Hemodynamics in Adults With the Shone Complex

C. Charles. Jain, MD[a], Carole A. Warnes, MD[a], Alexander C. Egbe, MBBS[a], Frank Cetta, MD[a,b], Hilary M. DuBrock, MD[c], Heidi M. Connolly, MD[a], and William R. Miranda, MD[a,*]

Patients with Shone complex (SC) have multiple left-sided obstructive lesions and thus are at risk for left ventricular (LV) remodeling, LV diastolic dysfunction and pulmonary hypertension. Yet, to date, there has been no description of hemodynamics in adults with SC. Retrospective chart review of 25 patients with SC who underwent cardiac catheterization at Mayo Clinic, MN between 2002 and 2019 was performed. SC was defined as multiple left-sided obstructive lesions in the presence of an anatomically abnormal mitral valve. Median age was 32 years (22.5, 42) and 15 patients (60%) were female. The majority of patients (84%) had history of coarctation of the aorta, 10 (40%) had subaortic stenosis, 11 (44%) had prior aortic valve replacement, and 10 (40%) had prior mitral valve replacement. Structural disease at the time of catheterization which warranted intervention within the next year was present in 13 patients (52%). The mean LV end-diastolic pressure was 21.3 ± 9.0 mm Hg (>15 mm Hg in 71%), pulmonary artery peak systolic pressure was 55.4 ± 13.4 mm Hg, and the pulmonary artery mean pressure was 37.0 ± 9.4 mm Hg (>20 mm Hg in 96%). During a mean follow-up of 8.3 ± 4.4 years, there were 7 deaths (28%) and 3 additional patients (12%) underwent cardiac transplantation. In conclusion, adults with SC who underwent catheterization showed significant left-sided heart and pulmonary vascular remodeling. Elevated LV end-diastolic pressure and pulmonary artery pressures were highly prevalent. There were high mortality and cardiac transplant rates in our cohort. **(Am J Cardiol 2020;130:137−142)**

In 1963, Shone et al described a complex of multi-level left-sided obstructive lesions in 8 children.[1] The initial description of the Shone complex (SC) included coarctation of the aorta, subvalvular aortic stenosis, parachute mitral valve, and supravalvular mitral ring (Figure 1). Noteworthy, only 2 of the 8 children had all 4 of these lesions, while others had alternative obstructive lesions (e.g., stenosis of a bicuspid aortic valve). In addition, several of these children had a ventricular septal defect (VSD). Surgical case series of children with SC have described high early mortality but variable long-term prognosis.[2−4] In children with SC, pulmonary hypertension (PH) has been associated with worse outcomes.[1−6] However, in those who survive to adulthood, it is unclear how much left-sided heart and pulmonary vascular remodeling occurred prior to relief of the obstructive lesions. Moreover, the progression of the valvular disease or recurrence of previously repaired lesions (such as coarctation of aorta) would also put these patients at risk for early left ventricular (LV) diastolic dysfunction and post-capillary PH. Given the increasing number of patients with SC surviving to adulthood, it is important to characterize the hemodynamics of SC so that providers can better understand prognosis and tailor appropriate management.[2,7,8]

Methods

An electronic query was performed to identify adults (age ≥18 years) who received a diagnosis of SC and underwent cardiac catheterization at Mayo Clinic, MN between January 2002 and December 2019. In the absence of a universally accepted definition for the clinical entity of SC and given the known association between coarctation of the aorta and bicuspid aortic valve, SC was arbitrarily defined as multiple left-sided obstructive lesions (subvalvular, valvular aortic stenosis and/or coarctation of the aorta) *and* an anatomically abnormal mitral valve. After reviewing the medical records of 29 patients initially identified, 25 fulfilled the inclusion criteria. The Institutional Review Board approved this study. Patients were only included if they had previously provided authorization for their records to be used in research.

