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Living at Altitude Adversely Affects Survival Among Patients With a Fontan Procedure

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Objectives This study sought to determine whether survival in this cohort of patients was adversely affected by increased residential altitude.

Background The success of the Fontan procedure depends in large part on low pulmonary vascular resistance (PVR). Factors that increase PVR, including an increase in residential altitude, may adversely affect long-term outcome. Higher altitude has been shown to affect functional well-being in patients with a Fontan circulation.

Methods Databases from a tertiary cardiac care center in the Intermountain West (elevation 5,000 feet) were analyzed for patients born with single-ventricle anatomy who would now be of adult age. Complete data were then collected on all identified patients who subsequently underwent the Fontan operation. Correlates of, and time to, adverse outcome, defined as death, cardiac transplantation, or clinical decompensation requiring a move to sea level, were determined.

Results Of 149 patients with single-ventricle anatomy, 103 underwent the Fontan procedure, with 70 surviving to adulthood at moderate altitude. Adverse outcome occurred in 55, with death in 24 (23%), cardiac transplantation in 18 (17%), and clinical decompensation requiring move to sea level in 13 (13%). There was no relationship between type, age at, or era of Fontan procedure and long-term outcome. Correlates of long-term, transplant-free survival at moderate altitude included lower residential altitude (4,296 vs. 4,637 feet, $p < 0.001$), and lower pulmonary artery pressures before the Fontan procedure (13 vs. 15 mm Hg, $p = 0.01$), and after (14 vs. 18 mm Hg, $p = 0.01$).

Conclusions Long-term outcome after the Fontan procedure is adversely impacted by higher residential altitude. (J Am Coll Cardiol 2013;61:1283–9) © 2013 by the American College of Cardiology Foundation

The Fontan procedure is the anticipated final surgical intervention in children with single-ventricle anatomy. The procedure, first described by Dr. Fontan in 1971, revolutionized the outlook of patients with single-ventricle anatomy as it allowed them to survive into adulthood. The surgical procedure requires rerouting of superior and inferior caval flow to the pulmonary arteries without an intervening pump, and thus, low pulmonary vascular resistance is critical to the success of the procedure (1).

With increased elevation, there is a reduction in the partial pressure of oxygen (pO_2), which serves as the stimulus for a number of physiological changes including an increase in plasma catecholamines and renin activity, resulting in an increase in systemic and pulmonary vascular resistance, as well as heart rate (2). These physiological adaptations may prove particularly detrimental to the patient who has undergone Fontan palliation. The negative impact of increased altitude on early Fontan hemodynamics has been described (3), as has acute clinical deterioration of sea level residents with a Fontan circulation who have been exposed to moderate altitude (4,5). The long-term outcome of patients residing at moderate altitude after the Fontan procedure, however, is unknown. We sought to assess morbidity and mortality in a group of patients with a Fontan circulation followed up at a tertiary center located at moderate altitude and to determine what, if any, effect residential elevation has had on long-term survival.

Methods

An institutional review board–approved retrospective review of surgical, cardiac catheterization, and clinical databases from a tertiary cardiac care center located at an elevation of 5,000 feet and serving a 3-state region in the Intermountain West was performed. Patients with single-ventricle anatomy who would now be of adult age (>18 years) were

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Abbreviations and Acronyms

BDCPS = bidirectional cavopulmonary shunt

NYHA = New York Heart Association

PA = pulmonary artery

PLE = protein-losing enteropathy

identified. Patients from this initial review were then included in the study for further analysis if they had undergone a Fontan operation.

Records were reviewed, and the following demographic and surgical variables were recorded: date of birth, sex, date of Fontan procedure, type of initial Fontan procedure (atriopulmonary, lateral tunnel, or extracardiac conduit), presence or absence of surgical fenestration, presence or absence of prior cavopulmonary anastomosis, interval between cavopulmonary anastomosis and subsequent Fontan procedure, presence and date of surgical conversion to an alternate type of Fontan, and need for surgical revision of the primary Fontan connection. Presence and absence of a pacemaker was noted. Cardiology variables including systemic ventricular morphology (right, left, or indeterminate), pulmonary artery (PA) pressures on pre-Fontan cardiac catheterization, subsequent percutaneous or spontaneous fenestration closure, and PA pressures at cardiac catheterization at last follow-up were noted.

