Acute and Mid-Term Outcomes Of Stent Implantation For Recurrent Coarctation Of The Aorta Between The Norwood Operation and Fontan Completion: *A Multi-center PICES (Pediatric Interventional Cardiology Early Career Society) Investigation*

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Abstract:

Objectives: We sought to evaluate outcomes of stent implantation (SI) for recurrent coarctation of the aorta (RC) following the Norwood operation.

Background: RC is common following the Norwood operation. Balloon angioplasty (BA) is standard treatment but may result in unsatisfactory relief of RC. SI may improve RC, but outcome data are limited.

Methods: We performed a multi-center retrospective study of patients who underwent SI for RC between the Norwood operation and Fontan completion. Outcomes were examined, including procedural success, serious adverse events (SAE), and freedom from re-intervention. A core laboratory was utilized to review angiograms. Coarctation Index (CI) was calculated before and after SI. Paired t-test and Wilcoxon signed-rank test were used to compare pre- and post-SI variables.

Results: Thirty-three patients at 8 centers underwent SI for RC at a median age of 5 months (IQR 4.1, 13.3) and weight of 5.9 kg (5.2, 8.6). Aortic arch gradient improved from 20 (15, 24) to 0 (0, 2) mmHg following SI ($p<0.0001$). The median CI improved from 0.54 (0.43, 0.62) to 0.97 (0.89, 1.06) following SI ($p<0.0001$). There were no procedural deaths but SAEs occurred in 12 (36%) patients. During a median follow-up duration of 29.7 months (6.8, 48.0), freedom from death or heart transplant was 82%, and from re-intervention was 45%, with median time to re-intervention of 20.1 months (11.4, 40.3).

Conclusions: SI for treatment of RC in patients after the Norwood operation provides excellent acute relief of obstruction. Intra-procedural hemodynamic instability is common and re-intervention is frequent at mid-term follow-up.

Introduction:

Postoperative recurrent coarctation (RC) of the aorta is reported in 9–37% of patients following the Norwood procedure for hypoplastic left heart syndrome (HLHS) and its variants (1,2). RC may be poorly tolerated in patients with HLHS and a single systemic right ventricle, potentially leading to ventricular dilation and dysfunction, increased tricuspid valve regurgitation, and a clinically relevant and harmful imbalance between the pulmonary and systemic circulations (3,4). For these reasons and others, RC has been shown to be a risk factor for long-term morbidity and mortality in single ventricle (SV) patients (3,5,6).

Transcatheter treatment of RC in SV patients using balloon angioplasty (BA) has been well described (2,7). While BA is generally considered the first-line treatment for SV patients with RC, BA may result in inadequate acute relief of aortic obstruction, non-durable relief of obstruction (e.g. early recurrence), or both (8-11). In these cases, treatment options include repeat BA, aortic stent implantation (SI) or surgical re-intervention. SI has the potential for improved acute relief of aortic obstruction and more durable results, avoiding the need for re-operation, but may be associated with a greater procedural complications compared to BA. Moreover, SI will necessarily require future stent re-dilation to match somatic growth, thus making transcatheter re-intervention a requirement. Existing data supporting SI post Norwood-related RC are limited to case reports and small single center series (11-13). Therefore, we sought to investigate a large multi-center cohort of patients undergoing SI for treatment of post-Norwood RC – prior to Fontan completion – to evaluate acute procedural outcomes and clinical outcomes at mid-term follow-up.

Materials and Methods:

We performed a multi-institutional retrospective study of SV patients who underwent SI for RC between the Norwood operation and Fontan completion at 8 participating centers between 2007 and 2015. All co-investigators were members of the Pediatric and Congenital Interventional Cardiology Early Career

Society (PICES). Institutional Review Board approval was obtained at each participating center. All SV patients who underwent SI for RC following the Norwood operation and prior to Fontan completion were included in the study. Baseline clinical characteristics, including cardiac diagnoses, surgical history and prior transcatheter interventions were collected on all patients. Echocardiographic data, catheterization-derived hemodynamic data, and angiographic data before, during and after SI were collected. Echocardiograms used for data collection were those closest to the SI and preferably within 1 week before and 1 week after SI procedure. Additionally, the technique for SI was collected and categorized for each patient as prograde (percutaneous venous access with catheter course anterograde across the neo-aortic valve and arch), retrograde (percutaneous arterial access with catheter course retrograde across aortic arch), trans-carotid (carotid artery access via surgical cut-down and catheter course anterograde across aortic arch), or hybrid (surgical access to a major systemic artery such as the transverse arch).

A core laboratory was used for angiography review and assessment (Syngo Dynamics workplace (version: 8.0.0SPC), Siemens Medical Solutions USA Inc., Ann Arbor, Michigan, USA). A single interventional pediatric cardiologist at University of Iowa Children's Hospital (OA) reviewed all angiograms. The core lab was blinded to the rest of the data and outcomes. Using a standard calibration process, measurements of the aortic arch were made using the lateral angiographic projection. A Coarctation Index (CI) was calculated for each patient, utilizing the aortic diameter at the coarctation site (minimal diameter) and the diameter of the descending aorta at the diaphragm ($Aorta_{Coarctation}$ / $Aorta_{Diaphragm}$) before and after SI. Additionally, the type of RC was classified as either discrete or long-segment based on whether the length of narrowing is $\leq$3 mm vs. $>$3 mm respectively. The diameter of the nominal stent compared to the narrowest aortic diameter and descending aorta were also calculated. Angiographic assessment included potential intervention-related complications, such as aortic wall injury, stent malposition or embolization, and jailing of brachiocephalic arteries.

Procedural success was defined as a post intervention peak-to-peak gradient across the aortic arch gradient of ≤ 10 mmHg (3,14). Serious adverse events (SAE) were recorded and defined based on published literature on catheterization risk score for pediatrics (15). Hemodynamic compromise was

defined as hemodynamic instability requiring an intervention (for example, inotropic medication or cardiopulmonary resuscitation). Patient follow-up data was collected through the time of the Fontan completion, specifically including any re-intervention on the aortic arch and clinical outcomes.

Statistical Analysis

Data are presented as frequency with percentage for categorical variables and median with interquartile range (IQR) for continuous variables. Paired t-test and Wilcoxon signed-rank test were used to compare pre- and post-SI variables. Freedom from re-intervention and freedom from death or heart transplant was computed using Kaplan-Meier method. Analyses were performed using software SAS version 9.4 and statistical significance set at P-value <0.05.

