Tailored strategy to match anatomy and physiology with intervention can improve outcomes of symptomatic neonates with Ebstein anomaly

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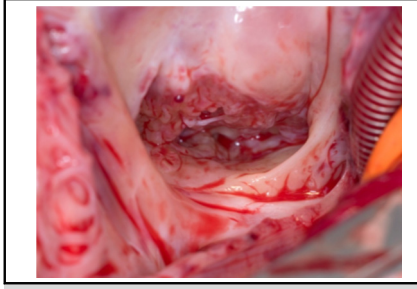
ABSTRACT

Objective: Neonatal presentation of Ebstein anomaly (EA) represents the most severe form of this condition. Despite significant advances, operative mortality remains high and management decisions represent a formidable challenge. We used a strategy aimed to match anatomy and physiology with type and time of intervention to increase survival.

Methods: We performed a review of all patients with fetal or neonatal diagnosis of EA managed at a single center between 2007 and 2020.

Results: Among 18 patients with EA, 8 underwent neonatal intervention. The most common indication included cyanosis and heart failure (8/8), end organ dysfunction (6/8), and maldistribution of cardiac output (6/8). Only 2/8 had antegrade pulmonary blood flow. Associated conditions included pulmonary regurgitation in 4/8, atrial tachyarrhythmia in 4, and a ventricular septal defect in 3. Three patients underwent initial stabilization with main pulmonary artery occlusion including bilateral pulmonary artery banding in 2. Five patients underwent biventricular repair with conversion to right ventricle exclusion in 2 cases. Three others underwent the Starnes procedure as initially planned. The median age at surgery was 10 days (range, 1-30) and median weight 2.6 kg (range, 1.9-4.0). The median duration of mechanical ventilation and intensive care unit stay were 9 days (range, 5-34) and 30 days (range, 15-100), respectively. Operative mortality was 1/8. At a median follow-up of 130 months (range, 5-146), there were no late deaths, and all survivors remain in functional class I and free of valvular reintervention.

Conclusions: Symptomatic neonates with EA can be effectively managed with good outcomes. Preoperative stabilization and choice of management pathway on the basis of anatomy and physiology can help reduce morbidity and mortality. (JTCVS Open 2022;12:344-54)



Ebstein anomaly of the tricuspid valve in a neonate.

CENTRAL MESSAGE

A tailored strategy to match anatomy and physiology with type and timing of intervention can improve outcomes of symptomatic neonates with Ebstein anomaly.

PERSPECTIVE

Surgical intervention for symptomatic neonates with Ebstein anomaly carries a significant operative risk based on the challenging physiology, technical demands, and the limited experience with this patient population. A management strategy based on anatomic features and physiology, preoperative stabilization, and recognition of the deleterious effect of RVOT obstruction might lead to increased survival rates.

Video clip is available online.

Neonatal presentation of Ebstein anomaly (EA) represents the most severe clinical form of this condition characterized by significant impairment in the function of the tricuspid valve, massive cardiomegaly, decreased effective antegrade

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Abbreviations and Acronyms
BVR = biventricular repair
EA = Ebstein anomaly
ECMO = extracorporeal membrane oxygenation
RV = right ventricle

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pulmonary blood flow, right heart failure, metabolic acidosis, as well as end organ dysfunction.[1,2] Although a significant number of patients can be managed with supportive measures to promote pulmonary blood flow and attain appropriate oxygen delivery during the early period until pulmonary vascular resistance decreases, others require an intervention to modify the pathophysiology during this critical period.[3-5] Despite significant advances in surgical technique and perioperative care, overall operative mortality for individuals who require an intervention remains very high and the decision regarding the optimal management strategy in consideration for a biventricular or a single ventricle management represents a significant challenge.[6-9] Effective surgical techniques to repair the tricuspid valve,[6,10,11] or to exclude the right ventricle (RV)[12,13] have been described, however, the risk remains considerable with either approach. As seen with other difficult choices in the management of newborns with congenital heart disease,[14,15] pushing a biventricular strategy in patients with right ventricular outflow obstruction has met with disappointing results[16,17] and raises the question of selection criteria or the need for modifications with this approach.

Moreover, in contradistinction to other clinical conundrums, the management of these critically ill newborns has remained problematic in no small measure, because of the low volume seen at individual centers. Therefore, it has taken a long time to solve essential questions regarding the optimal management pathway, timing of intervention, and other technical aspects.[8] We performed a review of our experience on the basis of a strategy that considers anatomic (tricuspid valve morphology and pulmonary atresia) as well as functional variables (antegrade pulmonary blood flow, pulmonary regurgitation, right ventricular pressure, direction of flow across the patent ductus arteriosus) to inform the management and improve the outcomes of this complex group of patients.

METHODS

Between 2007 and 2020, 18 consecutive patients with a fetal or neonatal diagnosis of EA were managed at our center. All diagnoses were made using echocardiogram with standard criteria, and all fetal and postnatal studies were reviewed by 2 senior cardiologists (G.B., M.A.B.). Diagnosis of EA was on the basis of the apical displacement of the septal and/or posterior leaflet of the tricuspid valve with obvious atrialization of the RV. The presence of additional cardiac defects, namely atrial and ventricular septal defects, pulmonary stenosis or pulmonary atresia, patent ductus arteriosus, and left ventricular hypoplasia as well as the presence of antegrade flow across the native pulmonary valve was documented. The diagnosis of anatomic pulmonary atresia was made in the presence of a muscular or membranous plate on 2-dimensional images with complete absence of antegrade flow or regurgitation through this area. Functional pulmonary atresia was described as the presence of well formed pulmonary valve leaflets, which did not open and therefore did not exhibit any antegrade pulmonary blood flow or the presence of a normal-appearing pulmonary valve with a trace of insufficiency but no antegrade flow.