Cardiac catheterization data were obtained from procedure logs and individually reviewed by one of the authors (WRM). For those who underwent more than 1 catheterization, the most recent one which included left heart catheterization was selected. The procedure was performed with conscious sedation in 23 patients and with general anesthesia in 2. Indications for invasive hemodynamic evaluation were: clinical deterioration in 13 patients, planned percutaneous interventions in 7, and cardiac transplantation work-up in 5. LV diastolic dysfunction was defined as LV end-diastolic pressure (LVEDP) >15 mm Hg. An elevated left atrial pressure (LAP) was defined as direct LAP or a pulmonary arterial wedge pressure (PAWP) >15 mm Hg in those not undergoing transseptal catheterization. PH was defined as mean pulmonary artery pressure >20 mm Hg and further defined as pre-capillary if pulmonary vascular resistance (PVR) ≥3

[a]Department of Cardiovascular Medicine, Mayo Clinic, Minnesota; [b]Department of Pediatric and Adolescent Medicine/Division of Pediatric Cardiology, Mayo Clinic, Minnesota; and [c]Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, Minnesota. Manuscript received April 15, 2020; revised manuscript received and accepted June 5, 2020.

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*Corresponding author: Tel: (507)284-1446.

E-mail address: miranda.william@mayo.edu (W.R. Miranda).

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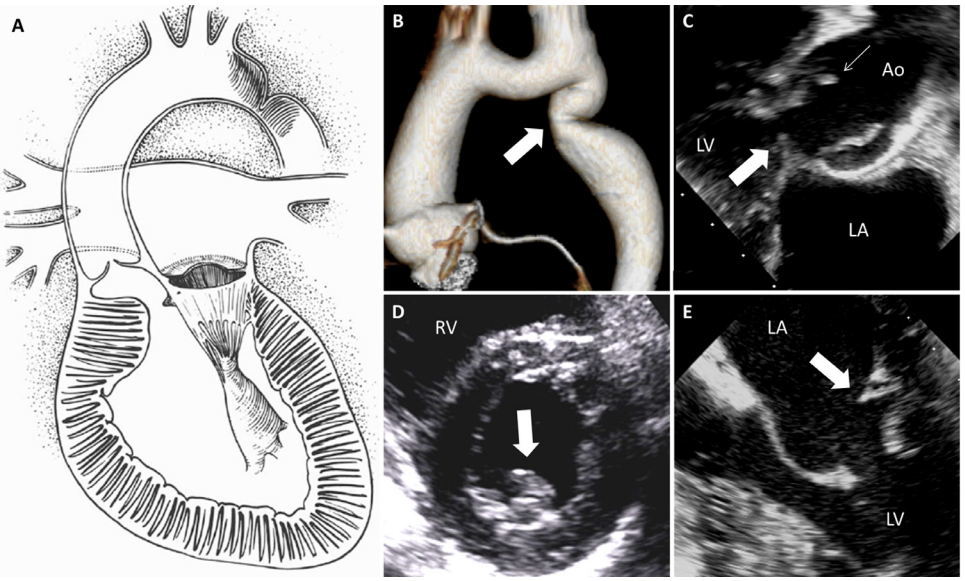

Figure 1. Illustrative examples of anatomical abnormalities in the Shone complex
Panel A. Original diagram from Shone et al illustrating the four obstructive anomalies seen in the complex: supramitral ring, parachute mitral valve, subaortic stenosis, and coarctation of the aorta. Panel B. Three-dimensional reconstruction from computed tomographic imaging reveals severe narrowing (arrow) of the proximal descending thoracic aorta in patient with previous coarctation repair. Panel C. Transesophageal echocardiography shows a subaortic membrane (thick arrow), along with doming of the aortic valve cusps (thin arrow) in the setting of a bicuspid aortic valve. Panel D. Parasternal short axis view from transthoracic echocardiography reveals a single functional left ventricular papillary muscle (arrow), consistent with a parachute mitral valve. Panel E. Transesophageal echocardiography reveals a ridge/membrane in the left atrium, consistent with a supravalvular mitral ring (arrow); note the abnormal mitral leaflets of the concomitant dysplastic parachute mitral valve.
Ao = aorta; LA = left atrium; LV = left ventricle; RV = right ventricle.
Diagram on left reprinted from *American Journal of Cardiology*, Shone JD, Sellers RD, Anderson RC, Adams P, Lillehei CW & Edwards JE, The Developmental Complex of "Parachute Mitral Valve, Supravalvular Ring of Left Atrium, Subaortic Stenosis, and Coarctation of the Aorta", 714-725, Copyright 1963, with permission from Elsevier.

