 (42%), coumadin in 6 (9%), aspirin in 51 (76%), pulmonary vasodilators in 20 (30%), angiotensin converting enzyme inhibitors (ACE-I) or angiotensin II receptor blockers (ARB) in 41 (61%), beta-blockers in 13 (19%), digoxin in 10 (15%), or other anti-arrhythmic in 8 (12%) patients.

The eGFR based on renal function category is listed in Table 1. Fifteen patients (22%) had eGFR < 90 (77.6 [69.8–84.2] mL/min/1.73 m^2) and were included in the "RD" group; 13 were classified as mild, one as mild to moderate, and one as moderate to severe RD.

Fontan patients with and without RD were compared based on demographics, co-morbidities, medication use, echocardiographic findings, hemodynamics assessed at time of catheterization (Tables 2 and 3). The relationship between renal function and Fontan pressure or CVP can be seen in Figure 1. Patients with RD had higher CVP compared to those with normal renal function (18.0 [15.0–21.0] mm Hg vs 13.5 [12.3–16.0] mm Hg ($P = 0.001$)). Additionally, patients with RD had lower pulmonary blood flow (Qp) 2.2 [1.9-2.6] L/min/m^2 vs 2.8 [2.3-3.7] L/min/m^2 ($P = 0.020$) and higher ventricular EDP 10.5 [7.0–17.3] mm Hg vs 8.0 [6.0–10.0] mm Hg ($P = 0.050$). Patients in the RD group were more likely to have moderate or severe atrioventricular valve regurgitation (AVVR; 40%) compared to patients with no RD (10%; $P = 0.02$) The RD group also had a higher proportion of African-American patients (33%) compared to the group without RD (4%; $P = 0.009$). Subanalysis of the RD group found those diagnosed with

TABLE 2 Demographics

Parameter	eGFR $\geq$= 90 Median [quartiles] or n (%)	eGFR $\leq$ 90 Median [quartiles] or n (%)	*P* value
Height (cm)	116 [102–146]	146 [105–160]	0.088
Sex (female)	16 (31)	6 (40)	0.502
Adult			
Race			
White	37 (76)	10 (67)	0.009
African American	2 (4)	5 (33)	
Asian	2 (4)	0 (0)	
Hispanic	8 (16)	0 (0)	
Ventricular morphology			
RV	18 (35)	9 (60)	0.079
LV	23 (44)	6 (40)	
Indeterminate	11 (31)	0 (0)	
Heterotaxy	17 (33)	3 (20)	0.344
Age at Fontan (yr)	4.0 [3.1–6.0]	5.1 [2.8–10.1]	0.470
Age at Cath (yr)	8.7 [5.1–14.8]	13.2 [5.6–19.9]	0.272
Duration of Fontan circulation (yr)	2.1 [0.2–10.6]	5.6 [0.6–13.4]	0.417
Patent Fenestration	24 (46)	6 (40)	0.673
Plastic Bronchitis	4 (8)	1 (7)	0.894
Protein losing enteropathy	14 (27)	6 (40)	0.330
Heart Failure	3 (6)	3 (20)	0.089
Arrhythmia	13 (25)	4 (27)	0.896
Thrombosis	10 (19)	1 (7)	0.247
Loop diuretic	38 (73)	12 (80)	0.587
Thiazide diuretic	10 (19)	2 (13)	0.580
Other diuretic	20 (38)	8 (53)	0.304
Coumadin	4 (8)	2 (13)	0.500
Aspirin	40 (80)	11 (73)	0.679
Sildenafil or similar	15 (29)	5 (33)	0.738
ACE-I/ARB	32 (62)	9 (60)	0.914
Beta blocker	9 (17)	4 (27)	0.419
Digoxin	8 (15)	2 (13)	0.844
Other Antiarrhythmic	5 (10)	3 (20)	0.275

HF (n = 3) were all African American and were the patients with severe systolic ventricular dysfunction by TTE. After performing multivariant analysis using hemodynamic parameters with *P* value <0.1, only CVP remained significantly associated with RD ($P = 0.035$).

4 | DISCUSSION

To our knowledge, this is the first study to demonstrate a relationship between CVP and renal function in patients with Fontan circulation. Other statistically significant associations with RD include Qp, EDP and AVVR. These latter parameters are intimately related to CVP; both higher EDP and significant AVVR increase pressure in the pulmonary venous atrium which is likely to impede Qp. Assuming a relatively static trans-pulmonary gradient, increased atrial pressures necessitate higher pressures in the Fontan circuit to drive flow across the pulmonary vascular bed increasing CVP.

