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Fontan-associated nephropathy: Predictors and outcomes

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ABSTRACT

Background: Nephropathy is a known complication of the Fontan circulation, but its determinants have not been identified and patient outcomes are also still unknown.
Methods: The Australia and New Zealand Fontan Registry was used to identify those who underwent Fontan operation before and survived beyond 16-years-old with an intact Fontan circulation. Serum creatinine values were collected for each patient between 16 and 25 years and at recent follow-up. The Modification of Diet in Renal Disease (MDRD) equation was used to calculate eGFR. Patient outcomes were obtained from the Registry. Fontan failure was defined as death, transplantation, plastic bronchitis, protein losing enteropathy, Fontan takedown and NYHA class III-IV.
Results: Serum creatinine measurements were available for 328 patients. Renal dysfunction was defined as eGFR <90 mL/min/1.72m^2. Renal dysfunction was present in 67/328 (20%) and 3/328 (1%) patients had an eGFR <60 mL/min/1.72m^2. The 10-year survival and 10-year freedom from death and transplantation were the same, 96% (95% CI: 0.9–1) for those with renal dysfunction, and 89% (0.83–0.95; $p = 0.1$) and 87% (95% CI: 0.81–0.94; $p = 0.05$) for patients without dysfunction. The 10-year freedom from failure were also similar, 83% (95% CI: 0.70–0.97) for those without renal dysfunction vs 80% (95% CI: 0.74–0.89; $p = 0.84$). There was no change in mean eGFR for the renal dysfunction group over a mean of 8 ± 5.5 years.
Conclusion: By the time they reach adulthood, 20% of patients with a Fontan circulation have renal dysfunction by eGFR calculation. Over the course of one decade, Fontan-associated nephropathy appears well tolerated.

1. Introduction

As a larger proportion of patients with a Fontan circulation are entering adulthood, the deleterious effects of this physiology on end-organs is being recognised [1]. Arrhythmia and liver fibrosis have been broadly investigated [1–3], but Fontan-associated nephropathy has barely been explored in the literature [4]. Approximately 10–30% of patients living with a Fontan circulation have evidence of mild to moderate renal dysfunction [1,4–6]. In adults living with congenital heart disease, those who have concomitant kidney disease have been shown to have a mortality rate 3-times higher than those with normal kidney function [7]. The determinants of Fontan-associated nephropathy and the natural course of this condition remain unclear at this time.

Abbreviations: ACE, angiotensin-converting enzyme; ACR, albumin creatinine ratio; AP, atriopulmonary; BCPS, bidirectional cavopulmonary shunt; CAVC, common atrioventricular canal; ccTGA, congenitally-corrected transposition of the great arteries; CI, confidence interval; CKD, chronic kidney disease; DILV, double-inlet left ventricle; DORV, double-outlet right ventricle; ECC, extracardiac conduit; eGFR, estimated glomerular filtration rate; HLHS, hypoplastic left heart syndrome; IQR, interquartile range; LT, lateral tunnel; MCR, microalbumin creatinine ratio; MDRD, Modification of Diet for Renal Disease; mGFR, measured glomerular filtration rate; NYHA, New York Heart Association; PA-IVS, pulmonary atresia with intact ventricular septum; RD, renal dysfunction; SCr, serum creatinine; SD, standard deviation; TA, tricuspid atresia; VD, ventricular dysfunction.

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The purpose of this present study is to determine the prevalence of nephropathy in young adults with a Fontan circulation, identify predictors and characterise their long-term outcomes.

2. Methods

2.1. Study design

This study was performed in patients enrolled in the Australia and New Zealand Fontan Registry, the design of which has been previously described [8]. Informed consent is obtained from each patient prior to enrolment in the Registry. Ethics approval is recurrently obtained from national and local hospital human research ethics committees and include waiver of consent for all retrospective studies for patients enrolled in the Registry. Baseline characteristics and follow-up data were collected from the Registry database. Individual charts were reviewed to extract operative reports, biochemistry results, discharge summaries, and outpatient correspondences.

