Association of Hemodynamic Profiles With Wait-List Mortality in Children Listed for Heart Transplantation With Idiopathic Dilated Cardiomyopathy

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The prognostic significance of intracardiac hemodynamics in children with advanced heart failure is unknown. The purpose of this study was to describe hemodynamic profiles in children with idiopathic dilated cardiomyopathy (IDC) listed for heart transplant (HT) and to assess their association with wait-list mortality. We identified all US children <18 years with IDC listed for HT during 2000 to 2010 with available pulmonary capillary wedge pressure (PCWP) and cardiac index (CIx) data. We excluded children on ventilator or mechanical support at listing. CIx >2.2 L/min/m^2 (warm) and PCWP >18 mm Hg (wet) were used to define 4 hemodynamic profiles: warm-dry, warm-wet, cold-dry, and cold-wet. The primary end point was death on the wait-list or becoming too sick to transplant. Of 476 children analyzed, 248 (52%) children had PCWP >18 mm Hg and 300 (63%) had CIx >2.2 L/min/m^2. Overall, 36% children were warm-dry, 27% were warm-wet, 12% were cold-dry, and 25% were cold-wet; 32 (6.7%) children reached the primary end point. In adjusted analysis, cold-dry (hazard ratio [HR] 3.5, 95% confidence interval [CI] 1.1, 11.5) and cold-wet (HR 3.2, 95% CI 1.2, 8.6) children were at higher risk of wait-list death versus warm-dry children, whereas warm-wet children were not (HR 2.3, 95% CI 0.8, 6.6). All groups were equally likely to receive HT and had similar 1-year post-transplant survival. In conclusion, in children with IDC listed for HT, those with low cardiac output at evaluation are at higher risk of wait-list mortality. Defining hemodynamic profiles may improve risk stratification of children with IDC listed for HT. **(Am J Cardiol 2015;115:243−248)**

Left-sided congestion or volume overload is the primary hemodynamic abnormality in the vast majority of adults with heart failure and has been associated with increased risk of adverse outcomes such as death or rehospitalization.[1−5] In contrast, cardiac index (CIx) has not shown a similar association with outcomes in these patients. How best to evaluate and treat volume overload has been a major area of investigation in adults with heart failure.[3,6−9] No study has systematically assessed intracardiac hemodynamics in children with systemic ventricular dysfunction and heart failure. The purpose of this study was to use right-sided cardiac catheterization data to define 4 hemodynamic profiles (warm-dry, warm-wet, cold-dry, and cold-wet) in children with idiopathic dilated cardiomyopathy (IDC) listed for heart transplant (HT) and to assess the association of these profiles with wait-list mortality. Our hypothesis was that warm-wet, cold-dry, and cold-wet children will be at higher risk of wait-list mortality compared with warm-dry children.

Methods

Using the Organ Procurement and Transplant Network (OPTN) database, we identified all children <18 years listed for HT in the United States during 2000 to 2010 with a diagnosis of IDC who had pulmonary capillary wedge pressure (PCWP) and CIx data reported at listing. We excluded children with (1) a diagnosis of myocarditis, (2) listing for retransplantation or multiorgan transplantation, and (3) ventilator or mechanical support at listing. The OPTN database includes clinical information in all children listed for HT in the United States submitted by transplant centers. The Health Resources and Services Administration, US Department of Health and Human Services, provides oversight to the activities of the OPTN contractor, United Network of Organ Sharing (UNOS).

We used CIx and PCWP data (CIx >2.2 L/min/m^2 defined as warm, ≤ 2.2 defined as cold; PCWP >18 mm Hg defined as wet, and ≤18 defined as dry)[10] reported at HT listing to divide study children into 4 hemodynamic groups: warm-dry, warm-wet, cold-dry, and cold-wet. The groups were compared for baseline characteristics and outcomes. The primary end point was a composite of death on the wait-list or becoming too sick to transplant (delisting because of deterioration) and was assessed using time-to-event analysis up to 1 year after listing. Children who received HT or were removed from the list because of recovery or other reasons were censored. A secondary end point was post-transplant graft loss (death or retransplantation) in children in the 4

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See page 247 for disclosure information.

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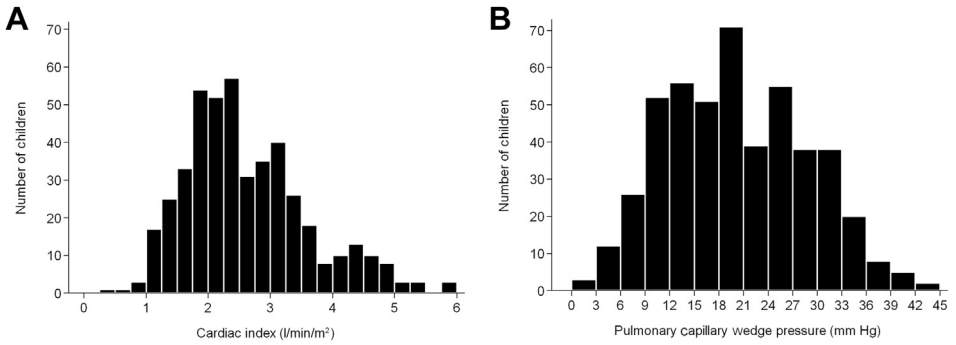

Figure 1. Distribution of cardiac index *(A)* and pulmonary capillary wedge pressure *(B)* in the study cohort.