WU, post-capillary if the LAP or PAWP >15 mm Hg, or combined.[9] Pressures are reported as the mean over 6 to 8 consecutive beats, depending on heart rate.

Clinical, echocardiographic, and surgical data were abstracted from the medical charts. "Relief of pressure overload" was used to collectively describe any procedure to repair obstructive coarctation, supravalvular aortic stenosis, valvular aortic stenosis, or subvalvular aortic stenosis. Echocardiographically, LV mass index was defined as elevated if >95 g/m^2 for women or >115 g/m^2 for men whereas left atrial volume index (LAVI) was considered increased if >34 ml/m^2.[10]

Continuous variables are presented as mean ± standard deviation or median with interquartile range. Comparisons between groups were performed using the Fisher's exact test and Wilcoxon rank-sum for categorical and continuous data, respectively. Linear regression was used for correlation between filling pressures. Survival data were ascertained using the Mayo Clinic registration database and the survival curve built using the Kaplan-Meier method. JMP for SAS (Cary, NC) version 14.1 was used for statistical analyses. p values <0.05 were considered statistically significant.

Results

Demographic and clinical data are presented in Table 1. Median age at the time of catheterization was 32 years

Table 1
Clinical and demographic data

Variable	(n = 25)
Women	14 (60%)
Age at catheterization (years)	32 (22.5,42)
Body mass index (m/kg^2)	24.2 (20.4, 29.3)
Coarctation of the aorta	21 (84%)
Supravalvular aortic stenosis	2 (8%)
Valvular aortic stenosis	11 (44%)
Bicuspid aortic valve	15 (60%)
Subvalvular aortic stenosis	10 (40%)
Status post aortic valve replacement	11 (44%)
Parachute mitral valve	11 (44%)
Dysplastic mitral valve	4 (16%)
Supravalvular mitral ring	3 (12%)
Unrepaired congenital mitral stenosis	12 (48%)
Status post mitral valve replacement	10 (40%)
Prior cardiac surgical/percutaneous interventions	3 (1,3)
Hypertension	7 (28%)
Hyperlipidemia	3 (12%)
Obstructive coronary disease	0 (0%)
Prior stroke	1 (4%)
Atrial fibrillation or flutter	6 (24%)
Pacemaker	6 (24%)
Implantable cardioverter defibrillator	2 (8%)
Smoker (prior or current)	3 (12%)
Chronic obstructive pulmonary disease	0 (0%)
Obstructive sleep apnea	4 (16%)

(22.5, 42) and 60% of individuals were female. Anatomic abnormalities at birth included coarctation of the aorta in 21 patients (84%), supravalvular aortic stenosis in 2 (8%), valvular aortic stenosis (regardless of cusp morphology) in 11 (44%), and subvalvular aortic stenosis in 10 (40%). A VSD was present in 5 patients (20%); 4 had undergone previous VSD closure and 1 had an unrepaired small-moderate sized muscular defect with bidirectional shunting. Mitral valve abnormalities included parachute mitral valve in 11 patients (44%), thickened/dysplastic leaflets in 4 (16%), supravalvular mitral ring in 3 (12%), and other in 2 (8%). Five patients (20%) had undergone mitral valve replacement (MVR) elsewhere and details regarding their original mitral valve anatomy were not available for review.