2.2. Patients

Patients were included in this study if they were <16 years of age at the time of Fontan surgery, were alive after 16 years of age with an intact Fontan circulation, and had a recorded serum creatinine result between the ages of 16 to 25 years old. Patients were excluded if they had a primary renal diagnosis, underwent a Fontan takedown procedure, received a heart transplant or died before 16 years of age. Patients who were lost to follow-up and for whom insufficient data concerning their renal function could be obtained were also excluded.

2.3. Assessment of renal function

Baseline renal function was assessed for each patient between the ages of 16–25 years by calculation of estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) equation [6]:

$$\text{GFR}\ (\text{mL}/\ \text{min}/1.73\ \text{m}^2) = 175 \times (S_{cr})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$$

Biochemistry reports were obtained and serum creatinine values (SCr) were collected. The most recent SCr values available for all patients were also collected. Results were only collected from routine outpatient follow-up appointments, not inpatient admission or emergency department presentations, in order to achieve an accurate reflection of baseline renal function. Renal dysfunction and no renal dysfunction were defined as eGFR <90 mL/min/1.73 m^2 and eGFR ≥90 mL/min/1.73 m^2, respectively.

2.4. Outcomes

The primary end-point was Fontan failure defined as death, heart transplantation, plastic bronchitis, protein losing enteropathy, Fontan takedown, and New York Heart Association (NYHA) class III-IV. Patient outcomes were obtained from the Registry database. A secondary endpoint was chronic kidney disease (CKD) defined as eGFR <90 mL/min/1.73m^2.

2.5. Statistical analysis

Categorical variables were described as number (percentage). Continuous variables were reported as mean (± standard deviation (SD)) or median (interquartile range (IQR), 25th–75th percentile). A p value <0.05 was considered the threshold for statistical significance. Multiple Cox regression analyses were performed to identify variables independently associated with renal dysfunction. Multivariable models were constructed to assess the impact of renal dysfunction on patient outcomes and adjusted for any potential confounders. Survival, freedom from death and transplantation and freedom from Fontan failure were examined using Kaplan-Meier analysis and equality of survivorship functions was tested using a log-rank test. t-Tests for 2 groups were used to compare means for normally distributed variables. All analyses were performed using R (Version 3.5.1, http://www.r-project.org/).

3. Results

The cohort of this study consisted of a total of 328 patients who met the inclusion criteria from a Registry of 1630 patients total. Baseline patient characteristics are detailed in Table 1.

3.1. Renal dysfunction

The mean age at time of creatinine collection was 20 ± 3 years. Baseline characteristics of patients in the renal dysfunction vs no renal dysfunction group are displayed in Table 2. The prevalence of renal dysfunction in this cohort as it reached young adulthood was 67/328

Table 1
Baseline characteristics – participants vs rest of Registry population.