Table 1
Distribution of study children in the hemodynamic groups

PCWP (mm Hg)	Cardiac Index (l/min/m^2)		Total
	>2.2 (Warm)	≤2.2 (Cold)	
≤18 (Dry)	173 (36%)	55 (12%)	228 (48%)
>18 (Wet)	127 (27%)	121 (25%)	248 (52%)
Total	300 (63%)	176 (37%)	476 (100%)

Data are presented as number (%).
PCWP = pulmonary capillary wedge pressure.

hemodynamic groups who received HT. For analyzing wait-list outcomes, children were followed from listing until death, delisting, HT, or for 1 year. For analyzing post-transplant survival, children who received an HT were followed until death, retransplant, or for 1 year.

Baseline variables were defined at listing for analyzing wait-list outcomes and at HT for analyzing post-transplant outcomes. Race/ethnicity was analyzed as white (non-Hispanic white), black (non-Hispanic black), Hispanic, or other. Renal function was analyzed as estimated glomerular filtration rate (GFR, ml/min/1.73 m^2) and calculated from serum creatinine using the modified Schwartz formula.[11] Normal renal function in children ≥1 year was defined as estimated GFR >60, moderate dysfunction as 30 to 60, and severe dysfunction as <30 or dialysis support. Because of lower GFR in normal infants <1 year, normal renal function, moderate dysfunction, and severe dysfunction were defined as GFR >40, 20 to 40, and <20 or dialysis support, respectively. No subject had missing data for the variables age, gender, race/ethnicity, blood type, medical insurance (Medicaid), UNOS listing status, dialysis at listing or HT, mechanical support at HT, and the dates of listing, HT, death, or removal from the wait-list.

Summary data are presented as median (interquartile range [IQR]) or number (%). Baseline characteristics among the 4 hemodynamic groups were compared using the chi-square test for categorical and the Kruskal-Wallis test for continuous variables. Cumulative wait-list outcomes were characterized using competing outcome analyses.[12,13] A multivariable Cox model for the composite primary end point was developed using a forward selection procedure retaining variables significant at the 0.10 level based on a likelihood ratio test. Post-transplant survival (freedom from death or retransplantation) was characterized using Kaplan-Meier survival analysis and compared among groups using the log-rank test. A Cox model was used to compare post-transplant outcomes among HT recipients in the 4 hemodynamic groups. Assumptions for Cox models were verified for wait-list and post-transplant end points. Finally, a Cox model was used to identify PCWP and CIx values that dichotomized patients to maximize the likelihood ratio chi-square statistic for the composite primary end point.

Data were analyzed using SAS statistical software, version 9.3 (SAS Institute Inc, Cary, North Carolina). All statistical tests were 2 sided, and $p < 0.05$ defined statistical significance. The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written.

Results

During the study period, 1,791 children <18 years were listed for a primary HT in the United States with a diagnosis of IDC. Of these, 582 children were on a ventilator or mechanical support (extracorporeal membrane oxygenation or ventricular assist device) at the time of listing and were excluded. Of the remaining 1,209 children, baseline CIx and PCWP data were reported in 476 (39%) who formed the study cohort. Children who were clinically eligible but were not analyzed because of missing hemodynamic data (n = 733) were younger but with a similar distribution of other baseline characteristics (Supplementary Table S1).

The median age of the study children was 11 years (IQR 3 to 15 years); 228 (48.7%) were women. Figure 1 illustrates the distribution of CIx and PCWP in the study cohort. The median CIx was 2.4 L/min/m^2 (IQR 1.9 to 3.2); 300 children (67%) had CIx >2.2. The median PCWP was 19 mm Hg (IQR 13 to 26). Half (51%) of the children underwent hemodynamic assessment while on inotropes or vasodilators. CIx in children on inotropes (median 2.4, IQR 1.9 to 3.1) at the time of hemodynamic assessment was similar to those not on inotropes (median 2.5, IQR 1.9 to 3.3). There were 178 (37%) children with PCWP >22, 205 (43%) with PCWP >20, and 248 (52%) with PCWP >18. Overall, 173 (36%) children were warm-dry, 127 (27%) were warm-wet, 55 (12%) were cold-dry, and 121 (25%) were cold-wet (Table 1). Baseline characteristics at listing in the 4 hemodynamic groups are listed in Table 2. Warm-dry children were younger than the other 3 groups. Cold-dry and cold-wet children had higher pulmonary vascular resistance compared with warm-dry and warm-wet children.