Median number of prior surgical/percutaneous interventions was 3 (1, 3). Twenty patients (80%) had previously undergone coarctation repair; 8 of these (32%) underwent surgical repair within the first year of life. Three additional patients (12%) underwent relief of LV outflow tract obstruction before age 1. Eleven patients (44%) had prior aortic valve replacement with 9 of these being performed for isolated stenosis, 1 for mixed aortic valve disease, and 1 for regurgitation following aortic valvuloplasty. MVR (40%) had been performed in 10 patients: 7 for valvular or supravalvular LV inflow obstruction, 1 for mixed stenosis and regurgitation, and 2 for mitral regurgitation. At the time of catheterization, 19 patients were in sinus rhythm with intrinsic ventricular conduction, 3 were sequentially atrially and ventricularly paced, and 3 were in an atrial arrhythmia with ventricular pacing.

Pre-procedural transthoracic echocardiography revealed a median LV ejection fraction of 64% (53.5, 67.5) with 4 patients (16%) having an ejection fraction <50% (Table 2). Eleven of 22 patients (50%) had an elevated LV mass index. Mean LAVI was 51.3 ± 23.4 ml/m^2 and two-thirds of the cohort had an increased LAVI. Mean medial tissue Doppler early diastolic velocity (e') was 0.07 ± 0.02 m/s in those without a mitral prosthesis. There were 4 patients (16%) with a mean descending aortic systolic mean gradient >20 mm Hg. Median LV outflow tract/aortic valve gradient in patients with native aortic valves was 16 mm Hg (13, 37) and mean gradient was 26.5 ± 4.9 mm Hg in those with prior AVR. Mean transmitral diastolic gradient in patients with native valves was 6.2 ± 3.0 mm Hg and median gradient was 6.5 mm Hg (5, 9.75) in those with prior MVR.

Right heart catheterization was performed in 22 patients (88%) and left heart catheterization performed in 21 patients (84%) (Table 2). Mean LVEDP was 21.3 ± 9.0 mm Hg and an elevated LVEDP was present in 15 (71%). Mean PAWP was 19.6 ± 6.0 mm Hg (PAWP v-wave 27.1 ± 10.2 mm Hg). Five patients had direct LAP measured and mean LAP was 21.2 ± 7.0 mm Hg. In those with direct LAP measurement, there was a strong correlation with mean PAWP (r = 0.91). LAP (direct or PAWP) was >15 mm Hg in 17 patients (77%).

Thirteen patients (52%) with severe left-sided structural lesions required intervention either at the time of catheterization (e.g., re-coarctation stenting) or within 1 year of catheterization. Compared with those who did not require structural intervention within 1 year, this group had comparable degree of diastolic dysfunction (LVEDP 20.6 ± 2.7 mm Hg vs 22.3 ± 3.0 mm Hg, respectively; p = 0.67), similar LAP or PAWP (18.8 ± 2.0 mm Hg vs 20.4 ± 2.0 mm Hg, respectively; p = 0.58), and prevalence of PH (91% vs 100%, respectively; p = 0.99).