Results:

A total of 33 patients met the inclusion criteria and comprised the study cohort (Table 1). The majority of patients (n= 29, 88%) underwent BA before SI; 21 of 29 underwent BA during a separate procedure and 13 patients during the same procedure as SI, of which 4 patients for the second time. Thirteen patients (39%) underwent SI between the Norwood procedure and superior cavopulmonary anastomosis (SCPA) while 20 (61%) underwent SI between SCPA and Fontan completion. The type of RC was discrete in 52% and long-segment in 48% of patients (Figure 1-A and B). The approach for SI was prograde in 21 patients (64%), retrograde in 5 (15%), hybrid in 5 (15%), and trans-carotid in 2 (6%).

Acute Outcomes

Successful SI was possible in 100% of patients based on our hemodynamic definition (Figure 1- C and D) although in one patient, initial stent embolized and another one was successfully placed. The median peak-to-peak gradient across the coarctation site improved from 20 (15, 24) to 0 (0, 2) mmHg following SI

(p<0.0001) (Figure 2-a). By echocardiography, median uncorrected peak instantaneous pressure gradients by Doppler decreased from 34 mmHg (20, 44) to 15 mmHg (5, 18) (p<0.0001) (Figure 2-b). There was no statistically significant change in the degree of atrioventricular valve regurgitation or systemic ventricular function after SI (Figure 3-a, 3-b). Angiographically, after SI, the median narrowest aortic arch diameter increased from 3.8 mm (3.3, 4.4) to 6.6 mm (6.0, 7.5) (p<0.0001) (Table 2). The median CI improved from 0.54 (0.43, 0.62) to 0.97 (0.89, 1.06) after SI (p<0.0001) (Figure 2-c, 2-d). The nominal stent diameters were approximately equal to the descending aortic diameter and twice the coarctation diameter (Table 2).

Procedural SAE were observed in 12 patients (36%). Hemodynamic compromise occurred in 7 patients, with 6 of the patients having undergone SI from a prograde approach and 1 from a retrograde approach. In 3 of these 7 patients, hemodynamic insult progressed into bradycardiac arrest requiring cardiopulmonary resuscitation. All patients were successfully resuscitated with no procedural mortality or need for initiation of extracorporial membrane oxygenation (ECMO) support. There was no association between timing of SI (before or after SCPA) and hemodynamic instability.

Other SAEs included blood loss requiring transfusion (n=3, 9%), AV block (eventually treated with pacemaker placement at the time of SCPA; n=1, 3%), access-related vascular injury (n=1, 3%) and stent embolization (n=1, 3%). In the single case of aortic stent embolization, the stent was subsequently affixed to the vascular wall (e.g. implanted) in the descending aorta and a second stent was successfully implanted across the coarctation site. No patients experienced angiographically-evident aortic wall injury.

Minor adverse events included jailing of the left subclavian artery, which occurred in 11 patients (33%). All patients had unobstructed flow into the left subclavian artery through the bare metal stent on post SI angiography. One patient (3%) had minor stent malposition (stent was not centered over the stenosis area) that did not affect the procedure outcome and 1 (3%) patient had transient junctional rhythm that

resolved spontaneously. There were 2 patients already on ECMO support at the time of SI. No peri-procedural complications occurred in this group, however, both patients subsequently died unrelated to the SI procedure.

Mid-Term Outcomes

During a median follow-up duration of 28.3 months (6.7, 44.5), freedom from death or heart transplant was 82%. Freedom from re-intervention on the aortic stent was 81.1% at 6 months, 72.1% at 12 months, and 43.3% at 24 months with a median time to re-intervention of 20.1 months (11.4, 40.3) (Figure 4). Amongst those patients not on mechanical support (ECMO) at the time of catheterization for SI, freedom from death or transplant was 85.1% during a median follow-up of 31 months (6.9, 51.4). Freedom from re-intervention was 81.7% at 6 months, 73.5% at 12 months, and 50.6% at 24 months with a median time for re-intervention of 24.6 months (11.4, 40.3). Of the 18 patients (54%) who underwent re-intervention, the indication was somatic growth in 9 (50%), in-stent stenosis in 3 (17%), re-stenosis in 3 (17%), and stent fracture in 3 (17%). Among the 3 patients with stent fracture, 2 had a significant gradient seen on echocardiogram and the third stent fracture was found incidentally on CXR. All patients with stent fracture underwent re-intervention with balloon angioplasty of the existing stent. In one case, stent integrity was lost following BA resulting in distal embolization of a stent fragment which was successfully removed percutaneously during the same procedure. The other 2 patients with stent fracture but intact integrity underwent successful BA without complications. Six patients (18%) underwent a second re-intervention, 2 (33%) for in-stent stenosis, 2 (33%) for re-stenosis, and 2 (33%) for somatic growth.

During the study period, 18 (55%) patients had undergone Fontan completion, 5 (15%) were awaiting Fontan completion, 2 (6%) were awaiting second stage palliation and 1 (3%) underwent cardiac transplantation secondary to severe atrioventricular valve regurgitation and progressive heart failure. In addition, mortality occurred in 5 (15%) patients unrelated to SI procedure with median time of 26 days (25, 146) from SI. Causes of death were multiorgan failure following cardiac arrest in 2, respiratory failure

in 1, intraoperative death during cavopulmonary anastomosis surgery in 1, and the last patient was electively made DNR secondary to poor candidacy for second stage repair in a patient with known genetic syndrome and extracardiac anomalies. Two subjects (6%) were lost to follow-up.

Discussion:

In this multi-center study of SV patients with recurrent coarctation treated with transcatheter stent implantation prior to Fontan completion, we demonstrated a high rate of technical success and procedural efficacy. Notably, SI for RC was associated with a significant rate of SAE, including hemodynamic compromise in 21%. As anticipated, re-intervention was common at mid-term follow-up, largely for purposes of stent dilation to match interval somatic growth. To our knowledge, this is the first multi-center collaborative to evaluate acute and mid-term outcomes of SI for RC in SV patients.

RC is a common cause of morbidity and mortality in SV patients after the Norwood procedure (3,5,6). Although typically attempted first, BA to treat RC is not uniformly acutely successful and often does not provide durable gradient relief. Studies have suggested a high success rate of BA but variable freedom of re-intervention (2,7,16). Factors found to contribute to successful BA were larger balloon size, lower initial peak-to-peak gradient and larger diameter of descending aorta in one study (7). Factors associated with higher rates of RC after BA included smaller patients and older age at the time of Norwood procedure (16). In our study, 88% of patients who ultimately underwent SI for RC had previously undergone BA, which is consistent with estimates from prior studies that 15-20% of patients would be non-responders to BA (7,16). This also suggested BA being the first line treatment of RC for most operators and SI would be considered if unsatisfactory BA results. Several possible mechanisms to explain the ineffectiveness of aortic BA include vessel recoil, vessel torsion (compared to true stenosis) and external compression. In these circumstances, SI is likely to provide improved procedural success, when compared to BA.

