Hypoplastic Left Heart Syndrome: The Giessen Approach – History, Technique, and Results

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28.1 Introduction

Patients with small left heart belong to a spectrum of a wide variety of possible combinations of hypoplastic heart structures. The treatment of newborns with hypoplastic left heart syndrome (HLHS) follows a well-established classical three-step algorithm for most institutions worldwide [1–4]. In Giessen, the hybrid approach was developed as a primary palliation for newborns with HLHS and later on for patients with hypoplastic left heart complex (HLHC). The hybrid procedure has moved from a rescue approach to an alternative modality of a Norwood palliation [4–7]. The "Giessen hybrid" stage I consists of surgical bilateral pulmonary artery banding (bPAB) combined with percutaneous stenting of the arterial duct and atrial septum manipulation, if necessary. The lessons learned by the hybrid strategy for the treatment of HLHS, HLHC, and variants have added a novel impulse for treating selected patients with cardiovascular failure beyond the neonatal period [8–10]. In our center meanwhile all types of HLHS and variants are treated with the modified Giessen hybrid strategy [4, 11]. Since June 1998 almost 200 patients received the Giessen hybrid stage I procedure as an initial approach. The physiological objectives of the hybrid approach are similar as for the classical Norwood procedure by alternative techniques in controlling pulmonary blood flow, whereas unobstructed systemic perfusion is maintained via an open arterial duct. This strategy involves off-pump bilateral pulmonary artery banding (bPAB) and interventional stenting or continuous prostaglandin therapy of the ductus arteriosus mostly, but not exclusively performed in the neonatal period (hybrid stage I). Aortic arch reconstruction using cardiopulmonary bypass combined with a superior cavo-pulmonary connection summarized as comprehensive stage II or as indicated a biventricular correction

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is deferred until the age of 4–8 months [6, 10]. In our institution hybrid therapy has initially been proposed to overcome obvious drawbacks of the classical Norwood operation and aims to improve survival and outcome for these patients in a less invasive way [4, 7]. The hybrid approach could be established as a highly effective treatment in particular for newborns with cardiovascular collapse and even for premature babies or neonates to small for gestational age [4].

In recent years hybrid treatment has moved to an alternative modality in a growing number of institutions globally but usually applied to high-risk patients in comparison with the classical Norwood palliation so far [12–15]. Therefore, it has to be emphasized that there are substantial differences in the patient selection, the operative and medical treatment strategies, and the detailed further management of the patients who undergo hybrid palliation with an impact on early and late outcomes. The presented data of hybrid stage I therapy performed for all types of HLHS, HLHC, and variants was applied in a standard manner with very few variations based on our learning curve and due to novel developments of material for duct stenting and IAS manipulation [4, 7, 10, 11]. Within the last decade, the surgical technique of bilateral pulmonary banding was changed, as described at first by Galantowicz et al. [3]. In addition, manipulations of the atrial septum were perfromed if necessary.

28.2 Giessen Hybrid Features

Since in Giessen in June 1998, the first HLHS neonate was treated by bPAB as a rescue approach; further 192 patients received a hybrid stage I approach as an initial palliation until October 2015. The first patient, Brandon, meanwhile 17 years old, was borne with HLHS and unrestricted atrial septum defect. After a couple of postnatal days, he was admitted to our institution in a cardiogenic shock with lactate acidosis due to pulmonary runoff and systemic low cardiac output. By utilizing the hybrid approach with first bPAB, he entirely recovered and received consecutively in the same year the first comprehensive stage II operation worldwide followed by Fontan completion two years later [10].

Considering the retrospective analysis of our experience with hybrid stage I over the last 15 [4, 7] nowadays 17 years [11], three groups of patients could be differentiated, those with the postnatal option of a univentricular palliation (HLHS-group I) or biventricular repair (HLHC-group II) and a small group of patients, who received hybrid stage I procedure for primarily listing to cardiac transplantation or for compassionate therapy in agreement with the parents decision (group III). Additionally, retrospective data collection included postnatal variables and admission, operative and postoperative variables, as well as follow-up information obtained during the 17-year observational period.