Characteristics	Study participants (n = 328)	Registry (n = 1302)[a]	p-Value
Male, n (%)	169 (52%)	766 (59%)	0.02
Age in years, mean (SD)	26 (6.5)	23.5 (10)	0.01
Dextrocardia/Mesocardia, n (%)	27 (8%)	116 (9%)	0.7
Isomerism, n (%)			
Left atrial isomerism	11 (3%)	34 (4%)	0.007
Right atrial isomerism	24 (7%)	42 (3%)	
Ventricular morphology, n (%)			
Left	219 (67%)	706 (56%)	0.001
Right	82 (25%)	451 (36%)	
Biventricular	15 (5%)	83 (7%)	
Intermediate	11 (3%)	30 (2%)	
Primary diagnosis, n (%)			
TA	88 (27%)	265 (21%)	<0.001
DILV	66 (20%)	199 (16%)	
DORV	50 (15%)	181 (14%)	
CAVC	31 (10%)	98 (8%)	
HLHS	16 (5%)	178 (14%)	
ccTGA	24 (7%)	79 (6%)	
PA-IVS	30 (9%)	140 (11%)	
Other	21 (6%)	141 (11%)	
Prior BCPS, n (%)	160 (49%)	744 (59%)	0.001
Fontan type, n (%)			
AP	49 (15%)	181 (14%)	<0.001
LT	107 (33%)	178 (14%)	
ECC	172 (52%)	920 (72%)	
Fontan CPBT mins, mean (SD)	118.6 (52.5)	115.6 (50.3)	0.3
Fenestrated at time of Fontan, n (%)	128 (39%)	467 (37%)	0.5
NYHA classification, n (%)			
I	237 (74%)	799 (72%)	0.4
II	81 (25%)	277 (25%)	
III	4 (1%)	22 (2%)	
IV	0 (0%)	9 (1%)	
VD ≥ moderate after Fontan, n (%)	37 (11%)	44 (3%)	<0.001
Permanent pacemaker in situ, n (%)	290 (88%)	1213 (93%)	0.005
Current medications, n (%)			
ACE-inhibitor	79 (24%)	317 (24%)	0.94
Aspirin	132 (40%)	473 (36%)	0.2
Beta-blocker	50 (15%)	137 (11%)	0.02
Warfarin	166 (51%)	509 (39%)	<0.001

TA: tricuspid atresia; DILV: double-inlet left ventricle; DORV: double-outlet right ventricle; CAVC: common atrioventricular canal; HLHS: hypoplastic left heart syndrome; ccTGA: congenitally-corrected transposition of the great arteries; PA-IVS: pulmonary atresia with intact ventricular septum; BCPS: bidirectional cavopulmonary shunt; AP: atriopulmonary; LT: lateral tunnel; ECC: extracardiac conduit; ACE: angiotensin-converting enzyme; NYHA: New York Heart Association; VD: ventricular dysfunction.
[a] Patients enrolled in the Registry who were excluded from the study.

Table 2
Baseline characteristics – Renal dysfunction vs no renal dysfunction.

Characteristics	Renal dysfunction	No renal dysfunction
Male, n (%)	22 (33%)	147 (56%)
Current age in years, mean (SD)	28.5 (6.5)	25.5 (5.7)
Duration from Fontan to test[a] in years, mean (SD)	14.9 (4.2)	13.3 (3.8)
Duration of follow-up from test[a] in years, mean (SD)	8.3 (5.5)	6.8 (5.0)
Dextrocardia/Mesocardia, n (%)	5 (8%)	22 (8%)
Isomerism, n (%)		
Left atrial isomerism	2 (3%)	9 (3%)
Right atrial isomerism	6 (9%)	18 (7%)
Ventricular morphology, n (%)		
Left	48 (74%)	171 (65%)
Right	13 (20%)	69 (26%)
Biventricular	1 (2%)	14 (5%)
Indeterminate	3 (5%)	8 (3%)
Primary diagnosis, n (%)		
TA	22 (34%)	66 (25%)
DILV	16 (25%)	50 (19%)
DORV	10 (16%)	40 (15%)
CAVC	6 (9%)	25 (10%)
HLHS	0 (0%)	16 (6%)
ccTGA	3 (5%)	21 (8%)
PA-IVS	6 (9%)	24 (9%)
Other	1 (2%)	20 (8%)
Prior BCPS, n (%)	22 (33%)	138 (53%)
Fontan type, n (%)		
AP	16 (24%)	33 (13%)
LT	24 (36%)	83 (32%)
ECC	26 (40%)	146 (56%)
Fontan CPBT mins, mean (SD)	122.2 (41.8)	117.9 (54.6)
Fenestrated at time of Fontan, n (%)	22 (34%)	106 (41%)
NYHA classification, n (%)		
I	46 (73%)	191 (74%)
II	16 (25%)	65 (25%)
III	1 (2%)	3 (1%)
VD ≥ moderate after Fontan, n (%)	8 (12%)	29 (11%)
Permanent pacemaker in situ, n (%)	9 (14%)	29 (11%)
Current medications, n (%)		
ACE inhibitor	9 (14%)	70 (27%)
Aspirin	33 (50%)	99 (38%)
Beta-blocker	8 (12%)	42 (16%)
Warfarin	24 (36%)	142 (54%)