Surgical revision of the aortic arch is an alternative therapy for RC, either in lieu of BA, or following BA with unsatisfactory results. A recent study reviewed the surgical outcomes after RC repair including both single and biventricular repair. Although post-Norwood cases made up only a small portion of the study cohort (n=17), this sub-group responded satisfactorily to surgical re-intervention, with freedom from repeat re-intervention of 94% at a median follow up of 7.2 years (17). Despite the efficacy of surgical re-intervention, this approach carries inherent risks that are distinct from SI, including those related to repeat sternotomy, cardiopulmonary bypass, sternal wound, and deep tissue dissection. Although most of the post-Norwood cases included in this study were performed at the time of SCPA, thus avoiding an additional surgery, arch revision does add risks to the SCPA procedure, including the potential for greater support times, with the risk of inducing greater lung (inflammatory) pathology placing the new SCPA circulation at risk. Further, delaying relief of arch obstruction to the planned SCPA surgery could place the post-Norwood patient at risk for greater morbidity or mortality.

The most notable SAE in our cohort was hemodynamic instability, which was seen in 21% of patients. Importantly, this was most often seen using the prograde approach and is similar to the risk of hemodynamic compromise reported with BA using a prograde approach in single ventricle patients (8,13). The prograde approach, which typically involves femoral venous access and a catheter course across the tricuspid and neo-aortic valves to gain access to the aortic arch, has the advantage of utilizing femoral venous access, which is preferred to femoral arterial access since SI often requires a relatively large bore (6-8 French) sheath. However, because of the catheter/wire/sheath course, the tricuspid and neoaortic valves may be temporarily stented open, which can result in acute tricuspid and neoaortic valves insufficiency associated with significantly diminished ventricular ejection and inadequate systemic blood pressure and cardiac output. Additionally, the effect of stretching the atrioventricular node or atrial tissue could contribute to atrioventricular block and/or bradycardia which may worsen the resultant hypotension and low output (13). Therefore, a retrograde approach, carotid artery cut-down, or hybrid approach may reduce hemodynamic instability during SI, which may be beneficial especially in patients with pre-procedural evidence of depressed ventricular function or significant tricuspid valve regurgitation (18,19).

Other consideration includes advancing premounted stent without long introducer to avoid the additional stretching effect of the long sheath (13). Access-related vascular injury is another important SAE following SI, especially in patients with large bore arterial access (11,12). In our cohort, access related vascular injury was relatively uncommon, occurring in only 1 patient. This patient had pulse loss after the catheterization, without risk to the limb.

Over 50% of our study cohort required re-intervention during a relatively short follow-up period. This rate is higher than what has been reported with BA (39%) for a similar group of patients (2). Re-intervention following SI is partially anticipated as stents placed in small children invariably require dilation to match interval somatic growth. The intervals between dilation would be anticipated to increase over time, but early after implantation in small and young children, this interval would be expected to be rather short (months to a year or two). In our cohort, ~25% of patients required re-intervention because of somatic growth. Fortunately, stent dilation with BA is typically a straight forward procedure that requires smaller sheaths compared to SI, and therefore is typically performed from a retrograde approach, with a lower incidence of procedural hemodynamic instability and SAE (20). More importantly, however, we found that an additional 25% of our study cohort required re-intervention for in-stent stenosis, residual arch obstruction, or stent fracture. Both in-stent stenosis and stent fracture are recognized long-term sequelae following SI in congenital heart disease, not just for RC. Thus, close monitoring is recommended after SI in all CHD patients (21,22). These outcomes are less predictable than patient-stent mismatch due to somatic growth, and can be more challenging to manage, often requiring repeat stent implantation. Given our small sample size, we were unable to identify stent specific risk factors for development of in-stent stenosis or stent fracture.

An important consideration when treating recurrent coarctation in young patients is stent choice. The ideal stent would be ultimately dilatable to a diameter matching that of the typical adult aorta. In our cohort, 4 stents (12%) were not able to meet this ideal state. Historically these stents would require surgical transection or removal as patients reach adult size. More recently, in vitro and animal studies have shown the ability to intentionally fracture, or un-zip, small stents using high pressure balloons from a

percutaneous approach (23,24). Clinical data from late intentional stent fracture in the aorta, in either the coarctation or single ventricle populations, do not yet exist. Nevertheless, we conclude that in this cohort, while stents capable of dilation to adult aortic diameters are preferred, the use of medium diameter premounted stents may not be a critical limiting factor for SI in small children. Moreover, future availability of bioabsorbable stent platforms in this working range might shift practice, hypothetically allowing for similar procedural efficacy without the need for early or recurrent stent re-intervention (25). This population would be an ideal candidate group in which to study the applications of such technology.

An important limitation of the current literature on the treatment of recurrent coarctation is a lack of descriptive clinical outcomes following repeat balloon angioplasty or surgical repair, especially in single ventricle patients. Future studies including these outcomes, especially if able to directly compare medium-term results of SI, repeat BA, and surgical repair - for the treatment of RC in SV patients - would add greatly to the understanding of how to manage these complex and high-risk patients with recurrent aortic obstruction after the Norwood operation.

Limitations

The retrospective design, small sample size and short follow-up duration are the main limitations of this study. The indication for re-intervention was reported by the participating sites but subsequent re-intervention angiograms were not reviewed in the core lab. Other limitations include the heterogeneity of patient population and the broad number of different types of stents used. Nevertheless, the multi-center collaborative nature of this cohort may help to partially offset the limitations in statistical power. Other limitation includes the non-standardized approach of treatment that reflects the multi-center nature of this study.

Conclusion:

Stent implantation for treatment of recurrent coarctation in single ventricle patients prior to Fontan completion provides excellent acute relief of aortic arch obstruction. This includes those patients that demonstrated an inadequate response to balloon angioplasty alone. Procedural adverse events are common, especially intra-procedural hemodynamic compromise when utilizing a prograde approach, but did not result in the need for mechanical support or mortality. Arch re-intervention is common during mid-term follow-up. Long-term outcomes, including the fate of the aortic stent years beyond implantation, are necessary to study.

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FIGURES LEGENDS:

Figure 1: A- A discrete coarctation of the aorta and C- Post coarctation SI angiogram. B- Long segment coarctation of the aorta and D- Post SI angiogram. SI: Stent implantation.

Figure 2: a- Drop in peak-to-peak catheterization gradient post SI. b- Peak instantaneous echocardiogram gradient improvement on post SI. c- Angiographic improvement of the coarctation diameter post SI. d- Improvement of CI post SI. SI: stent implantation, PIG: peak instantaneous gradient.

Figure 3: a- Echocardiographic single ventricular function pre- and post SI. b- The degree of atrioventricular valve regurgitation pre- and post SI. AVVR: atrioventricular valve regurgitation.

