

### **Echocardiographic Predictors of Mortality in Adults with a Fontan Circulation**

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Dear Editor:

Adults with univentricular physiology repaired with a Fontan-type procedure are at increased risk of premature death. We investigated echocardiographic indices that are predictive of mortality in this setting because the prognostic utility of such imaging is not well-characterized.

Fontan-adults seen at our institution since 2005 were screened. Exclusion criteria were Kawashima repair, pregnancy, ventricular outflow gradient  $>2.0$  m/sec, supraventricular arrhythmia during transthoracic echocardiogram (TTE) or paced ventricular rhythm. Follow-up continued until time of death, total cavopulmonary connection (TCPC) conversion or most recent review.

Standard two-dimensional and Doppler echocardiographic assessments were performed. In addition, systolic duration was measured from the onset to the end of atrioventricular (AV) valve regurgitation. Diastolic duration was measured from the end of AV valve regurgitation to the onset of the subsequent AV valve regurgitation signal. The AV systolic to diastolic duration ratio (S/D duration ratio) was then calculated.

One-hundred-and-twenty-eight patients (64 male, median age 25 [20-30] years, 107 (84%) dominant left ventricle) were included. NYHA Class was I/II in 120 (94%) and III/IV in 8 (6%) patients. Forty-eight had atriopulmonary connection (APC) and 80 had TCPC, of whom 16 had had adult APC to TCPC conversion. Median follow-up was 4.2 [1.5-6.6] years. Overall, 75 (59%) patients had good systolic function by qualitative assessment. Thirty-eight patients (30%) had mild, 8 (6%) had moderate and 7 (5%) had severe systolic impairment. One hundred and eight (84%) patients had none or mild AV valve regurgitation and 20 (16%) had moderate to severe AV valve regurgitation.

Twelve patients (9%) died during follow-up (aged 37 [29-45] years). Seven of those had APC, 3 had TCPC and 2 had TCPC conversion. Eight deaths were due to heart failure, 2 were sudden and 2 were due to liver failure. The results of univariable Cox regression analysis are shown in Figure 1A. When accounting for Bonferroni correction (significance  $P < 0.003$ ), only functional class and S/D duration ratio remained significant predictors of death. Kaplan-Meier survival analysis is shown in Figure 1B. We performed post-hoc analysis to assess whether atrioventricular S/D duration ratio correlated with other TTE measures of ventricular function. A significant correlation existed with subjective grade of ventricular function ( $R=0.32$ ,  $p=0.006$ ), fractional area change ( $R=-0.25$ ,  $p=0.04$ ) and E/A ( $R=-0.23$ ,  $p=0.009$ ). Atrioventricular S/D duration ratio did not correlate with age ( $R=-0.04$ ,  $p=0.7$ ) but had a strong correlation with heart rate ( $R=0.58$ ,  $p<0.0001$ ). On univariable analysis S/D duration ratio corrected for heart rate remained a strong predictor (HR 7.5,  $p<0.0001$ ) while heart rate was associated with a lesser hazard ratio (HR 1.1,  $p=0.02$ ).

