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Research Letter

The Association of Lower Venous Disease to Outcomes in Adults With Fontan Physiology: CALF Revisited

Over the past decade, the number of adults living with complex congenital heart disease has doubled. Of the complex conditions, those requiring a Fontan operation are at some of the highest risk for adverse outcomes.[1] As this population ages, there are increasing morbidities and mortality largely related to thromboembolism, heart failure, and arrhythmias.[2] The role of the peripheral vasculature contributing to central hemodynamics in these patients is not well known. In 2010, the *Journal of American College of Cardiology* published the CALF (Congenital Heart Disease in Adults Lower Extremity Systemic Venous Health) study highlighting the high prevalence of chronic venous insufficiency (CVI) in adults with Fontan physiology using the standardized Clinical, Etiologic, Anatomical, and Pathophysiological (CEAP) classification.[3,4] Additionally, the prevalence of severe venous insufficiency (CEAP classification grade ≥4) was 3 to 4 times higher than the general population. In a recent investigation of over 12,000 adults in the Gutenberg Health Study, CVI was associated with increased mortality.[5] With increased recognition of morbidities in the Fontan population over the past decade, our goal was to revisit the original CALF cohort to determine if baseline CVI was associated with adverse clinical outcomes.

We performed a retrospective chart review of all subjects included in the original CALF cohort from Boston Children's Hospital (n = 103) to explore time from study enrollment to first outcome event comprised of all-cause mortality (classified as sudden cardiac death, sudden death revival, cardiac-other, noncardiac, or unknown), heart transplantation, thrombotic or thromboembolic event, infectious conditions defined as cellulitis, infective endocarditis, or presumed or definite vascular graft infection since the time from original enrollment. Patients who did not experience an outcome were censored at last follow-up; the median follow-up was 11.3 years (interquartile range: 5.6-12.4 years). **Table 1** characterizes the clinical characteristics of this cohort.

Thirty patients (29%) met the composite primary outcome, and the median time to the composite outcome was 3 years (interquartile range: 1.4-10 years). This included 28 deaths, 20 thrombotic/thromboembolic events, 9 infectious complications (cellulitis [5], graft infection [2], and endocarditis [2]), and 2 heart transplantations. In the univariate analysis, CVI, older age, older age at Fontan operation, type of Fontan operation, and use of diuretic agents and warfarin were all associated with the composite outcome. In multivariable Cox regression adjusting for baseline risk factors such as age at enrollment, type of Fontan, and use of diuretic agents or warfarin, CVI at baseline (both nonsevere CVI [CEAP <4] and severe CVI [CEAP ≥4]) remained significantly associated with the composite outcome (hazard ratio: 9.1 [95% CI: 1.1-72.0], $P = 0.04$, and 9.5 [95% CI: 1.2-78.0], $P = 0.04$, respectively, versus the reference group no CVI).

Adults with Fontan physiology are among the most challenging groups followed in adult congenital clinics, with high morbidity and mortality. Thromboembolism, exercise intolerance, arrhythmias, infections, and heart failure are common and increase both in incidence and severity with age. Understanding the hemodynamic consequences of this palliative surgery and the relationship between the peripheral hemodynamics and long-term venous dysfunction is important in order to develop long-term treatment strategies to improve quality of life and survival. Our original study illustrated that the prevalence of CVI and particularly, severe CVI is high in this population, likely due to the lack of pulsatile flow which influences the loading conditions and high venous pressures in the peripheral veins, endothelial dysfunction, and multiorgan dysfunction.

Revisiting this patient population, a decade later, roughly one-third of the original cohort met our composite outcome and our findings suggest that the presence of CVI appears to be associated with

TABLE 1 Clinical Characteristics of the CALF Cohort

	Total (n = 103)	Composite Outcome (n = 30)	No Composite Outcome (n = 73)	*P* Value
Age at enrollment (y)	28 (22-37)	36 (26-45)	25 (20-35)	<0.001
Male	51 (50%)	16 (53%)	35 (48%)	0.81
BMI at enrollment (kg/m^2)	23.7 (20.6-26.9)	25.1 (21.8-27.8)	23.3 (20.5-26.2)	0.10
Age at Fontan operation (y)	7 (3-15)	12 (5-24)	5 (3-14)	0.004
Type of Fontan procedure				
Atriopulmonary connection	47 (46%)	17 (57%)	30 (41%)	0.003
TCPC intracardiac lateral tunnel	41 (40%)	5 (17%)	36 (49%)	
Extracardiac lateral tunnel	6 (6%)	4 (13%)	2 (3%)	
RA-RV connection	7 (7%)	4 (13%)	3 (4%)	
Other	2 (2%)	0 (0%)	2 (3%)	
Baseline deep venous thrombosis	8 (8%)	4 (14%)	4 (6%)	0.12
Baseline Fontan pathway thrombosis	14 (15%)	5 (19%)	9 (13%)	0.47
Baseline pulmonary thrombus/embolism	4 (4%)	2 (7%)	2 (3%)	0.27
Antiarrhythmic agent	35 (34%)	16 (53%)	19 (26%)	0.019
ACE inhibitors/ARBs	49 (49%)	14 (48%)	35 (49%)	0.75
Beta-blocker	29 (28%)	11 (37%)	18 (25%)	0.33
Diuretic agent	45 (44%)	24 (80%)	21 (29%)	<0.001
Warfarin	52 (51%)	24 (80%)	28 (39%)	<0.001
Aspirin	41 (40%)	6 (20%)	35 (49%)	0.020
CVI classification at baseline				
0: No visible or palpable signs of venous disease	35 (34%)	1 (3%)	34 (47%)	-
1: Telangiectasias or reticular veins	14 (14%)	6 (20%)	8 (11%)	
2: Varicose veins	26 (25%)	7 (23%)	19 (26%)	
3: Edema	1 (1%)	1 (3%)	0 (0%)	
4a: Skin changes ascribed to venous disease	22 (21%)	11 (37%)	11 (15%)	
5: Skin changes as defined above with healed venous ulcer	4 (4%)	3 (10%)	1 (1%)	
6: Skin changes as defined above with active venous ulcer	1 (1%)	1 (3%)	0 (0%)	
CVI at baseline				0.005
None	35 (34%)	1 (3%)	34 (47%)	
CEAP 1-3	41 (40%)	14 (47%)	27 (37%)	
CEAP 4-6	27 (26%)	15 (50%)	12 (16%)	

Values are median (IQR) or n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensinogen receptor blocker; BMI = body mass index; CALF = Congenital Heart Disease in Adults Lower Extremity Systemic Venous Health in Fontan Patients; CEAP = Clinical, Etiologic, Anatomical, and Pathophysiological; CVI = chronic venous insufficiency; RA = right atrium; RV = right ventricle; TCPC = total cavopulmonary connection.

important adverse outcomes in adults with Fontan physiology, adjusting for baseline risk factors. This association provides the foundation for the next step in developing innovative therapies to mitigate CVI and potentially improve long-term outcomes in these patients. It is our hope that recognition of CVI in patients with Fontan physiology may lead to earlier therapeutic strategies. Potential interventions range from daily use of gradient compression stockings to superficial vein ablation, which can decrease edema, cellulitis, and venous gangrene. Future studies looking at the effectiveness of these therapies in Fontan patients are needed. As CVI is an easily identifiable clinical finding, treatment of CVI may lead to more timely strategies for interventions aimed at reducing morbidity and mortality in Fontan patients.

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