Figure 4: Kaplan-Meier curve of freedom of Heart Transplant/ Death and Re-intervention.

Table 1: Baseline Characteristics of the cohort.

HLHS: Hypoplastic left heart syndrome, MA: mitral valve atresia, AA: aortic valve atresia, MS: mitral valve stenosis, AS: aortic valve stenosis, RV: right ventricle, LV: left ventricle, BT shunt: Blalock Taussig shunt, SI: stent implantation, SCPA: Superior cavo-pulmonary anastomosis, ECMO: extracorporeal membrane oxygenation.

Table 2: Angiographic and procedural details.

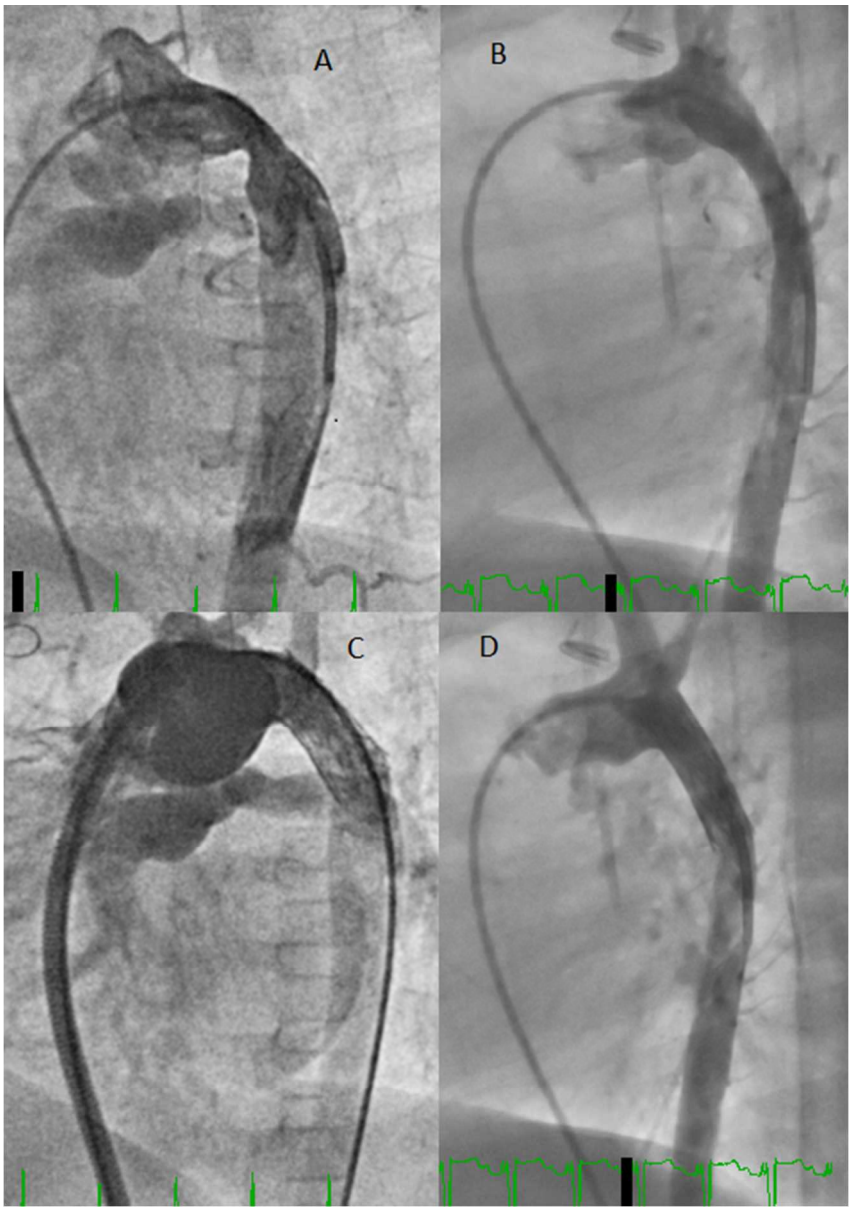

Figure 1: A- A discrete coarctation of the aorta and C- Post coarctation SI angiogram. B- Long segment coarctation of the aorta and D- Post SI angiogram. SI: Stent implantation.

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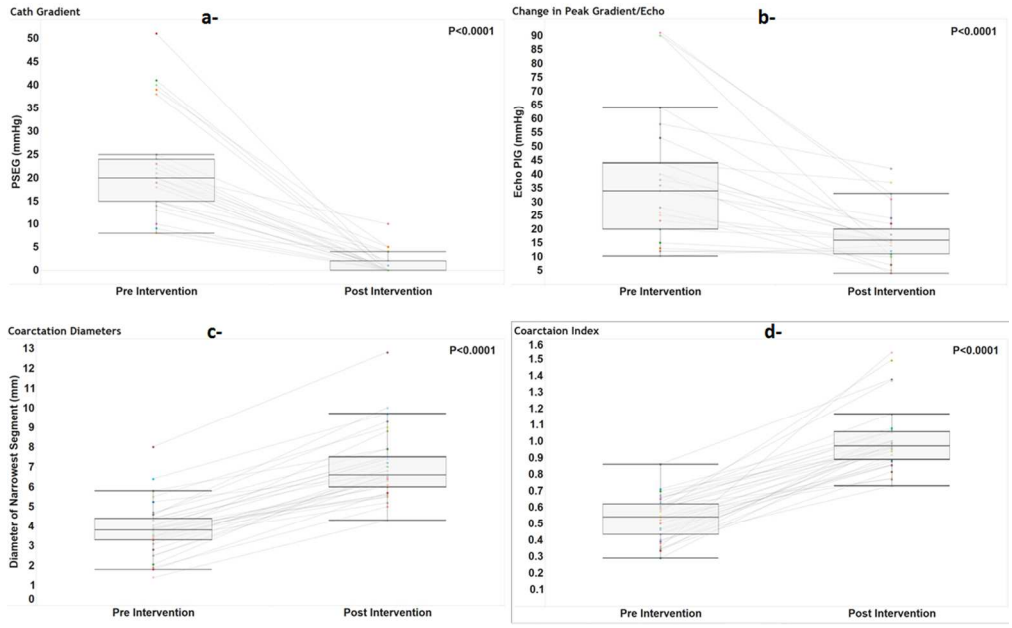

Figure 2: a- Drop in peak-to-peak catheterization gradient post SI. b- Peak instantaneous echocardiogram gradient improvement on post SI. c- Angiographic improvement of the coarctation diameter post SI. d- Improvement of CI post SI. SI: stent implantation, PIG: peak instantaneous gradient.