Table 2
Hemodynamic data

Echocardiogram		n
LV ejection fraction (%)	64 (53.5, 67.5)	25
LV mass index (g/m^2)	102 (75.25, 129.25)	25
Descending aorta systolic mean gradient (mm Hg)	13 (8, 20)	15
Aortic valve/LVOT systolic mean gradient (mm Hg)	19 (13, 29.5)	21
Mitral diastolic mean gradient (mm Hg)	6 (5, 9)	23
Left atrial volume index (ml/m^2)	51.3±23.4	17
Aortic regurgitation ≥ mild	2 (8%)	25
Mitral regurgitation ≥moderate	6 (24%)	25
Tricuspid regurgitation ≥ moderate	8 (32%)	25
RV size > mildly enlarged	6 (24%)	25
RV function > mildly reduced	6 (24%)	25
Cardiac catheterization		
Mean right atrial pressure (mm Hg)	10.1±4.9	22
RV end-diastolic pressure (mm Hg)	13.6±5.3	22
Pulmonary artery systolic pressure (mm Hg)	55.4±13.4	22
Pulmonary artery diastolic pressure (mm Hg)	22.9±7.5	22
Pulmonary artery mean pressure (mm Hg)	37.0±9.4	22
Pulmonary vascular resistance (WU)	3.8 (1.9, 6.6)	22
Pulmonary hypertension	21 (96%)	22
Pre-capillary PH	3 (14%)	
Combined pre- & post-capillary PH	11 (52%)	
Post-capillary PH	7 (33%)	
LV systolic pressure (mm Hg)	127.2 ± 27.9	21
LV end-diastolic pressure (mm Hg)	21.3 ± 9.0	21
PAWP (mm Hg)	19.6 ± 6.0	21
PAWP v-wave (mm Hg)	27.1 ± 10.2	21
Left atrial pressure (mm Hg)	21.2 ± 7.0	5
Left atrial pressure v-wave (mm Hg)	34.2 ± 12.1	5
Aortic systolic pressure (mm Hg)	110.2 ± 20.3	24
Aortic diastolic pressure (mm Hg)	59.5 (52.25, 65.0)	24
Aortic mean pressure (mm Hg)	81.5 ± 14.1	24
Cardiac index (L/min/m^2)	2.4 (2.0, 2.8)	21

LV = left ventricle; LVOT = left ventricular outflow tract; PAWP = pulmonary artery wedge pressure; RV = right ventricle.

Diastolic dysfunction (defined as LVEDP >15 mm Hg) was present in 15 patients (71%) with all of them having PH. Patients with diastolic dysfunction were more likely to be treated with a beta-blocker compared with those without diastolic dysfunction (80% vs 20% respectively; p = 0.03). Of those who underwent ≥2 interventions for relief of pressure overload, 79% had LVEDP >15 mm Hg compared with 57% of other patients (LVEDP 23.8 ± 2.3 mm Hg vs 16.4 ± 3.2 mm Hg, respectively; p = 0.08). Otherwise, there was no difference in anatomic, clinical, or echocardiographic findings. Notably, for those with diastolic dysfunction, only 50% had elevated LV mass index and 70% had an increased LAVI.

PH was present in 21 out of 22 patients (96%) undergoing right heart catheterization. The single patient without PH was 21 year-old status post coarctation repair at 1 week of life who had a parachute mitral valve with trivial obstruction. PH

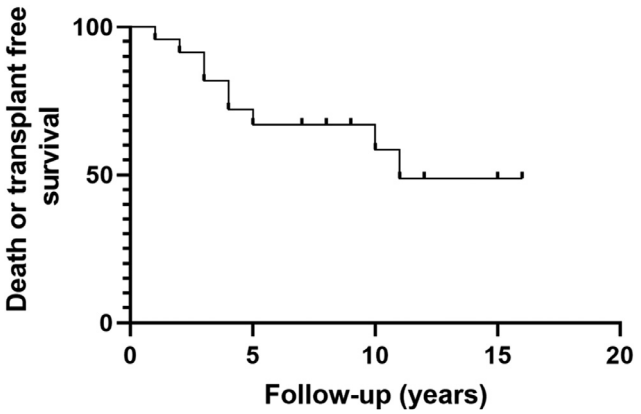

Figure 2. Death or transplant free-survival in patients with the Shone complex.

was pre-capillary in 3 patients (14%), combined pre- and post-capillary in 11 (52%), and isolated post-capillary in 7 (33%). Of the 5 patients with history of VSD, PH was pre-capillary in 1 and combined pre- and post-capillary in 4. In those with VSD compared with those without VSD, there was no significant difference in mean pulmonary artery pressure (39.4 ± 9.7 mm Hg vs 36.4 ± 9.6 mm Hg, respectively; $p = 0.54$) or PVR (3.7 [2.3; 10.8] WU vs 3.8 [1.8; 6.2] WU, respectively; $p = 0.61$).