Patients with corrected transposition of the great arteries and other cardiac anomalies associated with Ebstenoid malformation of the tricuspid valve were excluded. Operative mortality was defined according to the Society of Thoracic Surgeons Congenital Heart Surgery Database criteria. Primary outcome measures included: 1) operative and late mortality, 2) need for reintervention, 3) perioperative extracorporeal membrane oxygenation (ECMO) support, and 4) need for permanent pacemaker.

Follow-up was obtained by direct contact with the primary cardiologist as of July 2020. The study was approved by the institutional review board (study 711848-11; April 6, 2015) and need for consent was waived.

RESULTS

Of the 18 patients in this cohort, 16 patients presented with moderate to severe clinical signs. Eight of these were medically managed, allowing eventual closure of the patent ductus arteriosus and progression of antegrade pulmonary blood flow, while exhibiting oxygen saturations above 80%. These patients were subsequently discharged, and all achieved a biventricular circulation. The remaining 8 patients received an operative intervention, which consisted of right ventricular exclusion with a fenestrated patch and a systemic to pulmonary artery shunt (modified Starnes) or a biventricular repair (BVR; Figure 1, Table E1).

The most common indications for intervention were progressive and/or severe hypoxemia, defined as a partial arterial oxygen pressure (Pao_2) of <30 mm Hg with mechanical ventilation, and receiving supplemental oxygen and nitric oxide. Additional criteria for intervention included persistent ductal dependent pulmonary blood flow (beyond a week) as well as heart failure characterized by the presence of pleural effusion, ascites and/or anasarca, maldistribution of cardiac output, persistent lactate elevation, and end organ dysfunction. Nearly half of the patients exhibited new onset of arrhythmias, most commonly supraventricular tachycardia. All patients met more than 2 criteria for intervention.

Characteristics of the cohort are shown in Table 1. These characteristics are similar to the previously published national benchmark study, including age and size at first intervention.[18] However, in our cohort most had a prenatal diagnosis, and a greater proportion of genetic abnormalities was observed, including cri du chat, trisomy X, and other chromosomal deletions. Associated anatomic diagnoses were common, including an atrial septal communication

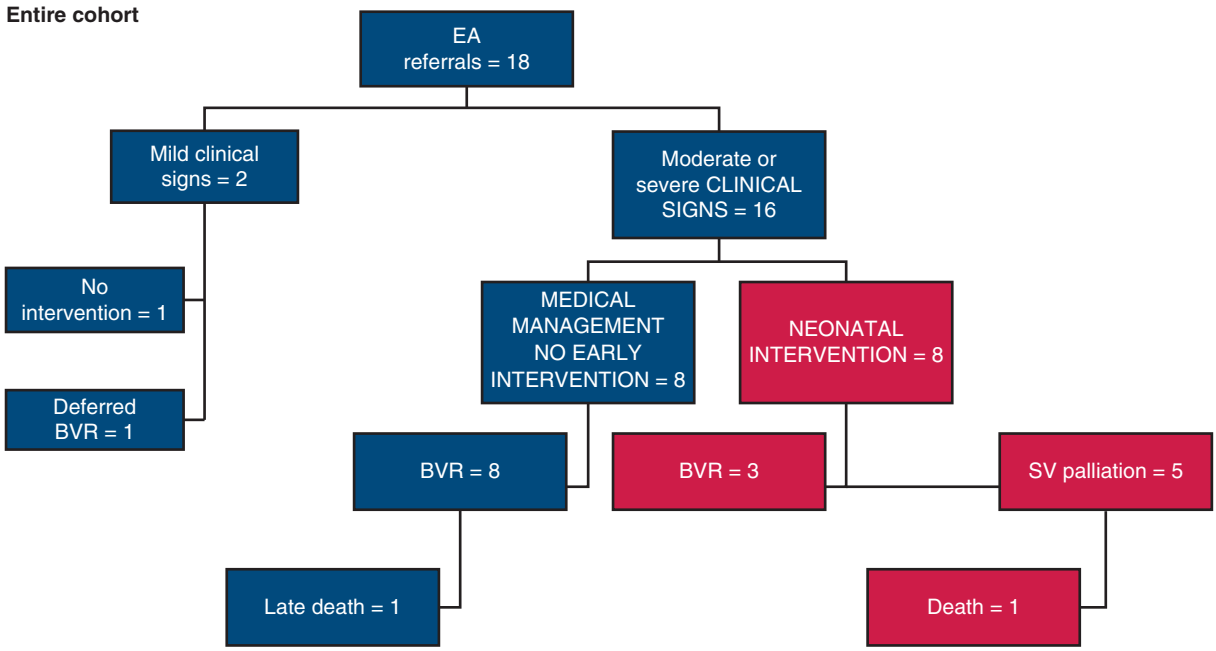


FIGURE 1. Entire cohort and management pathway. *EA*, Ebstein anomaly; *BVR*, biventricular repair; *SV*, single ventricle.