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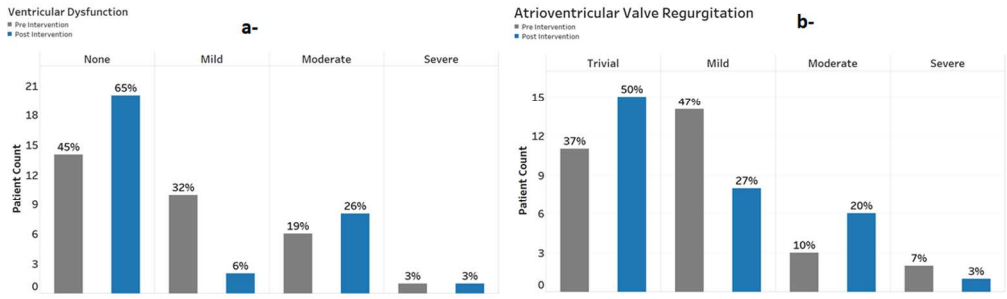

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335x99mm (96 x 96 DPI)

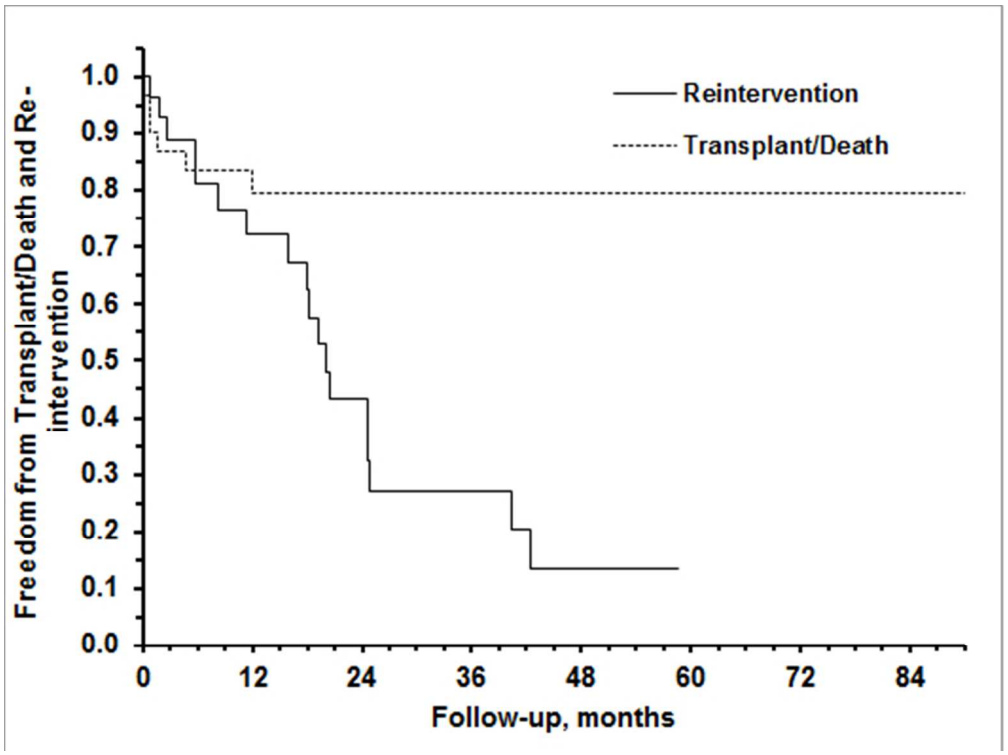

Figure 4: Kaplan-Meier curve of freedom of Heart Transplant/ Death and Re-intervention.

139x104mm (96 x 96 DPI)

Table 1: Baseline Characteristics of the cohort.

	Median (IQR) or percentages
Number of patients	33
Cardiac diagnosis	HLHS 26 (79%)
	MA/AA 14 (42%)
	MS/AA 2 (6%)
	MA/AS 4 (12%)
	MS/AS 6 (18%)
	Other systemic RV 6 (18%)
	Other systemic LV 1 (3%)
Gender (Male)	23 (70%)
Genetic disorder	2 (6%)
Type of systemic-pulmonary shunt	Sano shunt 23 (70%)
	BT shunt 10 (30%)
Age at procedure, months	5.0 (4.1-13.3)
Weight at procedure, kg	5.9 (5.2-8.6)
Interval from BA to SI, days	70 (50-162)
Interval time from Norwood to SI, months	4.5 (3.1-11.3)
Surgical stage at procedure	Before SCPA 13 (39%)
	After SCPA 20 (61%)
Presenting to lab on ECMO support	2 (6%)

HLHS: Hypoplastic left heart syndrome, MA: mitral valve atresia, AA: aortic valve atresia, MS: mitral valve stenosis, AS: aortic valve stenosis, RV: right ventricle, LV: left ventricle, BT shunt: Blalock Taussig shunt, SI: stent implantation, SCPA: Superior cavo-pulmonary anastomosis, ECMO: extracorporeal membrane oxygenation.

Table 2: Angiographic and procedural details.

	Median (IQR) or percentage
Type of coarctation	Discrete 17 (52%) Long segment 16 (48%)
Baseline narrowest aortic diameter (mm)	3.8 (3.3-4.4)
Coarctation index	0.54 (0.43-0.62)
Implanted stent diameter to coarctation ratio	2.1 (1.8-2.6)
Implanted stent diameter to descending ratio	1.1 (1.0-1.2)
Largest implantation sheath size (Fr)	7 (6-8) -Prograde: 7 -Retrograde: 6 -Hybrid:8 -Carotid: 8
Implanted stent diameter (mm)	8 (7-9) -Between first and second stage: 7 -Between second and third stage: 8.5
Stent length (mm)	19 (min 12, max 30)
Close cell design stent	23 (70%)
Non-premounted stents	22 (67%)
Genesis XD	18
Mega LD	3
Max LD	1
Premounted stents	11 (33%)
Premounted Palmaz stents	5
Bard Valeo	2
Express	2
Formula	1
Zues II	1
Fluoroscopy time, minutes	25.5 (10.4-34.5)

Acute and Mid-Term Outcomes Of Stent Implantation For Recurrent Coarctation Of The Aorta Between The Norwood Operation and Fontan Completion: *A Multi-center PICES (Pediatric Interventional Cardiology Early Career Society) Investigation*

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Abstract:

Objectives: We sought to evaluate outcomes of stent implantation (SI) for recurrent coarctation of the aorta (RC) following the Norwood operation.

Background: RC is common following the Norwood operation. Balloon angioplasty (BA) is standard treatment but may result in unsatisfactory relief of RC. SI may improve RC, but outcome data are limited.