Renal congestion is increasingly recognized as a contributor to renal dysfunction in the setting of heart failure. Traditionally, the paradigm of renal injury and dysfunction in patients with heart disease was thought to be a result of decreased renal artery perfusion. However, there is growing evidence that venous congestion is a significant contributor to renal injury and chronic kidney disease.[16–18] Glomerular filtration is a key component of kidney function and partially depends on

TABLE 3 Echocardiographic and hemodynamic findings

Parameter	eGFR ≥= 90 Median [quartiles] / n or n (%)	eGFR ≤ 90 Median [quartiles] / n or n (%)	*P* value
AV valve regurgitation			
Normal/trivial	23 (44)	7 (47)	0.020
Mild	24 (46)	2 (13)	
Moderate	4 (8)	5 (33)	
Severe	1 (2)	1 (7)	
(neo) aortic valve regurgitation			
none/trivial	45	13	0.990
Mild/moderate	7	2	
Systemic ventricular (dys)function			
Normal/low normal	39 (75)	10 (67)	0.053
Mild	8 (15)	2 (13)	
Moderate	4 (8)	0 (0)	
Severe	1 (2)	3 (20)	
Qs (L/min/m^2)	3.0 [2.4-3.9] n=51	2.6 [2.5-3.8]	0.383
Qp (L/min/m^2)	2.8 [2.3-3.7] n=49	2.2 [1.9-2.6] n=13	0.012
Ventricular end-diastolic pressure (mm Hg)	8.0 [6.0–10.0] n=51	10.5 [7.0–17.3] N=14	0.050
Fontan pressure (mm Hg)	13.5 [12.3–16.0]	18.0 [15.0–21.0]	0.001
Hepatic wedge pressure (mm Hg)	16.0 [14.0–18.0} n=23	19.5 [16.0–29.0] n=4	0.082
SVR (Wood Units *m^2)	13.7 [10.8–16.1] n=26	20.6 [12.9–29.0] n=3	0.150
PVR (Wood Units *m^2)	1.6 [1.3-2.6] n=50	2.1 [1.3-3.0] n=12	0.349

venous pressure; and therefore, it is not surprising venous congestion/high CVP alters kidney function. Venous congestion is innate in the Fontan circulation and many investigators have long suspected potential deleterious long-term effects on the kidneys.[10,11] Thus far, renal dysfunction related to venous congestion and high CVP have principally been described in the context of (right) heart failure.[16,18]

Renal function has many important implications to patients with Fontan circulation; studies have demonstrated higher mortality in adults with congenital heart disease who have renal dysfunction and Fontan patients may be disproportionately affected.[9,19] Previously, other investigators sought correlates between the Fontan circulation and kidney health. Anne et al. analyzed 21 patients at least two years after Fontan circuit completion and found 45% of patients had abnormal microalbumin/creatinine ratio which had a positive correlation with both mean superior vena cava pressures and post-Fontan completion pulmonary vascular resistance.[10] In a study of 68 Fontan survivors more than 10 years post-Fontan completion, patients were more likely to have proteinuria and elevated parathyroid hormone levels than controls.[11] Investigators found eGFR in the Fontan group was slightly higher than that of the control group. It was hypothesized lower serum creatinine levels, which result in higher eGFR calculation, may be a function of lower BMI and lower height. In contrast, a different study showed adults with Fontan circulation (mean age of ~31 years) had a lower eGFR calculated with cystatin C than age-matched controls.[9] An important finding in the adult study was eGFR calculated using creatinine only was not statistically different from the control group.

In a landmark study, Damman et al. described data from over 2500 adult patients undergoing right heart catheterization and found elevated CVP were associated with low eGFR, independent of cardiac index[18] which is consistent with our results. Our data suggest elevated Fontan pressures are associated with eGFR < 90 mL/min/1.73 m^2; though due to our small cohort and heterogenous follow-up, we were underpowered to effectively investigate associations with chronic kidney disease. Also due to data limitations, we are unable to classify patients as having acute kidney injury and defined the study groups as aforementioned. Cardiac output was not associated with RD in this small cohort of patients. The mechanism by which elevated CVP affects