in all patients, a ventricular septal defect in nearly half, and a patent ductus arteriosus in all but 1 patient. Anatomic pulmonary atresia was documented in 1 patient, whereas only 2 patients had evidence of antegrade pulmonary blood flow on echocardiogram leaving the diagnosis of functional pulmonary atresia for the remaining 5 patients. Considering traditional risk criteria, all patients exhibited a cardiothoracic ratio >0.8 on chest radiograph, and a Great Ormond Street (GOS) score >1.1, which, in association with cyanosis, placed all patients in a high-risk category with near 100% mortality.[1,2]

Regarding the preoperative patient condition (Table 2), a large proportion of patients received preoperative mechanical ventilation and a prostaglandin infusion. A significant number also presented evidence of end organ dysfunction, most commonly renal, which was evident by persistent and/or progressive creatinine elevation associated with low urine output. As shown in Figures 2 and 3 patients underwent an initial stabilizing intervention, within the first 48 hours of life, to optimize the hemodynamics in preparation for a more definitive intervention with cardiopulmonary bypass. These patients had a median lactate of 6.7, and as high as 12 mmol/dL, due to circulatory compromised largely associated with a circular shunt in the presence of significant tricuspid regurgitation, pulmonary valve regurgitation, and a patent ductus arteriosus. The stabilizing interventions included clip occlusion of the pulmonary valve in 3 patients, 1 of whom also received a bilateral pulmonary artery banding. These interventions were aimed at elimination of the circular shunt and control of the pulmonary blood flow to facilitate the overall balance of distribution of cardiac output, which commonly led to normalization of lactates and a prompt recovery of end organ dysfunction. The median preoperative lactate at the time of the main intervention was 1.5 mg/dL.

TABLE 1. Baseline characteristics of the cohort

	Value
Age, d	10.0 (1-30)
Male sex, %	54.5
Weight, kg	2.6 (2.0-4)
Gestational age, wk	37.0 (35-40)
Prenatal diagnosis, %	87.5 (7/8)
Genetic abnormality, %	37.5 (3/8)

Data are presented as median (range).

Surgical Intervention

Choice of surgical strategy was on the basis of a combination of anatomic and physiologic variables. In broad terms, a BVR was planned in the presence of a functional tripartite RV with a patent outflow and an estimated RV pressure >35 mm Hg. Patients left the operating room with a BVR unless the residual tricuspid regurgitation was greater than moderate, the tricuspid valve repair was not deemed durable, and/or there was inadequate effective pulmonary blood flow associated with severe hypoxemia. In contradistinction, patients with a functional unipartite RV, with poor function and muscular pulmonary atresia were planned for RV exclusion (Figure 3). Five patients were

TABLE 2. Preoperative variables

	Value
ECMO support, %	0 (0/8)
Preoperative ventilation, %	87.5 (7/8)
PGE1-dependent, %	62.5 (5/8)
Cyanosis, %	100 (8/8)
Circular shunt, %	50 (4/8)
Shock, %	12.5 (1/8)
Resolved shock, %	50 (4/8)
Organ dysfunction, %*	87.5 (7/8)
Peak lactate, mmol/dL	6.0 (3.5-12)
Stabilizing intervention, %	37.5 (3/8)
RV pressure > 35 mm Hg, %	62 (5/8)

Data are presented as median (range). *ECMO*, Extracorporeal membrane oxygenation; *PGE1*, prostaglandin E1; *RV*, right ventricular. *Does not include hypoxemia.

scheduled to have a BVR whereas right ventricular exclusion was planned in 3. Among those planned for a BVR, 1 patient underwent a conventional BVR creating a bileaflet tricuspid valve with commissural plication of as well as a Sebening stitch.[6] The remaining individuals underwent a Cone reconstruction (Video 1) with circumferential leaflet coverage and posterior annular plication, on the basis of the original description of the technique.[10] However, this was modified to avoid the plication of the atrialized portion of the RV as well as a circumferential annuloplasty, to permit future growth of the tricuspid valve.[11] Two of these patients had an intraoperative conversion from BVR to a right ventricular exclusion because of inadequate tissue to pursue a Cone repair or the reconstruction was deemed nonsatisfactory because of moderate to severe residual regurgitation. Therefore, 3 patients left the operating room with a BVR whereas 5 received a single-ventricle palliation, which consisted of a right ventricular exclusion with a systemic to pulmonary artery shunt (Figure 4). The source of pulmonary blood flow was a 3.5-mm right modified Blalock-Taussig shunt in 4 patients, whereas a central shunt was used in a patient with a chromosomal anomaly, severe branch pulmonary artery hypoplasia, and left diaphragmatic eventration (Table 3).

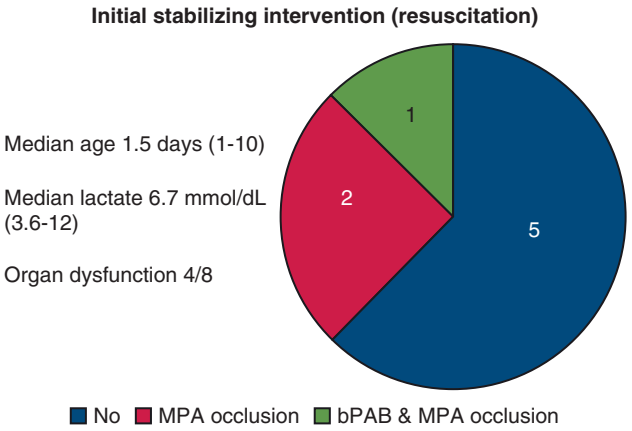


FIGURE 2. Initial interventions to optimize the physiology. *MPA*, Main pulmonary artery; *bPAB*, bilateral pulmonary artery banding.