The following outcomes were noted to be present or absent: protein-losing enteropathy (PLE) defined by an elevated stool alpha-1 antitrypsin and associated hypoalbuminemia, plastic bronchitis, thrombosis defined as a clinically symptomatic thromboembolic event, death, listing for cardiac transplantation, and clinical decompensation prompting relocation to lower altitude. New York Heart Association (NYHA) classification and oxygen saturations at rest and with exercise were recorded at last follow-up before death, transplantation, or move from moderate altitude to sea level. For the purposes of this study, moderate altitude was defined as >3,000 feet elevation (4).

Subjects were categorized as: 1) those with composite adverse outcome; and 2) those without composite adverse outcome, defined as death, cardiac transplantation or listing for cardiac transplantation, or move to sea level for cardiac decompensation. Adverse outcomes of death and cardiac transplantation were also analyzed individually. Date of composite adverse outcome and cause of composite adverse outcome were recorded. Cause of adverse outcome was identified as heart failure, Fontan failure, thrombosis, PLE, hepatic dysfunction, sudden death, perioperative death, or other. Heart failure was defined as NYHA class III or greater symptoms in the face of qualitatively impaired systemic ventricular function on echocardiogram. Fontan failure was defined as NYHA class III or greater symptoms in the face of qualitatively normal systemic ventricular function on echocardiogram and elevated PA pressures on cardiac catheterization. Hepatic dysfunction was defined as functional abnormalities noted on serology in association with structural alterations present on liver biopsy. Sudden death was defined as death within 3 h of the onset of symptoms and perioperative death was defined as death within 28 days of cardiac surgery. The "other" category included patients who died of noncardiac reasons or patients for whom the cause of death could not be elucidated.

Residential elevation was determined by using an adjusted average of the elevation of the zip codes at which the patient resided between the Fontan operation and the clinical endpoint (death, cardiac transplantation, move to sea level, last visit).

Patients were classified by initial Fontan type defined as atriopulmonary connection, lateral tunnel type, or extracardiac conduit, depending on the surgical procedure performed. Repeat analyses using final Fontan type was also performed to assess for clinical effect in patients undergoing conversion from one type of Fontan to another.

All patients were followed up in either a pediatric cardiology or an adult congenital cardiology academic practice. Patients were seen with the frequency that their clinical condition demanded, with recommended follow-up at least annually. Echocardiograms were obtained at the discretion of the patients' primary cardiologist but were performed at least annually. Patients with symptoms of heart failure or functional deterioration underwent cardiac catheterization. If the source of heart failure was myocardial dysfunction, heart transplant work-up was considered and discussed with the patient. In light of prior publications noting an almost universal decline in functional status of sea level Fontan patients traveling to moderate altitude (4), patients with preserved myocardial function but elevated PA pressures were given a trial of oxygen and medical therapies for pulmonary hypertension. If they continued to have incapacitating symptoms of heart failure, or persistent symptomatic desaturation, and if they had noted improvement in these symptoms at lower elevations, a move to sea level was discussed. For patients unwilling or unable to relocate, cardiac transplantation was discussed. Patients were listed for cardiac transplantation at the discretion of the heart failure/transplant team at our center. Medications, including anticoagulants, were prescribed at the discretion of the patient's primary cardiologist and were not standardized across providers. All patients were treated with either aspirin or warfarin for anticoagulation therapy. All patients with prior thromboembolic events or sustained atrial arrhythmias were managed on warfarin.

Statistical analysis. Statistical analysis was conducted using SAS version 9.2 (SAS Institute, Cary, North Carolina). Continuous data were expressed as means with standard deviations or medians with ranges as appropriate, and categorical data were tabulated. A 2-sided p value of < 0.05 was considered statistically significant. Demographic and clinical data for adult survivors with adverse outcome, and survivors without an adverse outcome were compared using a chi-square test, for dichotomous or categorical variables, and a Student *t* test or Wilcoxon rank-sum test for continuous variables depending on their normality. Patient data were censored on the basis of their last known visit if they were lost to follow-up. Kaplan-Meier survival curves were