Methods: We performed a multi-center retrospective study of patients who underwent SI for RC between the Norwood operation and Fontan completion. Outcomes were examined, including procedural success, serious adverse events (SAE), and freedom from re-intervention. A core laboratory was utilized to review angiograms. Coarctation Index (CI) was calculated before and after SI. Paired t-test and Wilcoxon signed-rank test were used to compare pre- and post-SI variables.

Results: Thirty-three patients at 8 centers underwent SI for RC at a median age of 5 months (IQR 4.1, 13.3) and weight of 5.9 kg (5.2, 8.6). Aortic arch gradient improved from 20 (15, 24) to 0 (0, 2) mmHg following SI ($p<0.0001$). The median CI improved from 0.54 (0.43, 0.62) to 0.97 (0.89, 1.06) following SI ($p<0.0001$). There were no procedural deaths but SAEs occurred in 12 (36%) patients. During a median follow-up duration of 29.7 months (6.8, 48.0), freedom from death or heart transplant was 82%, and from re-intervention was 45%, with median time to re-intervention of 20.1 months (11.4, 40.3).

Conclusions: SI for treatment of RC in patients after the Norwood operation provides excellent acute relief of obstruction. Intra-procedural hemodynamic instability is common and re-intervention is frequent at mid-term follow-up.

Introduction:

Postoperative recurrent coarctation (RC) of the aorta is reported in 9–37% of patients following the Norwood procedure for hypoplastic left heart syndrome (HLHS) and its variants (1,2). RC may be poorly tolerated in patients with HLHS and a single systemic right ventricle, potentially leading to ventricular dilation and dysfunction, increased tricuspid valve regurgitation, and a clinically relevant and harmful imbalance between the pulmonary and systemic circulations (3,4). For these reasons and others, RC has been shown to be a risk factor for long-term morbidity and mortality in single ventricle (SV) patients (3,5,6).

Transcatheter treatment of RC in SV patients using balloon angioplasty (BA) has been well described (2,7). While BA is generally considered the first-line treatment for SV patients with RC, BA may result in inadequate acute relief of aortic obstruction, non-durable relief of obstruction (e.g. early recurrence), or both (8-11). In these cases, treatment options include repeat BA, aortic stent implantation (SI) or surgical re-intervention. SI has the potential for improved acute relief of aortic obstruction and more durable results, avoiding the need for re-operation, but may be associated with a greater procedural complications compared to BA. Moreover, SI will necessarily require future stent re-dilation to match somatic growth, thus making transcatheter re-intervention a requirement. Existing data supporting SI post Norwood-related RC are limited to case reports and small single center series (11-13). Therefore, we sought to investigate a large multi-center cohort of patients undergoing SI for treatment of post-Norwood RC – prior to Fontan completion – to evaluate acute procedural outcomes and clinical outcomes at mid-term follow-up.

Materials and Methods:

We performed a multi-institutional retrospective study of SV patients who underwent SI for RC between the Norwood operation and Fontan completion at 8 participating centers between 2007 and 2015. All co-investigators were members of the Pediatric and Congenital Interventional Cardiology Early Career

Society (PICES). Institutional Review Board approval was obtained at each participating center. All SV patients who underwent SI for RC following the Norwood operation and prior to Fontan completion were included in the study. Baseline clinical characteristics, including cardiac diagnoses, surgical history and prior transcatheter interventions were collected on all patients. Echocardiographic data, catheterization-derived hemodynamic data, and angiographic data before, during and after SI were collected. Echocardiograms used for data collection were those closest to the SI and preferably within 1 week before and 1 week after SI procedure. Additionally, the technique for SI was collected and categorized for each patient as prograde (percutaneous venous access with catheter course anterograde across the neo-aortic valve and arch), retrograde (percutaneous arterial access with catheter course retrograde across aortic arch), trans-carotid (carotid artery access via surgical cut-down and catheter course anterograde across aortic arch), or hybrid (surgical access to a major systemic artery such as the transverse arch).

A core laboratory was used for angiography review and assessment (Syngo Dynamics workplace (version: 8.0.0SPC), Siemens Medical Solutions USA Inc., Ann Arbor, Michigan, USA). A single interventional pediatric cardiologist at University of Iowa Children's Hospital (OA) reviewed all angiograms. The core lab was blinded to the rest of the data and outcomes. Using a standard calibration process, measurements of the aortic arch were made using the lateral angiographic projection. A Coarctation Index (CI) was calculated for each patient, utilizing the aortic diameter at the coarctation site (minimal diameter) and the diameter of the descending aorta at the diaphragm ($Aorta_{Coarctation}$ / $Aorta_{Diaphragm}$) before and after SI. Additionally, the type of RC was classified as either discrete or long-segment based on whether the length of narrowing is $\leq$3 mm vs. $>$3 mm respectively. The diameter of the nominal stent compared to the narrowest aortic diameter and descending aorta were also calculated. Angiographic assessment included potential intervention-related complications, such as aortic wall injury, stent malposition or embolization, and jailing of brachiocephalic arteries.

Procedural success was defined as a post intervention peak-to-peak gradient across the aortic arch gradient of ≤ 10 mmHg (3,14). Serious adverse events (SAE) were recorded and defined based on published literature on catheterization risk score for pediatrics (15). Hemodynamic compromise was

defined as hemodynamic instability requiring an intervention (for example, inotropic medication or cardiopulmonary resuscitation). Patient follow-up data was collected through the time of the Fontan completion, specifically including any re-intervention on the aortic arch and clinical outcomes.

Statistical Analysis

Data are presented as frequency with percentage for categorical variables and median with interquartile range (IQR) for continuous variables. Paired t-test and Wilcoxon signed-rank test were used to compare pre- and post-SI variables. Freedom from re-intervention and freedom from death or heart transplant was computed using Kaplan-Meier method. Analyses were performed using software SAS version 9.4 and statistical significance set at P-value <0.05.

Results:

A total of 33 patients met the inclusion criteria and comprised the study cohort (Table 1). The majority of patients (n= 29, 88%) underwent BA before SI; 21 of 29 underwent BA during a separate procedure and 13 patients during the same procedure as SI, of which 4 patients for the second time. Thirteen patients (39%) underwent SI between the Norwood procedure and superior cavopulmonary anastomosis (SCPA) while 20 (61%) underwent SI between SCPA and Fontan completion. The type of RC was discrete in 52% and long-segment in 48% of patients (Figure 1-A and B). The approach for SI was prograde in 21 patients (64%), retrograde in 5 (15%), hybrid in 5 (15%), and trans-carotid in 2 (6%).

