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The CALF (Congenital Heart Disease in Adults Lower Extremity Systemic Venous Health in Fontan Patients) Study

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Objectives The objective of this study was to document the prevalence of chronic venous insufficiency (CVI) and its associated factors in adults with Fontan physiology.

Background As the population of adults with complex congenital heart disease and Fontan physiology increases, so does the occurrence of highly morbid and mortal outcomes, including heart failure and thromboembolism. The presence of abnormal peripheral hemodynamic conditions in this population and their potential contribution to adverse outcomes is not well known. The primary objective of this study was to document the prevalence of CVI in adults with Fontan physiology.

Methods A total of 159 adults with Fontan physiology from 7 adult congenital heart centers were prospectively assessed for lower extremity CVI, with the assignment of clinical, etiological, anatomical, and pathophysiological classification grades, and compared with age-matched and sex-matched controls. Leg photographs were independently reassessed to confirm interobserver reliability.

Results The prevalence of CVI was significantly greater in the Fontan population (60%; 95% confidence interval [CI]: 52% to 68%) compared with healthy controls (32%; 95% CI: 15% to 54%) ($p = 0.008$). Strikingly, the prevalence of severe CVI (clinical, etiological, anatomical, and pathophysiological grade ≥ 4) was significantly higher in the Fontan group (22%; 95% CI: 16% to 29%) versus the healthy controls (0%; 95% CI: 0% to 14%) ($p = 0.005$). In a multivariate analysis, several factors were independently associated with severe CVI, including increased numbers of catheterizations with groin venous access, lower extremity itching, and deep venous thrombosis.

Conclusions CVI is common in adult patients with congenital heart disease with Fontan physiology. The contribution of abnormal peripheral hemodynamic conditions to comorbidities, including thromboembolism and heart failure, and interventions to improve peripheral hemodynamic conditions require further exploration. (J Am Coll Cardiol 2010;56:144–50) © 2010 by the American College of Cardiology Foundation

The Fontan operation has evolved over the past 4 decades from palliation for tricuspid atresia to its wider current application for many single-ventricle circulations (1). Gradual attrition in survival in adults with Fontan physiology is related to thromboembolism, heart failure and sudden death (2), whereas loss of functional ability has largely been correlated with central hemodynamic status, alterations in neurohormonal activation, and imbalance in ventilatory function (3–7).

More recently, there has been recognition of the potential impact of changes in peripheral hemodynamic conditions,

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skeletal muscle metabolism, and endothelial dysfunction on the failing Fontan physiology. Endothelium-dependent circulating levels of von Willebrand factor, flow-mediated dilation, and blood flow supply to skeletal muscle with subsequent effect on exercise capacity have all been shown to be abnormal in patients with Fontan palliation (8–11).

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Chronic venous insufficiency (CVI) is a common clinical problem. In the general population, CVI is associated with a reduced quality of life, particularly in relation to pain, depression, social isolation, mobility, and physical function (12). Several pathophysiologic mechanisms appear common to the occurrence of both CVI and Fontan failure, including abnormalities in central and peripheral hemodynamic status. However, to date, CVI has not been described in patients who have undergone the Fontan procedure.

Risk factors for CVI in the general population (including heredity, age [13–15], female sex, leg trauma, obesity, history of phlebitis or deep vein thrombosis [16], pregnancy [17], oral contraceptive use, and prolonged standing) and symptoms referable to CVI (including aching, heaviness, a sensation of swelling, and skin irritation) can be determined by clinical history. Inspection and palpation define physical findings to further classify CVI. CVI can be thereby identified and graded according to a well-established scale describing clinical, etiological, anatomical, and pathophysiological (CEAP) classifications (18,19).

The objective of this study was to document the prevalence of CVI and its associated factors in adults with Fontan physiology. The hypothesis was that patients with Fontan physiology have chronically elevated systemic venous pressure, and this finding in the setting of nonpulsatile pulmonary blood flow may place them at increased risk for CVI. These results may further elucidate the complex relationships between central and peripheral hemodynamic conditions, as well as provide a foundation for future studies aiming to improve functional outcomes in this population.

Methods

Study design. This multi-institutional, cross-sectional, observational study prospectively recruited successive subjects age ≥18 years who had previously undergone Fontan procedures and presented in stable condition for outpatient evaluation at 1 of 7 U.S. adult congenital heart disease centers for evaluation. The protocol was developed by the core institution (Children's Hospital Boston, Boston, Massachusetts) and was refined by the consensus of participating centers within the Alliance for Adult Research in Congenital Cardiology framework (20). Subjects were excluded if they had histories of cardiac transplantation or had major surgery or traumatic injury within the previous 10 weeks. Clinical, anatomical, and surgical data were collected at enrollment (July 2007 to May 2009) by medical record review and patient interview using standardized forms. Control subjects consisting of hospital employees without histories of congenital heart disease were identified and enrolled. A comparison group of subjects cared for by the core institution who had previously undergone tetralogy of Fallot (TOF) surgical repair were also included. The protocol was approved by each center's institutional review board, and written informed consent was obtained.

Abbreviations and Acronyms

CEAP = clinical, etiological, anatomical, and pathophysiological

CI = confidence interval

CVI = chronic venous insufficiency

TOF = tetralogy of Fallot

Recruitment protocol. Standardized case report forms included basic demographic information, congenital cardiac anatomical diagnosis as designated by the treating center using standardized nomenclature (21), surgical procedures including type of Fontan operation, current medications, family history of venous disease, and symptoms. Laboratory values and historical imaging data that were collected within 1 year of enrollment were included.

A directed physical examination was performed, including a thorough evaluation of the subjects' lower extremities with the assignment of CEAP classification grades by the investigator at each center. The clinical signs in the affected legs are categorized into 7 classes designated C0 to C6 (Table 1) (18). Patients with CEAP grades ≥4 are categorized as having severe CVI, given the presence of end-organ changes from lipodermatosclerosis to ulceration (22).

Each center used a digital camera to photograph the lower extremities according to a standardized protocol. The photographs were taken at a distance of 1 to 2 feet from the subject while he or she was standing in 4 distinct positions. Additional photographs were taken at close range of any ulcers, discoloration, or other skin changes.

Interobserver agreement. To test agreement of CEAP classification by each center, a vascular medicine specialist (M.G.H.) blinded to the subjects' assigned CEAP classifications reviewed 50 randomly selected subjects and determined CEAP grades on the basis of visual inspection of the photographs provided.

Statistical analysis. Continuous demographic and clinical data are summarized as mean ± SD or as medians and

Table 1 CEAP Classification

Class	Characteristics
0	No visible or palpable signs of venous disease
1	Telangiectasias or reticular veins
2	Varicose veins
3	Edema
4a	Skin changes ascribed to venous disease (pigmentation, eczema)
4b	Skin changes including lipodermatosclerosis and/or atrophie blanche
5	Skin changes as defined above with healed venous ulcer
6	Skin changes as defined above with active venous ulcer

CEAP = clinical, etiological, anatomical, and pathophysiological.