The median aortic crossclamp was 51 minutes, and the median cardiopulmonary bypass duration was 110 minutes. Analysis of the perfusion conduct during the operative intervention revealed that although the duration of cardiopulmonary bypass was not significantly different for each strategy, patients who underwent BVR had a median period of myocardial ischemia approximately 20 minutes longer compared with those who underwent single-ventricle palliation, even if intraoperative conversion had occurred. This was likely a reflection of the fact that the decision to pursue conversion was made relatively early during the operation and while attempting to minimize the period of myocardial ischemia in these vulnerable newborns. A delayed sternal closure was performed in nearly all (6/8) patients.

Outcomes

As shown in Table 4, there was a single death in 8 patients. This was a low birth-weight neonate with EA and trisomy X, who had low Apgar scores, pulmonary atresia, hypoplastic central pulmonary arteries associated with moderate lung hypoplasia, and a diaphragmatic eventration, who in the early phase of this experience underwent right ventricular exclusion and placement of a 4-mm central shunt because of anticipated difficulty in providing enough pulmonary blood flow. Despite appropriate hemodynamics and gas exchange in the first 24 hours, the patient exhibited acute decompensation secondary to ectopic atrial tachycardia which required cardiopulmonary resuscitation with extracorporeal support and subsequently exhibited maldistribution of cardiac output, acute kidney injury, and subsequently expired on postoperative day 37.

Two patients received postoperative mechanical circulatory support. One of these just was described. A second patient with a birth weight of 2.3 kg and cri du chat underwent initial stabilization with clip occlusion of the pulmonary valve because of maldistribution of cardiac output associated with severe tricuspid regurgitation and a circular shunt, followed by right ventricular exclusion with a 3.5-mm right modified Blalock-Taussig shunt. Early in the postoperative period he presented with acute hemodynamic decompensation secondary to supraventricular tachyarrhythmia for which he received emergency ECMO cannulation. After 48 hours of support, the patient was successfully weaned, then discharged and eventually underwent Fontan completion.

Unplanned cardiac reoperations occurred in 2 patients. One patient who received ECMO support underwent right ventricular reduction because of progressive RV dilatation

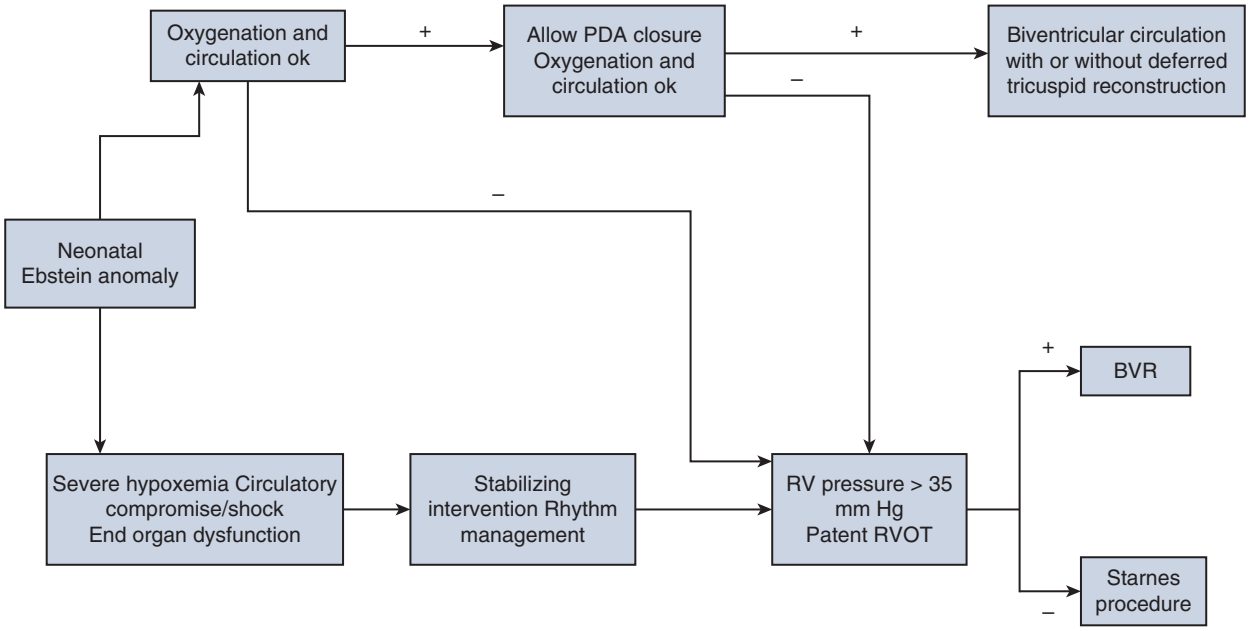


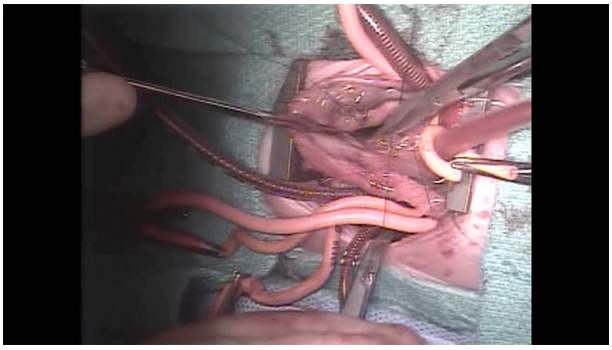
FIGURE 3. Management algorithm. +, Yes; −, no; *pDA*, patent ductus arteriosus; *BVR*, biventricular repair; *RV*, right ventricle; *RVOT*, right ventricular outflow tract.