Pre-capillary or combined pre- and post-capillary PH was associated with increased LAVI (100% vs 20%; $p = 0.007$) and there was a trend toward having the first intervention later in life (3 years [0.5; 12] vs 0.5 year [0.03 to 2.5]; $p = 0.05$) and having higher total number of prior cardiac surgeries (3 [2; 3.5] vs 1 [0; 3]; $p = 0.09$) among these patients compared with rest of the cohort. No other associations were found.

During a mean follow-up of 8.3 ± 4.4 years, there were 7 deaths (28%) with 3 additional patients (12%) undergoing isolated cardiac transplantation. The overall death or transplant-free survival for the entire cohort is shown in Figure 2. Five-year survival for those with pre-capillary or combined PH was 44% compared with 14% for the rest of the cohort. Transplantation was indicated for severe diastolic dysfunction in 1 patient and heart failure with reduced ejection fraction in 2 patients. All patients postcardiac transplantation were alive and clinically doing well at time of data collection (7 to 11 years post-transplant).

Discussion

We describe herein the invasive hemodynamics in adults with SC and the prevalence of elevated left filling pressures and PH in this population. The main findings from our paper are: (1) despite the relatively young age of our cohort, there was a high prevalence of LV diastolic dysfunction (71%) and PH (96%); (2) PH had a significant pre-capillary or combined pre- and post-capillary component; (3) there was significant mortality and high cardiac transplant rates during follow-up.

Pressure overload on the LV is the most obvious physiological abnormality in SC. While age is typically the strongest predictor for diastolic dysfunction in the general population, patients with congenital LV outflow obstruction experience ventricular remodeling early on in life.[11] Elegant studies by Carabello and colleagues in the 1980s showed that congenital valvular aortic stenosis and/or coarctation of the aorta respond differently to pressure overload compared with those with acquired aortic valve disease.[12–14] The authors showed that the myocardial hypertrophy that occurs in the congenital group is not "dysfunctional," rather the LV has supranormal contractile function and low wall stress.[13] This was attributed to the long period of time over which the pressure overload develops.[11] While there may be normal or supranormal systolic function, our cohort shows that diastolic dysfunction may occur even with low systolic wall stress. Our study demonstrated this not just by the prevalence of elevated LVEDP but also by medial mitral tissue Doppler e' velocities being lower than expected for the age group, suggesting myocardial relaxation is indeed abnormal.[15]

One possible explanation for the prevalence of LV diastolic dysfunction in patients with SC is the marked degree of pressure overload and the short time course over which it develops. This is compared with a more insidious course in most patients with isolated congenital aortic stenosis.[13] Patients with coarctation (repaired or unrepaired) are known to have increased vascular stiffness and abnormal diastolic function in utero, as neonates, throughout childhood, and as adults.[16–21] There was a trend toward diastolic dysfunction being associated with a history of ≥2 interventions for relief of pressure overload. It is intuitive that the combination of severe obstruction at multiple levels would promote a more severe increase in afterload than in individuals with a single lesion. Moreover, repeated surgical procedures might have resulted in more myocardial ischemic injury during cardiopulmonary bypass and decreased myocardial compliance, a phenomenon which preferentially affects hypertrophied ventricles.[22] It has also been suggested the mitral stenosis itself can contribute to LV diastolic dysfunction due to chronic ventricular underfilling.[23] Endocardial fibroelastosis could also have developed as this phenomenon is known to be associated with worsened hemodynamics in children with severe left-sided obstructive lesions.[24,25] Lastly, the high prevalence of elevated LVEDP and LAP as well as multiple interventions likely contributed to the high percentage of patients with a history of atrial arrhythmias (24%), almost comparable to more complex forms of congenital heart disease.[26,27]