Based on the institutional experience, an admission of each patient is classified concerning anatomic features and risk factors. HLHS is morphologically subdivided in mitral and/or aortic atresia or stenosis, respectively. Neonates with HLHS, but even HLHC, remain stable as long as a parallel circulation is

balanced or still in part assured. It has to be considered that about 6 % of HLHS patients have a complete intact atrial septum at birth and up to 22 % a severely restrictive atrial septum, which is associated with an increased rate of mortality [16, 17]. Additionally, the HLHS patients have to be classified in order to adjust the complexity according to specific patient and procedural characteristics prior to initial hybrid stage I palliation. Risk factors are examined for their potential influence on procedure-related mortality which includes age, prematurity, birth weight, weight at surgery, multiple pregnancies, prenatal diagnosis, lowest preoperative pH, organ dysfunction, and, in addition to the exact cardiac diagnosis of HLHS or variant with or without the presence of aortic atresia, genetic or chromosomal abnormality; we recommend to calculate the comprehensive Aristotle score in term if the neonate would receive a Norwood palliation [18]. In HLHC patients the exact cardiac diagnosis has to be determined in assessment of an early corrective or Norwood-like palliation before hybrid procedure is considered. In case of a decision for hybrid approach, the time and mode of the follow-up corrective surgery is hypothesized not at least for fair parental counseling, which has to include the current operative mortality for the staged procedure of hybrid strategy [4, 7, 11].

28.3 Diagnostic Tools

28.3.1 Fetal Echocardiography

The outlook for newborns with hypoplastic left heart (HLH) has substantially improved over the last decade. However, differences in outcome among various anatomical subgroups are still described. In Giessen a strong fetal diagnostic and prenatal therapeutic program improved the outcome of all congenital heart defects most prominent in the group of HLHS and HLHC. Even highly dedicated diagnosis is carried out. In this context, prenatal assessment of ventriculocoronary connections and ventricular endocardial fibroelastosis (EFE) in hypoplastic left heart did not limit the results of surgical-interventional palliation and short-term outcome. We could find that EFE predominantly occurred in the subgroup of MS/AA and MA/AA and in those cases with aortic valve stenosis and evolving HLH. The overall hospital survival on an intention-to-treat basis was 91.2 % (52/57 newborns). Hospital survival was 91 % for the subgroup of cases with MS/AA and for all other anatomical subgroups [19].

In summary, prenatal diagnostics allows to offer hybrid approach with low procedural mortality and with high success rate. For neonates born with HLHS and HLHC at the University of Giessen, cardiogenic shock becomes a rarity over the last decade; only two patients with complete obstructive interatrial septum and lymphangiectasia could postnatally not be treated with long-term success despite cardiac transplantation in one of them. Considering our animal studies the use of self-expnadable stents (Sinus-SuperFlex-DS, Optimed, Germany) are currently our stents of choice to unload left atrial pressure, even by transhepatic access [20].

28.3.2 Neonatal Echocardiography: Magnetic Resonance Imaging

The anatomic diagnosis of HLHS and HLHC and the cardiovascular function are based on the immediately performed two-dimensional echocardiography. Magnetic resonance imaging (MRI) and heart catheterization are added for analysis of special anatomical and functional details. The presence of aortic valve atresia or annulus hypoplasia or absence of the left ventricle and a duct-dependent systemic circulation with or without retrograde flow in the aortic arch should be evaluated as well as the atrioventricular valve(s) and right (left) ventricular function. Obstruction of one or all pulmonary venous connections and even a stenosis within an anomaly of return have to be treated, if a significant mean gradient greater than 5–8 mmHg is present on Doppler interrogation at the level of the interatrial septal communication or anomalous pulmonary venous connection.