after the Starnes procedure, whereas another required evacuation of cardiac tamponade in the immediate postoperative period. Two patients exhibited postoperative worsening of the preoperative acute kidney injury (creatinine >2.0 from baseline and/or urine output <0.5 mL/kg/h for >12 hours), but did not require replacement therapy. There were no shunt-related reoperations or reinterventions and no permanent pacemaker implantations. At a median follow-up of 130 months (range, 5-146), there were no late deaths, and all survivors remained in functional class I and free of valvular reintervention (Figure 5).

DISCUSSION

Neonates with EA exhibit a complex physiology that is multifactorial, including the presence of severe tricuspid valve regurgitation, and physiological elevation pulmonary vascular resistance of the newborn. This is aggravated by abnormal lung development and pulmonary hypoplasia, with reduced generation of alveoli and alveolar simplification.[19] Moreover, in cases of EA, a myopathy of the right ventricular muscle can add to the inability to achieve effective antegrade pulmonary blood flow. Ineffective filling of the left ventricle and the frequent association of supraventricular arrhythmias can further aggravate a very precarious circulatory balance, which, in the presence of pulmonary regurgitation and a circular shunt could become unmanageable. Not surprisingly, the reported mortality rate for these symptomatic neonates remains very high.[1,2,18,20] In addition, the severity of the circulatory compromise can become evident in utero, with signs of heart failure, hydrops, and even fetal demise. These prenatal data convey a grim prognosis and has frequently led to a high rate of termination, further compromising the outlook of patients with this condition.[5,21]

Although the ideal management strategy for these symptomatic neonates might be supportive allowing time for the physiologic decrease in pulmonary vascular resistance, this might not be attainable in some patients, particularly in those who present with anatomic obstruction of the RV outflow tract, those with RV dysfunction, or in those who exhibit circulatory compromise associated with arrhythmias or the presence of a circular shunt. In this cohort of 18 neonates, approximately half of those with clinical signs received medical management and achieved a biventricular circulation. This compares favorably with the Pediatric Health Information System (PHIS) cohort of >400 patients



VIDEO 1. Cone procedure and ventricular septal defect closure on a neonate with Ebstein anomaly. Video available at: https://www.jtcvs.org/article/S2666-2736(22)00358-8/fulltext.

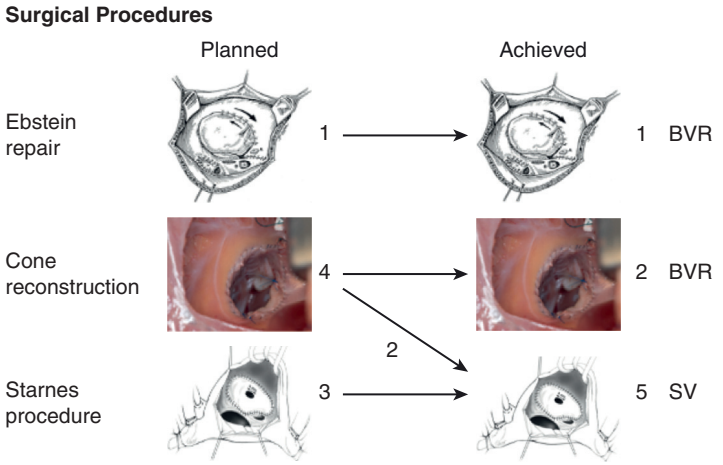


FIGURE 4. Planned surgical interventions versus final intervention. *BVR*, Biventricular repair; *SV*, single ventricle reconstruction.

of whom nearly two-thirds were managed medically with a 22% early mortality.[20] Although this could be attributed to an era effect, this difference in mortality might raise questions about the selection criteria to pursue medical management and perhaps the possibility that some of these newborns might have benefited from a timely surgical intervention.

The other half of our cohort underwent neonatal intervention, which consisted of single ventricle palliation or BVR with a 2:1 ratio. The anatomic characteristic of the tricuspid valve, contractility of the RV (estimated right ventricular pressure >35 mm Hg in the absence of a ventricular septal defect), patency of the right ventricular outflow tract, direction of flow across the patent ductus, as well as patient's condition at the time of intervention were important considerations when planning for the type and timing of the surgical intervention. One strategy was to achieve a biventricular circulation on the basis of the repair of the tricuspid valve[6] whereas alternatively newborns with less favorable anatomy usually underwent a right ventricular exclusion procedure or insertion of a systemic to pulmonary artery shunt alone if the predominant issue was hypoxia in the absence of heart failure. Using the Society of Thoracic Surgeons Congenital Heart Surgery Database as a reference allowed us to ascertain the overall applicability of our observations against the benchmark experience with surgical management of EA in neonates.[18] Although a greater incidence of prenatal diagnosis and chromosomal anomalies were evident in our cohort, their effect remains unclear. Although prenatal diagnosis can lead to a higher level of preparedness, particularly for those with ductal-dependent pulmonary circulation, it also has led to an increased frequency of interruption of pregnancy,[5,21] therefore, the overall benefit of prenatal diagnosis on patient survival remains debatable. Additionally, an increased incidence of chromosomal anomalies has conferred an additional level of risk when it comes to outcomes in these complex newborns,[22] particularly when this is associated with low birth weight. This has been documented by Curzon and colleagues,[9] who reported that low birth weight newborns with EA who underwent a systemic to pulmonary artery shunt had a sevenfold increase in mortality. Although the median weight in our cohort was 2.7 kg and as low as 1.9 kg, weight did not have a significant effect on outcome. We would urge caution about this observation that perhaps could be explained by the deliberate measures taken to optimize overall