Acute Outcomes

Successful SI was possible in 100% of patients based on our hemodynamic definition (Figure 1- C and D) although in one patient, initial stent embolized and another one was successfully placed. The median peak-to-peak gradient across the coarctation site improved from 20 (15, 24) to 0 (0, 2) mmHg following SI

(p<0.0001) (Figure 2-a). By echocardiography, median uncorrected peak instantaneous pressure gradients by Doppler decreased from 34 mmHg (20, 44) to 15 mmHg (5, 18) (p<0.0001) (Figure 2-b). There was no statistically significant change in the degree of atrioventricular valve regurgitation or systemic ventricular function after SI (Figure 3-a, 3-b). Angiographically, after SI, the median narrowest aortic arch diameter increased from 3.8 mm (3.3, 4.4) to 6.6 mm (6.0, 7.5) (p<0.0001) (Table 2). The median CI improved from 0.54 (0.43, 0.62) to 0.97 (0.89, 1.06) after SI (p<0.0001) (Figure 2-c, 2-d). The nominal stent diameters were approximately equal to the descending aortic diameter and twice the coarctation diameter (Table 2).

Procedural SAE were observed in 12 patients (36%). Hemodynamic compromise occurred in 7 patients, with 6 of the patients having undergone SI from a prograde approach and 1 from a retrograde approach. In 3 of these 7 patients, hemodynamic insult progressed into bradycardiac arrest requiring cardiopulmonary resuscitation. All patients were successfully resuscitated with no procedural mortality or need for initiation of extracorporial membrane oxygenation (ECMO) support. There was no association between timing of SI (before or after SCPA) and hemodynamic instability.

Other SAEs included blood loss requiring transfusion (n=3, 9%), AV block (eventually treated with pacemaker placement at the time of SCPA; n=1, 3%), access-related vascular injury (n=1, 3%) and stent embolization (n=1, 3%). In the single case of aortic stent embolization, the stent was subsequently affixed to the vascular wall (e.g. implanted) in the descending aorta and a second stent was successfully implanted across the coarctation site. No patients experienced angiographically-evident aortic wall injury.

Minor adverse events included jailing of the left subclavian artery, which occurred in 11 patients (33%). All patients had unobstructed flow into the left subclavian artery through the bare metal stent on post SI angiography. One patient (3%) had minor stent malposition (stent was not centered over the stenosis area) that did not affect the procedure outcome and 1 (3%) patient had transient junctional rhythm that

resolved spontaneously. There were 2 patients already on ECMO support at the time of SI. No peri-procedural complications occurred in this group, however, both patients subsequently died unrelated to the SI procedure.

Mid-Term Outcomes

During a median follow-up duration of 28.3 months (6.7, 44.5), freedom from death or heart transplant was 82%. Freedom from re-intervention on the aortic stent was 81.1% at 6 months, 72.1% at 12 months, and 43.3% at 24 months with a median time to re-intervention of 20.1 months (11.4, 40.3) (Figure 4). Amongst those patients not on mechanical support (ECMO) at the time of catheterization for SI, freedom from death or transplant was 85.1% during a median follow-up of 31 months (6.9, 51.4). Freedom from re-intervention was 81.7% at 6 months, 73.5% at 12 months, and 50.6% at 24 months with a median time for re-intervention of 24.6 months (11.4, 40.3). Of the 18 patients (54%) who underwent re-intervention, the indication was somatic growth in 9 (50%), in-stent stenosis in 3 (17%), re-stenosis in 3 (17%), and stent fracture in 3 (17%). Among the 3 patients with stent fracture, 2 had a significant gradient seen on echocardiogram and the third stent fracture was found incidentally on CXR. All patients with stent fracture underwent re-intervention with balloon angioplasty of the existing stent. In one case, stent integrity was lost following BA resulting in distal embolization of a stent fragment which was successfully removed percutaneously during the same procedure. The other 2 patients with stent fracture but intact integrity underwent successful BA without complications. Six patients (18%) underwent a second re-intervention, 2 (33%) for in-stent stenosis, 2 (33%) for re-stenosis, and 2 (33%) for somatic growth.

During the study period, 18 (55%) patients had undergone Fontan completion, 5 (15%) were awaiting Fontan completion, 2 (6%) were awaiting second stage palliation and 1 (3%) underwent cardiac transplantation secondary to severe atrioventricular valve regurgitation and progressive heart failure. In addition, mortality occurred in 5 (15%) patients unrelated to SI procedure with median time of 26 days (25, 146) from SI. Causes of death were multiorgan failure following cardiac arrest in 2, respiratory failure

in 1, intraoperative death during cavopulmonary anastomosis surgery in 1, and the last patient was electively made DNR secondary to poor candidacy for second stage repair in a patient with known genetic syndrome and extracardiac anomalies. Two subjects (6%) were lost to follow-up.

Discussion:

In this multi-center study of SV patients with recurrent coarctation treated with transcatheter stent implantation prior to Fontan completion, we demonstrated a high rate of technical success and procedural efficacy. Notably, SI for RC was associated with a significant rate of SAE, including hemodynamic compromise in 21%. As anticipated, re-intervention was common at mid-term follow-up, largely for purposes of stent dilation to match interval somatic growth. To our knowledge, this is the first multi-center collaborative to evaluate acute and mid-term outcomes of SI for RC in SV patients.

RC is a common cause of morbidity and mortality in SV patients after the Norwood procedure (3,5,6). Although typically attempted first, BA to treat RC is not uniformly acutely successful and often does not provide durable gradient relief. Studies have suggested a high success rate of BA but variable freedom of re-intervention (2,7,16). Factors found to contribute to successful BA were larger balloon size, lower initial peak-to-peak gradient and larger diameter of descending aorta in one study (7). Factors associated with higher rates of RC after BA included smaller patients and older age at the time of Norwood procedure (16). In our study, 88% of patients who ultimately underwent SI for RC had previously undergone BA, which is consistent with estimates from prior studies that 15-20% of patients would be non-responders to BA (7,16). This also suggested BA being the first line treatment of RC for most operators and SI would be considered if unsatisfactory BA results. Several possible mechanisms to explain the ineffectiveness of aortic BA include vessel recoil, vessel torsion (compared to true stenosis) and external compression. In these circumstances, SI is likely to provide improved procedural success, when compared to BA.

Surgical revision of the aortic arch is an alternative therapy for RC, either in lieu of BA, or following BA with unsatisfactory results. A recent study reviewed the surgical outcomes after RC repair including both single and biventricular repair. Although post-Norwood cases made up only a small portion of the study cohort (n=17), this sub-group responded satisfactorily to surgical re-intervention, with freedom from repeat re-intervention of 94% at a median follow up of 7.2 years (17). Despite the efficacy of surgical re-intervention, this approach carries inherent risks that are distinct from SI, including those related to repeat sternotomy, cardiopulmonary bypass, sternal wound, and deep tissue dissection. Although most of the post-Norwood cases included in this study were performed at the time of SCPA, thus avoiding an additional surgery, arch revision does add risks to the SCPA procedure, including the potential for greater support times, with the risk of inducing greater lung (inflammatory) pathology placing the new SCPA circulation at risk. Further, delaying relief of arch obstruction to the planned SCPA surgery could place the post-Norwood patient at risk for greater morbidity or mortality.