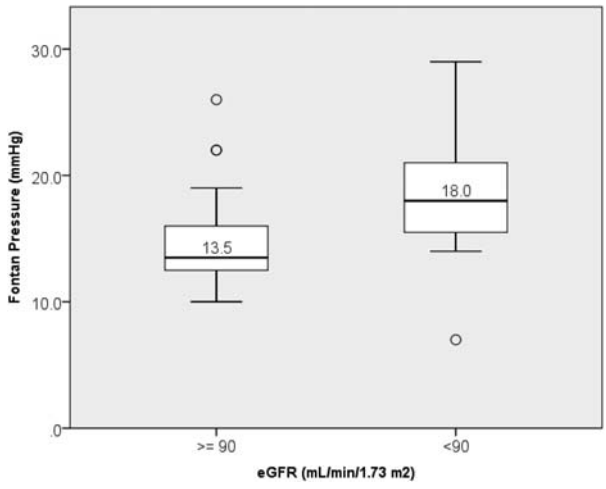

FIGURE 1 Relationship of Fontan pressure and renal function. Renal function is categorized by estimated glomerular filtration rate (eGFR, mL/min/1.73 m^2)

kidney function is not clear. Perhaps there is a critical threshold of venous congestion at which renal autoregulation is significantly attenuated. Likely, a more complex relationship exists in which the combination of unrelenting exposure to venous congestion and other physiological factors contribute to renal injury in the patient with Fontan circulation.

Other factors including but not limited to race, genetics, history of prematurity/low birth weight, other medical co-morbidities, exposure such as smoking/alcohol, and infection undoubtedly factor into a predisposition for nephropathy in the study population. Further, patients who receive Fontan circulation are at high risk for repeated renal insults due to the nature of repeat surgical interventions and recurrent exposure to cardiopulmonary bypass, significant changes in intrinsic cardiovascular physiology after surgical intervention, regular titration of nephrotoxic medications, and significant changes to cardiovascular hemodynamic at times of stress and illness. It is striking that African-American patients appear to disproportionally comprise the RD group, though we should note these patients also had HF and severe ventricular systolic dysfunction. In the adult population, it is well known African Americans are predisposed to chronic kidney disease.[20,21] Future studies should specifically investigate the relationship between African-American race and kidney health in patients with Fontan circulation. This study found no association with RD and any one particular class of medication; however, patients were not randomized to receive specific medications. Further investigation of the effects of medications on renal function is an important area for investigation.

5 | LIMITATIONS

There are several important limitations in this study. Due the retrospective nature of this study, we relied on serum creatinine to estimate GFR based on the Schwartz and MDRD equations. Future studies should include longitudinal data and other markers to detect nephropathy. The Fontan circulation population commonly have poor muscle mass/abnormal nutritional status which may limit estimating renal function (and, thus, detecting abnormal eGFR) based only on creatinine concentration[9,11]; an abnormally high proportion of our study population had PLE (30%)[8] which may compound this issue. Several formulas are available for use to calculate eGFR in patients,[11] we used the bedside Schwartz equation and MDRD as these are the most commonly used methods for clinical evaluation of renal function at our institution. It is likely patients included in this study represent a sicker subset of Fontan patients because we do not routinely perform surveillance catheterization and our study population had a high degree of co-morbidities. Thus, the incidence of abnormal eGFR may be overestimated in this study population. Perhaps, if a "healthier" and more representative population of Fontan patients were analyzed, the statistical outcomes of parameters measured may change. All but one patient received positive pressure ventilation (PPV) which may have artificially increased CVP. Hemodynamic assessment under anesthesia may not necessarily reflect the physiology a patient would typically experience on a daily basis. Patient follow-up was not standardized in this study preventing assessment of outcome measures.

6 | CONCLUSIONS

In this study population, renal dysfunction in patients with Fontan circulation is associated with increased CVP and factors that affect CVP. African Americans with Fontan circulation may be at particular risk for renal dysfunction. Continued investigation of the effects of venous congestion on kidneys and other factors associated with renal dysfunction in patients with Fontan circulation is warranted.

DISCLOSURES

Ayse Akcan-Arikan, MD has consulted for Baxter Healthcare, Inc. and receives research funding from NIH NIAID.

AUTHOR CONTRIBUTIONS

Concept: Broda, Price

Design: Broda, Sriraman, Wadhwa, Tunuguntla, Akcan-Arikan, Ermis, Price

Data collection: Broda, Sriraman, Wadhwa

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