TABLE 3. Intraoperative variables

	Value
Preoperative lactate, mmol/dL	1.8 (2.0-1.0)
Aortic crossclamp time, min	51 (24-105)
CPB time, min	110 (75-192)
Shunt size, mm	3.5 (3.0-4.0)
Central shunt, %	12.5 (1/8)
Open sternum, %	75 (6/8)

Data are presented as median (range). *CPB*, Cardiopulmonary bypass.

TABLE 4. Surgical outcome measures

	Comment
Operative mortality, %	1/8
Postoperative mechanical support, %	2 Occurrences of E-CPR; rhythm-related
Unplanned cardiac reoperation, %	1 Case of RV reduction and 1 case of tamponade
Reoperation for shunt placement or revision, %	None
AKI, %	25 (2/8)
Permanent pacemaker, %	None

E-CPR, Cardiopulmonary resuscitation with extracorporeal support; *RV*, right ventricle; *AKI*, acute kidney injury.

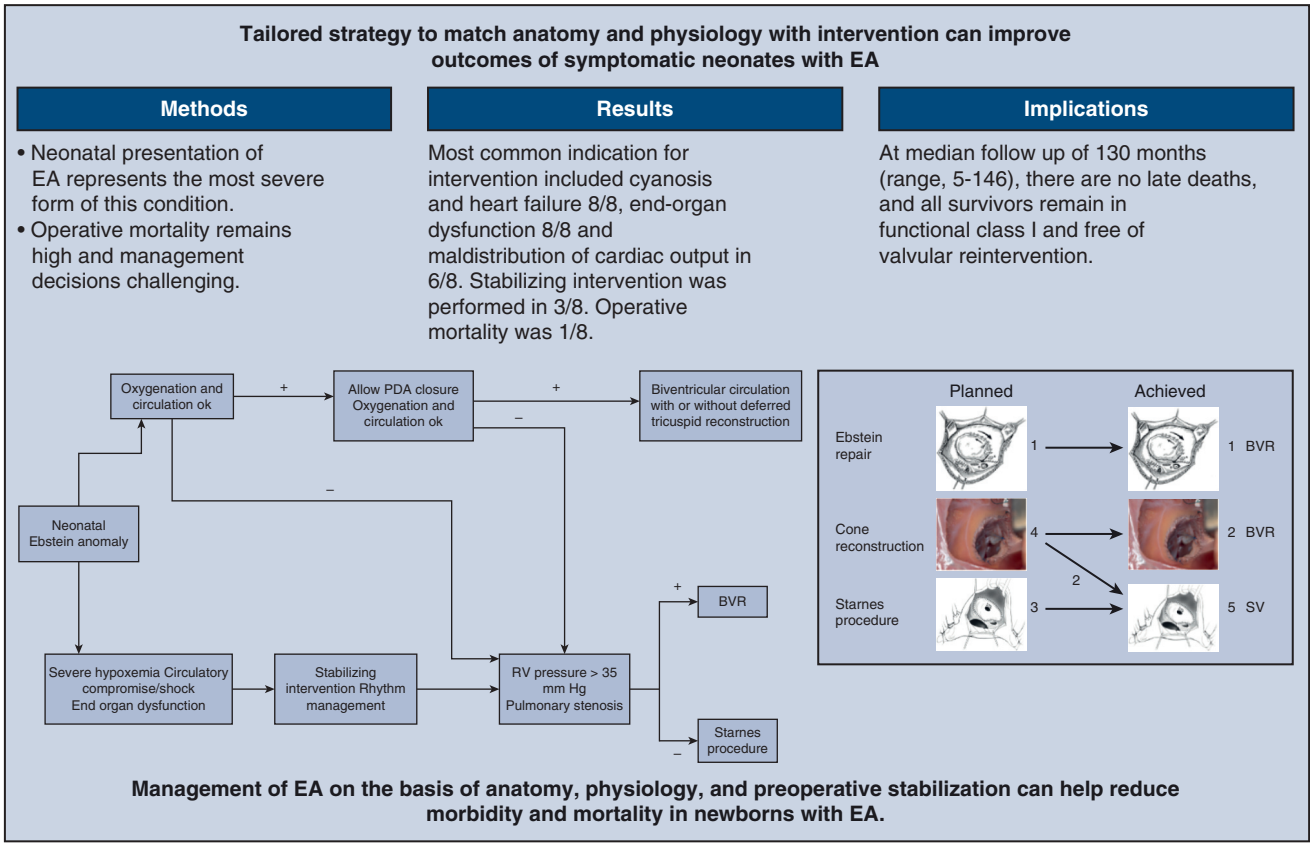


FIGURE 5. Graphical abstract. *PDA*, Patent ductus arteriosus; *BVR*, biventricular repair; *RV*, right ventricle; *SV*, single ventricle reconstruction.

patient condition and end organ function before surgery, as well a relatively short period of myocardial ischemia and a conservative management strategy in newborns with pulmonary atresia.