TA: tricuspid atresia; DILV: double-inlet left ventricle; DORV: double-outlet right ventricle; CAVC: common atrioventricular canal; HLHS: hypoplastic left heart syndrome; ccTGA: congenitally-corrected transposition of the great arteries; PA-IVS: pulmonary atresia with intact ventricular septum; BCPS: bidirectional cavopulmonary shunt; AP: atriopulmonary; LT: lateral tunnel; ECC: extracardiac conduit; ACE: angiotensin-converting enzyme; NYHA: New York Heart Association; VD: ventricular dysfunction.
[a] Test defined as time of creatinine collection between 16 and 25 years of age.

(20%). The majority of patients had mild renal dysfunction (eGFR 60–90 mL/min/1.73 m^2), with 3/328 (1%) patients found to have moderate renal dysfunction (eGFR <60 mL/min/1.73 m^2). Logistic regression models were constructed to identify predictors of renal dysfunction. Atrio-pulmonary connection (AP) Fontan type (OR 2.22, 95% CI 1.11–4.30, $p = 0.024$) and absence of prior bi-directional cavo-pulmonary shunt (BCPS) (OR 2.23, 95% CI 1.28–3.98, $p = 0.005$) were both associated with an increased risk of renal dysfunction. After multivariable analysis, AP Fontan type and absence of BCPS were no longer significantly associated with renal dysfunction. Time since Fontan surgery was also significantly different between the renal dysfunction and no renal dysfunction groups: 14.9 ± 4.2 vs 13.3 ± 3.8 years, $p = 0.003$). We found that none of the 16 patients with a primary diagnosis of hypoplastic left heart syndrome (HLHS) had renal dysfunction, compared to 21% (67/312) of patients who had other primary diagnoses who were identified to have renal dysfunction ($p < 0.01$).

3.2. Survival

In the renal dysfunction group and no renal dysfunction group, 2/67 (2%) and 19/261 (7%) patients died during the follow-up period, respectively. In the renal dysfunction group, the two deaths occurred within three years of their creatinine measurement. Ten-year survival for the renal dysfunction group vs no renal dysfunction group was 96% (95% CI 0.9–1) and 89% (95% CI 0.83–0.96) ($p = 0.1$) (Fig. 1). No independent risk factors for mortality were identified. Within the renal dysfunction group, one patient underwent transplantation compared to three patients in the no renal dysfunction group. Ten-year freedom from death and transplant for the renal dysfunction group vs no renal dysfunction group were 96% (95% CI 0.9–1) and 87% (95% CI 0.8–0.9) ($p = 0.05$) (Fig. 2).

3.3. Fontan failure

Fontan failure occurred in 38/328 (12%) patients over a mean follow-up period of 7 ± 5 years. There were no differences in the prevalence of Fontan failure between the two groups. Ten-year freedom from Fontan failure for the renal dysfunction group was 82.5% (95% CI 0.69–0.97) compared to the no renal dysfunction group 81% (95% CI 0.74–0.89) ($p = 0.84$) (Fig. 3). Having right atrial isomerism and developing ≥ moderate ventricular systolic dysfunction after Fontan surgery were independent risk factors for Fontan failure, HR = 3.18, 95% CI 1.32–7.64, $p = 0.01$ and HR = 2.39, 95% CI 1.18–4.83, $p = 0.01$, respectively.