The most notable SAE in our cohort was hemodynamic instability, which was seen in 21% of patients. Importantly, this was most often seen using the prograde approach and is similar to the risk of hemodynamic compromise reported with BA using a prograde approach in single ventricle patients (8,13). The prograde approach, which typically involves femoral venous access and a catheter course across the tricuspid and neo-aortic valves to gain access to the aortic arch, has the advantage of utilizing femoral venous access, which is preferred to femoral arterial access since SI often requires a relatively large bore (6-8 French) sheath. However, because of the catheter/wire/sheath course, the tricuspid and neoaortic valves may be temporarily stented open, which can result in acute tricuspid and neoaortic valves insufficiency associated with significantly diminished ventricular ejection and inadequate systemic blood pressure and cardiac output. Additionally, the effect of stretching the atrioventricular node or atrial tissue could contribute to atrioventricular block and/or bradycardia which may worsen the resultant hypotension and low output (13). Therefore, a retrograde approach, carotid artery cut-down, or hybrid approach may reduce hemodynamic instability during SI, which may be beneficial especially in patients with pre-procedural evidence of depressed ventricular function or significant tricuspid valve regurgitation (18,19).

Other consideration includes advancing premounted stent without long introducer to avoid the additional stretching effect of the long sheath (13). Access-related vascular injury is another important SAE following SI, especially in patients with large bore arterial access (11,12). In our cohort, access related vascular injury was relatively uncommon, occurring in only 1 patient. This patient had pulse loss after the catheterization, without risk to the limb.

Over 50% of our study cohort required re-intervention during a relatively short follow-up period. This rate is higher than what has been reported with BA (39%) for a similar group of patients (2). Re-intervention following SI is partially anticipated as stents placed in small children invariably require dilation to match interval somatic growth. The intervals between dilation would be anticipated to increase over time, but early after implantation in small and young children, this interval would be expected to be rather short (months to a year or two). In our cohort, ~25% of patients required re-intervention because of somatic growth. Fortunately, stent dilation with BA is typically a straight forward procedure that requires smaller sheaths compared to SI, and therefore is typically performed from a retrograde approach, with a lower incidence of procedural hemodynamic instability and SAE (20). More importantly, however, we found that an additional 25% of our study cohort required re-intervention for in-stent stenosis, residual arch obstruction, or stent fracture. Both in-stent stenosis and stent fracture are recognized long-term sequelae following SI in congenital heart disease, not just for RC. Thus, close monitoring is recommended after SI in all CHD patients (21,22). These outcomes are less predictable than patient-stent mismatch due to somatic growth, and can be more challenging to manage, often requiring repeat stent implantation. Given our small sample size, we were unable to identify stent specific risk factors for development of in-stent stenosis or stent fracture.

An important consideration when treating recurrent coarctation in young patients is stent choice. The ideal stent would be ultimately dilatable to a diameter matching that of the typical adult aorta. In our cohort, 4 stents (12%) were not able to meet this ideal state. Historically these stents would require surgical transection or removal as patients reach adult size. More recently, in vitro and animal studies have shown the ability to intentionally fracture, or un-zip, small stents using high pressure balloons from a

percutaneous approach (23,24). Clinical data from late intentional stent fracture in the aorta, in either the coarctation or single ventricle populations, do not yet exist. Nevertheless, we conclude that in this cohort, while stents capable of dilation to adult aortic diameters are preferred, the use of medium diameter premounted stents may not be a critical limiting factor for SI in small children. Moreover, future availability of bioabsorbable stent platforms in this working range might shift practice, hypothetically allowing for similar procedural efficacy without the need for early or recurrent stent re-intervention (25). This population would be an ideal candidate group in which to study the applications of such technology.

An important limitation of the current literature on the treatment of recurrent coarctation is a lack of descriptive clinical outcomes following repeat balloon angioplasty or surgical repair, especially in single ventricle patients. Future studies including these outcomes, especially if able to directly compare medium-term results of SI, repeat BA, and surgical repair - for the treatment of RC in SV patients - would add greatly to the understanding of how to manage these complex and high-risk patients with recurrent aortic obstruction after the Norwood operation.

Limitations

The retrospective design, small sample size and short follow-up duration are the main limitations of this study. The indication for re-intervention was reported by the participating sites but subsequent re-intervention angiograms were not reviewed in the core lab. Other limitations include the heterogeneity of patient population and the broad number of different types of stents used. Nevertheless, the multi-center collaborative nature of this cohort may help to partially offset the limitations in statistical power. Other limitation includes the non-standardized approach of treatment that reflects the multi-center nature of this study.

Conclusion:

Stent implantation for treatment of recurrent coarctation in single ventricle patients prior to Fontan completion provides excellent acute relief of aortic arch obstruction. This includes those patients that demonstrated an inadequate response to balloon angioplasty alone. Procedural adverse events are common, especially intra-procedural hemodynamic compromise when utilizing a prograde approach, but did not result in the need for mechanical support or mortality. Arch re-intervention is common during mid-term follow-up. Long-term outcomes, including the fate of the aortic stent years beyond implantation, are necessary to study.

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FIGURES LEGENDS:

Figure 1: A- A discrete coarctation of the aorta and C- Post coarctation SI angiogram. B- Long segment coarctation of the aorta and D- Post SI angiogram. SI: Stent implantation.

Figure 2: a- Drop in peak-to-peak catheterization gradient post SI. b- Peak instantaneous echocardiogram gradient improvement on post SI. c- Angiographic improvement of the coarctation diameter post SI. d- Improvement of CI post SI. SI: stent implantation, PIG: peak instantaneous gradient.

Figure 3: a- Echocardiographic single ventricular function pre- and post SI. b- The degree of atrioventricular valve regurgitation pre- and post SI. AVVR: atrioventricular valve regurgitation.

Figure 4: Kaplan-Meier curve of freedom of Heart Transplant/ Death and Re-intervention.

Table 1: Baseline Characteristics of the cohort.

HLHS: Hypoplastic left heart syndrome, MA: mitral valve atresia, AA: aortic valve atresia, MS: mitral valve stenosis, AS: aortic valve stenosis, RV: right ventricle, LV: left ventricle, BT shunt: Blalock Taussig shunt, SI: stent implantation, SCPA: Superior cavo-pulmonary anastomosis, ECMO: extracorporeal membrane oxygenation.

Table 2: Angiographic and procedural details.