Unfortunately, one of the biggest challenges we confronted was the high incidence of perioperative arrhythmias, which were particularly destabilizing, and led to cardiopulmonary resuscitation with extracorporeal support in 2 cases. Management of arrhythmias has proven to be particularly difficult in patients with a circular shunt and/or during the postoperative period, nevertheless no preemptive treatment strategies have been described, nor were used at our center to address this issue.

As expected, the overall preoperative condition had significant influence on the overall outcome of these patients. Approximately three-quarters of the patients exhibited inadequate circulation with significant lactate level elevation and important end organ dysfunction preoperatively. Directed interventions to eliminate a circular shunt[23,24] and/or balance the circulation by controlling pulmonary blood flow proved to be life-saving and had a profound salutary effect, allowing patients to arrive at the main intervention in an elective fashion after optimization of organ function had occurred. It should be noted that in patients with anatomic pulmonary atresia creation of pulmonary insufficiency by perforation of the pulmonary valve plate would be associated with the possibility of a circular shunt and therefore should be avoided. Although bilateral pulmonary artery banding might seem completely counterintuitive, it has become increasingly apparent that many patients who present with a circular shunt and severe volume overload might be affected by maldistribution of cardiac output, extreme systemic venous desaturation, and coronary perfusion issues, which ultimately contribute to unremitting shock. It has been our observation that when the circular shunt is eliminated, Pao_2 levels can rise above 35 mm Hg and therefore create the opportunity to balance the pulmonary blood flow and improve coronary and systemic perfusion. This observation has been replicated by Hasegawa and colleagues[25] in a patient with prenatal diagnosis of severe hydrops, and is similar to the initial intervention described in neonates who present in shock with delayed diagnosis of a ductal-dependent systemic circulation.[26]

Alternatively, ECMO support can provide the necessary stabilization, while avoiding the adverse effects associated with extreme ventilatory measures and suboptimal

perfusion, particularly if surgery is anticipated in the immediate future. Success with preoperative circulatory stabilization has been previously reported, including the successful management of a newborn with a significant degree of hydrops at birth.[27,28]

As the management of these sick neonates continues to improve, traditional risk criteria to predict outcomes like cardiothoracic ratio on chest x-ray and GOS echocardiographic score has been overcome, making predictions quite difficult. New imaging modalities that hold promise include lung volumetric calculation of the lung parenchyma using magnetic resonance imaging as well as evaluation of the pulmonary artery size and direction of flow.[29,30]

Over the past 30 years, distinct surgical approaches have been used largely on the basis of anatomic variables including the size of the tricuspid valve, the size of the functional (nonatrialized) right ventricular cavity, and the presence of pulmonary atresia.[1,12] It has been clearly shown that pulmonary atresia confers a twofold increase in mortality after BVR[16] and should be considered a significant prognostic factor when it comes to deciding the type of intervention. More recently, physiologic inferences using echocardiogram suggest that an estimated RV pressure >30 mm Hg and antegrade flow across the RV outflow tract and pulmonary valve are associated with better outcomes after BVR.[13] In our cohort, we used these variables along with a careful consideration for preoperative patient condition to plan on a management strategy we believed would be the most reproducible and likely associated with survival.

Although the strategy of BVR has been traditionally on the basis of the creation of a double-orifice valve with some partial leaflet attachment and rotation as well as augmentation and annuloplasty, significant improvements were achieved with a better understanding of the plane of coaptation and management of the right ventricular outflow obstruction. Moreover, the introduction of the Cone reconstruction has improved the reproducibility of the tricuspid valve repair even in the newborn, having a favorable effect on outcomes.[10,11,28] Additionally, successful conversion from RV exclusion to BVR has been described, raising the option of a staged approach to mitigate the additional challenge of BVR in the newborn.[31]

CONCLUSIONS

Although clinical presentation of EA in the neonate is associated with life-threatening physiology, an initial intervention aimed at physiologic stabilization and recovery of end organ function can have a favorable effect on outcomes, mitigating morbidity and overall mortality. The choice of management pathway between right ventricular exclusion versus biventricular intervention should be on the basis of anatomic and physiologic variables rather than on arbitrary anatomic criteria. Risk markers traditionally associated with a poor outcome are no longer valid and new predictors should be identified to better inform decisions and counsel parents about the management options and their likelihood of success in patients with this complex form of congenital heart disease.

Webcast

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Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: Ebstein, neonatal, tricuspid valve, surgery

Discussion

Presenter: Dr Christian Pizarro

Dr Christian Pizarro *(Wilmington, Del)*. I'll entertain any questions. Thank you.

Dr Richard Ohye *(Ann Arbor, Mich)*. Thanks, Christian. Really fantastic results with a very, very difficult group of patients. I have a couple of questions based upon your slides. When we think about these—as a group of patients—they tend to be those kids that do well on prostaglandin and can be weaned and go home. There are those that can't be weaned from prostaglandin, and they usually fall into 2 categories, either because of cyanosis or because of cyanosis and heart failure. In those kids that fail because of cyanosis, we can usually shunt them and let them go home and come back and fight another day. I saw that none of your patients were like that. Was it just bad luck with your patients, or do you prefer this sort of more aggressive initial step during the neonatal period to decide whether you're going to go single or 2 ventricles?