Since SC is by definition a disease of the left-sided heart, it would be natural that the elevation in LVEDP and LAP would predispose to post-capillary PH. However, in our cohort, a high number of patients demonstrated an elevation in PVR. There are 2 possible explanations for these findings: first, this subset of patients could have reactive elevation in PVR in the setting of increased pulmonary vascular loading from chronic elevation in LAP.[28–32] Based on data from patients with rheumatic heart disease, it has been appreciated that PH in the setting of mitral valve disease (stenotic or regurgitant) is often combined pre- and postcapillary.[33,34] A similar phenomenon has been described in patients with heart failure with preserved or reduced ejection fraction.[32,35,36] A second possible reason for PH/elevated PVR in this population would be a pre-capillary

component of PH outside of that readily explainable by reactive pulmonary vascular remodeling from the left heart. The presence of VSD in 5 of our patients might have led to intrinsic pulmonary vascular disease. Noteworthy, other than the presence of severe obstructive sleep apnea in 2 patients, there was no other clear explanation of a pre-capillary component of PH. One could also postulate that the diffuse arterial vasculopathy seen in patients with coarctation of the aorta would have the potential to manifest itself in the pulmonary circulation as well.[17,20,37] However, to the best of our knowledge, there is only one small study describing the prevalence of PH in patients with coarctation of aorta; interestingly, in this cohort of 30 patients with PH, only 60% had significantly elevated LV filling pressures assessed by echocardiography.[38]

Lastly, in regards to outcomes, this cohort had a high mortality rate at a young median age. These morbidity and mortality rates are almost comparable to those of our adult failing Fontan patients undergoing catheterization.[39] While this cohort is biased due to referral to a tertiary care center and their degree of illness prompting catheterization, these findings are in contrast to the only other study of outcomes in adults with SC which reported low mortality.[7] That study by Aslam et al reported high morbidity in 28 adults with SC, but only 2 requiring cardiac transplantation with a single death. Notably, patients in our cohort were older at presentation and might have been assessed later in their disease course. Both cohorts, however, highlight the predisposition for numerous interventions throughout life. It is conceivable that the cumulative load on the left-sided heart and pulmonary vascular bed, in addition to the morbidity associated with surgical interventions (such as valvular prostheses) and associated disorders (e.g., coarctation of the aorta) contribute to reduced life expectancy.

This study is limited by its retrospective nature and small sample size. This study most likely includes a more complex and sicker subset of patients of SC as these were individuals referred for cardiac catheterization. LV diastolic dysfunction was defined based on LVEDP (as this represents a simple, universally used measurement) and its prevalence could have been even higher if more sensitive parameters were used (such as tau). Limitations aside, this is the only study reporting hemodynamics of adults with SC and one of the few studies of invasive hemodynamics in SC at any age. Furthermore, currently there is a lack of data on prognosis of patients with SC.

This was the first study to show the high prevalence of LV diastolic dysfunction and PH in adults with the SC. Repeat interventions for coarctation, LV outflow, and LV inflow obstruction were common and were associated with worsened left-sided heart remodeling as revealed by elevated filling pressures. PH was seen in almost all patients in this cohort with most having a significant pre-capillary component. Freedom from death or transplant was reduced in this cohort even when compared with more complex forms of adult congenital heart disease.

Author Biography

C. Charles Jain: Methodology, Writing – Original Draft, Data Curation, Investigation, Formal Analysis. Carole A. Warnes: Conceptualization, Methodology, Writing – Review and Editing. Alexander C. Egbe: Writing – Review & Editing. Frank Cetta: Writing – Review & Editing. Hilary M. DuBrock: Writing – Review & Editing. Heidi M. Connolly: Writing – Review & Editing. William R. Miranda: Conceptualization, Methodology, Writing – Review & Editing, Data Curation, Investigation, Formal Analysis, Supervision.

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