3.4. Chronic kidney disease

Over a follow-up period of 8 ± 5.5 years, no significant differences in mean eGFR were found in the renal dysfunction group, eGFR 78 vs 80 mL/min/1.73m^2 ($p = 0.4$). Contrastingly, the eGFR of patients with normal renal function decreased over the follow-up period of 7 ± 5 years from 120 to 108 mL/min/1.73m^2 ($p < 0.001$). An additional 29 patients from the normal renal function group were found to have developed renal dysfunction at last follow-up.

4. Discussion

This cohort study explores the prevalence of renal dysfunction in young adults with a Fontan circulation and provides insight into possible determinants and outcomes of this condition. We explored the age bracket between 16 and 25 years of age as serum creatinine measurements for patients younger than 16 years-old do not correlate well with true GFR, and because it allowed a sufficient amount of time after surgery to observe potential effects of the Fontan circulation [9]. Our results show that 20% of patients with a Fontan circulation have mild to

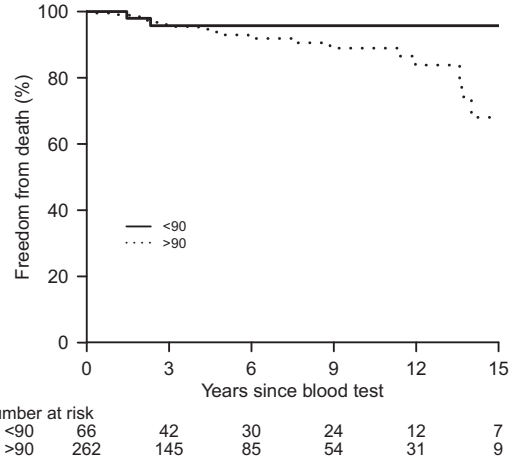

Fig. 1. Kaplan-Meier curve of survival for renal dysfunction group (<90) vs no renal dysfunction group (>90).

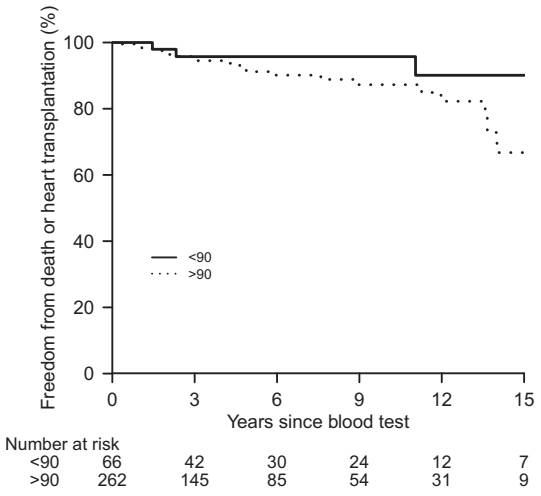

Fig. 2. Kaplan-Meier curve of freedom from Fontan death and transplantation for renal dysfunction group (<90) vs no renal dysfunction group (>90).

moderate renal dysfunction in young adulthood in fitting with previous publications [1,5].

Several studies have tried to elucidate the true prevalence of Fontan-associated nephropathy. Both Anne et al., and Sharma et al., found in their study population of children (<18 years-old), <10% had an abnormal eGFR [4,10]. Conversely, two other studies which assessed nephropathy in adult Fontan patients (>18 years-old) found a much higher prevalence. Lee et al., reported evidence of CKD in nearly 50% of their cohort using combined criteria of eGFR and urinary albumin creatinine ratio (ACR), and similarly, Wilson et al., found abnormal measured GFR (mGFR) and microalbuminuria in nearly 60% of patients [1,5].