Dr Pizarro. That's a great point, Rick, and perhaps a little bit of the former. The thing is you could see a lot of these patients had an organ dysfunction, and I think that our threshold to intervene was based not only in the fact that the patients remained blue, but the fact that they had actually a progressive rise in their creatinine, the urine output was not good, the lactate was trending up, and that really prompted us to intervene.

Dr Ohye. Okay. Thank you. On your slide that said, I think, it was initial stabilization intervention. I noticed that some of the patients actually decreased in their pulmonary blood flow with things like pulmonary banding and occlusion of the main pulmonary artery. It's a little bit counterintuitive, and I just thought maybe you could fill us in a little bit on that management strategy.

Dr Pizarro. You're absolutely right, and I think that this is something that I'm glad you pointed out on this particular slide, which I believe is probably one of the most important lessons that were learned in the management of these patients. I think that traditionally, we believed these patients are extremely blue and challenged just because of ineffective pulmonary blood flow, which I think is probably half

of the story. I think that it's been our experience that when we control, for example, severe pulmonary insufficiency in those patients with a ductus that is open and have a circular shunt. We ended up with Po_2s above 40, and I think that there is a component of maldistribution of cardiac output, which when we banded some of those branch pulmonary arteries, much like a hybrid, has resulted in a very prompt ability to resolve the hyperlactatemia, improve oxygen delivery, and those patients get better pretty quickly. So obviously something that needs to be tailored according to what the patient is telling us.

Dr Ohye. Okay, great. I also noticed in your conclusion slides where you said the criteria for poor outcome are probably not applicable in the current era. As you pointed out, most of your patients would have been predicted not to do well. So, I know there's only 1 death, but can you tell us anything about what you think are potential criteria for poor outcome?

Dr Pizarro. Only 1 death didn't help us to risk-stratify anything, but I think that overall, the GOS Score and the cardiothoracic ratios you pointed out, those patients—none of them would have survived in this particular cohort. I think that we ought to be very careful about making inferences about the potential prognosis on the basis of those old criteria. I think that nowadays, it seems to me that coexisting rhythm disturbances are incredibly challenging to manage and very destabilizing and perhaps something that should be included in any score. And the other thing is perhaps volume measurement with MRI, which I've seen that we've had patients with predictive volume less than 35% who have survived, but it seems like less than 30 is extremely difficult to get these patients through.

Dr Ohye. Thanks. I've had a couple patients where we patched out their tricuspid valve sort of in a supra-annular position and then went back—do that to allow for continued growth, and then went back and did a repair on their tricuspid valve. Have you had any experience with that?

Dr Pizarro. That's a great point. No, we haven't. We have entertained that a couple of times, and I think when we had discussion with the parents, they really had not been interested in pursuing an invention that might be potentially more morbid in the short-term and have some complications rather than taking a very simple, predictable intervention which would be a second stage. I think that's a great idea now that we have a good tool to repair those valves. It would be something that we should entertain, and I think that probably something that should be done sooner rather than later. So, we don't end up with a valve that has been subjected to a very limited amount of pulmonary blood flow and therefore has become small.

Dr Ohye. I think we probably have time for 1 more quick question before our 3 minutes are up. Your 1 patient where you did an RF perforation. I know that I've always been sort of afraid to balloon the pulmonary valve or do an RF perforation, getting sort of a circular shunt. So, what were your thoughts on that, and how did that patient do?

Dr Pizarro. Actually, the patient ended up in the cath lab without our knowledge. And there was a fair bit of enthusiasm. The patient didn't do well, and we ended up rescuing that patient. And that patient actually had a reintervention and I think that it didn't work as it was intended, and it was just probably an overoptimistic approach to this particular patient.

Dr Ohye. So still a bad idea?

Dr Pizarro. Yes.

Dr Ohye. Alright. Thanks, Christian. I know we're going to do a little bit of a live Q and A now, so I appreciate your time.

Dr Pizarro. Thank you for your comments.

TABLE E1. Clinical cohort evolution

Patient	Age	Weight	Gest age	Chro abn	Mech vent	VSD	Organ dysfx	PI	Init pall	BVR	Survival
1	30	1.9	35	Yes	Yes	Yes	Yes	No	No	Yes	Yes
2	2	2.7	37	No	Yes	No	Yes	Yes	No	Yes	Yes
3	20	2.3	36	No	Yes	No	Yes	Yes	Yes	No	Yes
4	5	2.7	36	No	Yes	No	Yes	Yes	Yes	No	Yes
5	13	3.2	38	No	Yes	Yes	No	No	No	Yes	Yes
6	10	2.3	35	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
7	1	2.8	38	Yes	Yes	No	Yes	No	No	No	No
8	6	4	40	No	No	No	No	No	No	No	Yes

Gest age, Gestational age in weeks; *Chro abn*, chromosomal abnormality; *Mech vent*, mechanical ventilation; *VSD*, ventricular septal defect; *dysfx*, dysfunction; *PI*, pulmonary insufficiency; *Init pall*, initial palliation; *BVR*, biventricular repair.