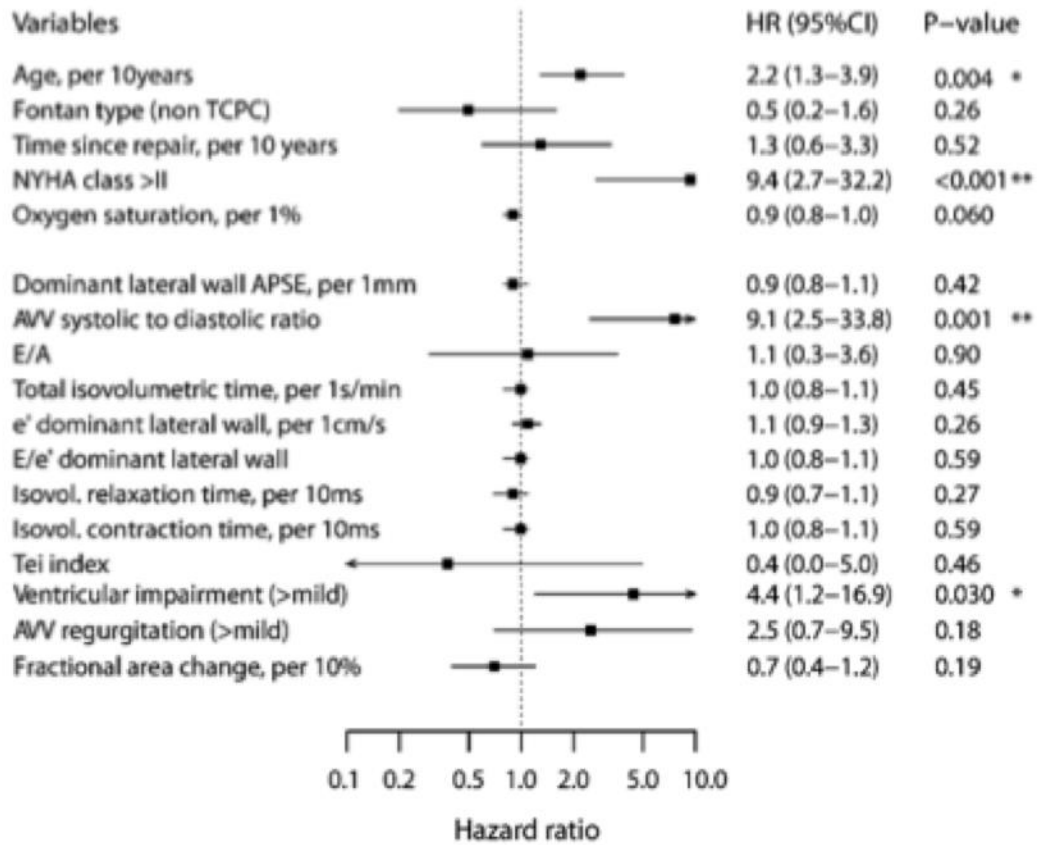
This study suggests that S/D duration ratio is an especially important prognostic marker in Fontan patients. Assessment of single-ventricular function with echocardiography, the mainstay of cardiac imaging in Fontan-adults, is challenging. S/D duration ratio reflects global ventricular function and can be measured simply and consistently, using continuous-wave Doppler assessment of the AV valve. This may be of particular significance in Fontan patients but has only previously been explored in a pediatric group with hypoplastic left heart syndrome at various stages of Norwood palliation(1) and tissue Doppler-derived S/D duration ratio has been reported not to correlate with MRI-derived measures of systolic function in that setting.(2) Tissue Doppler derived indices that reflect motion in one wall might be less useful due to dyssynchronous contraction, compared with continuous-wave Doppler derived measurement in the setting of complex, single ventricle hearts.

Data investigating the relation between echocardiography and clinical outcomes in the Fontan circulation are scarce. Poor ventricular function and degree of AV valve regurgitation has been retrospectively associated with risk of death.(3) In Fontan patients with protein-losing enteropathy, deceleration time <120msec predicted mortality.(4) Ghelani *et al.*(5) found that reduced systolic function and increased indexed ventricular volumes were associated with mortality; global circumferential strain with the strongest predictor.

S/D duration ratio is an independent predictor of mortality in adults with a Fontan circulation. It is easily measurable, even in complex univentricular hearts, and should be incorporated into the routine assessment of ventricular function in these patients.

**Figure Legend**

**Figure 1A:** Results of Univariable Cox regression analysis for mortality



**Figure 1B:** Kaplan-Meier survival analysis showed patients with good functional class (NYHA class I/II) and atrioventricular valve systolic to diastolic duration ratio below 1.1 have better survival compared to the remainder of the population (97% vs. 74% at 5 years,  $p < 0.001$ )

APSE-annular plane systolic excursion, AVV-atrioventricular valve, S/D ratio-systolic to diastolic duration ratio.



**References**

1. Friedberg MK, Silverman NH. The Systolic to Diastolic Duration Ratio in Children with Hypoplastic Left Heart Syndrome: A Novel Doppler Index of Right Ventricular Function. *J Am Soc Echocardiogr.* 2007;20(6):749-55.
2. Bellsham-Revell HR, Tibby SM, Bell AJ, Miller OI, Razavi R, Greil GF, et al. Tissue Doppler time intervals and derived indices in hypoplastic left heart syndrome. *Eur Heart J Cardiovasc Imaging.* 2012;13(5):400-7.
3. De Vadder K, Van De Bruaene A, Gewillig M, Meyns B, Troost E, Budts W. Predicting outcome after Fontan palliation: a single-centre experience, using simple clinical variables. *Acta Cardiol.* 2014;69(1):7-14.
4. Silvilairat S, Cabalka AK, Cetta F, Grogan M, Hagler DJ, O'Leary PW. Protein-losing enteropathy after the Fontan operation: associations and predictors of clinical outcome. *Congenit Heart Dis.* 2008;3(4):262-8.
5. Ghelani SJ, Harrild DM, Gauvreau K, Geva T, Rathod RH. Comparison Between Echocardiography and Cardiac Magnetic Resonance Imaging in Predicting Transplant-Free Survival After the Fontan Operation. *Am J Cardiol.* 2015;116(7):1132-8.