The only predictors of renal dysfunction that we could identify was having the atrio-pulmonary Fontan type and not having a staging procedure with BCPS. It is impossible to distinguish between these factors because staging was implemented in the region at the same time that the Lateral Tunnel was adopted as a technique. It is more likely that the known unfavourable haemodynamic characteristics of the atrio-pulmonary Fontan is the reason for the worse renal function observed in these patients. Wilson et al., in a cross-sectional study performed in the region, reported an association between lower mGFR and increasing time since Fontan, and hypothesized that renal function will progressively decline with prolonged exposure to the low cardiac output states and high central venous pressures associated with the Fontan circulation [1]. Our study seems to corroborate that fact as renal function appeared to deteriorate in the decade following the first assessment.

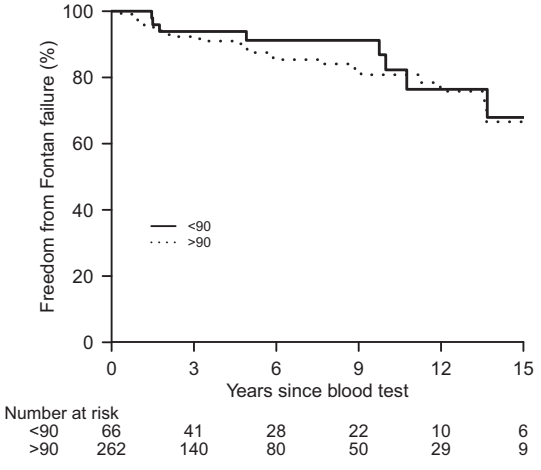

Fig. 3. Kaplan-Meier curve of freedom from Fontan failure for renal dysfunction group (<90) vs no renal dysfunction group (>90).

An interesting finding in our study was that no patients with a primary diagnosis of HLHS were identified to have renal dysfunction. It is important to note that in our region, patients with HLHS are much more likely to be placed on an ACE-inhibitor compared to any other heart defect [11]. ACE-inhibitors have been shown to exhibit a strong renal protective effect [12]. However, there is no evidence at this stage to suggest that this class of drugs may be effective in preventing the development of renal dysfunction in the Fontan circulation.

We were surprised to observe that renal dysfunction did not seem to impact the recorded outcomes, survival, freedom from death and transplantation and Fontan failure in our Fontan population. Fontan-associated nephropathy therefore seems to be well tolerated in early adulthood. Several factors intrinsic to the Fontan circulation may explain the prevalence of nephropathy at this age. Lower cardiac output, elevated central venous pressure and lower muscle mass may have all contributed to the observed results. No previous studies have assessed the relationship between Fontan-associated nephropathy and survival, and it is possible that the true impacts of renal dysfunction may be only be elicited with longer follow-up periods.

Therefore, even though our current estimates of the impact of renal dysfunction on late outcomes of patients with a Fontan circulation appear reassuring, this should not preclude efforts to prevent the degradation of renal function. As an example, we should investigate the benefits of the administration of ACE-inhibitors in inhibiting the progression of renal dysfunction. There are currently no routine protocols to monitor kidney function in patients with a Fontan circulation. Early initiation of kidney monitoring as part of routine follow-up after Fontan surgery should be recommended. Longitudinal studies with longer follow-up periods may elicit the true impacts of renal dysfunction in Fontan patients.

4.1. Limitations

The creatinine-based MDRD equation for eGFR has been shown to overestimate GFR, specifically in the Fontan population [5]. Therefore, the prevalence of renal dysfunction in our study population is likely underestimated. Future studies should utilise mGFR to achieve a more accurate representation of renal function.

5. Conclusion

Approximately one-fifth of young adults living with a Fontan circulation are experiencing Fontan-associated nephropathy. Within our current follow-up period of a decade, Fontan-associated nephropathy does not appear to be associated with an increased risk of mortality of Fontan failure. Further studies should focus on validating the predictors of Fontan-associated nephropathy using directly measured GFR and utilising longer follow-up periods to characterise the outcomes of renal dysfunction in the long-term.

Declaration of competing interest

Yves d'Udekem is a consultant for MSD and Actelion.

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