Cardiac magnetic resonance imaging (*CMRI*) becomes an important tool in neonatal period to analyze exactly the aortic arch and the junction of duct to descending aorta as well as to exclude myocardial perfusion deficits. The CMRI is in particular of high interest prior to comprehensive stage II and for diagnostic reasons before Fontan completion. In concert of a lot of answered questions, the persistence of aortopulmonary collateral flow, its relation to pulmonary artery size, as well as influence on ventricular dimensions can optimally visualized by CMRI [21].

28.3.3 Surgical-Interventional Aspects of the Hybrid Stage I

In terms of the physiopathology, hybrid approach consisting of bilateral pulmonary banding (bPAB), percutaneous duct stenting, or in some long-term prostaglandin infusion and atrio-septostomy including stent placement is performed for lung protection, preserving adequate systemic perfusion and unloading of the left atrium, respectively.

Bilateral pulmonary arterial banding is performed by median sternotomy followed by subtotal thymectomy and limited cranial pericardiotomy of 3–4 cm in length. Two pieces of 3.5 mm PTFE tube are cut in about 1.5–2 mm width for bPAB in patients with body weight above 2.5 kg and 3 mm PTFE bands in lower weight. The bands are fixed by using a 6/0 Prolene suture. Pericardial space is washed out with normothermic saline before closure of the pericardial space in that the pericardial ends are reapproximated completely with a running 6/0 PDS suture to limit adhesions at comprehensive stage II operation. Following these algorithms intrapericardial adhesions do not complicate or prolong comprehensive stage II operation.

Stenting of the ductus arteriosus is carried out in all patients by percutaneous transcatheter approach utilizing 4 F sheath for femoral vein or artery access, since novel designed self-expandable Sinus-SuperFlex-DS stents with the CE mark for duct stenting in newborns' (OptiMed, Karlsruhe, Germany) duct are

stented mostly from the arterial access [4, 11]. After the initial learning curve, heart catheterization for duct stenting and atrial septum manipulation is routinely performed in sedated patients, when surgical bilateral pulmonary artery banding (bPAB) is already finished and the patient extubated. In high-urgency patients, parts of stage I should be performed considering the reason for the patient's deterioration: surgical bPAB in case of a pulmonary runoff, duct stenting if the duct remained obstructed despite prostaglandin infusion, or interventions to solve life-threatening atrial septal or pulmonary vein obstructions [22, 23]. Stent size and positioning within the duct is based on a right lateral oblique 30° and 90° lateral angiogram, which can be done by hand injection of contrast medium through a 4 F Judkins or 4 F multipurpose catheters positioned in the pulmonary trunk and/or descending aorta, respectively. Initially, the different types of balloon-expandable stents were used for stenting the duct. Since 2006 nearly exclusively self-expandable sinus-Repo delivered through 5 F femoral sheath was used. Currently Sinus-SuperFlex-DS stents (OptiMed, Karlsruhe, Germany) are certificated with CE mark; they are deliverable through 4 F sheath and available in widths of 7, 8, 9, and 10 mm and lengths of 12, 15, 18, 20, and 24 mm, respectively. The choice of stents is largely influenced by the ductal anatomy and the morphology of the ductal-aortic junction. Additional narrowed aortic isthmus or aortic coarctation is treated, if necessary by 9 × 5 or 6 mm Sinus-Repo self-expandable stents. Therefore, flow acceleration or narrowing of the color Doppler jet is not per se considered a contraindication for stenting among patients with aortic atresia (for further details [24, 25, 26]).

The adequacy of the atrial septal communication is determined on echocardiographic and by invasive hemodynamic data. If the atrial septal communication is found to be restrictive or even absent, a balloon atrial septostomy or deployment of an atrial septal stent currently even exclusively with a Sinus-SuperFlex-DS (15 × 8 mm) is performed; in some, stenting is performed after reopening the atrial septum by Brockenbrough or alternatively by high-frequency technique. Even, an obstructed total anomalous venous return can be connected by catheter technique [23]. Considering the persistence of a parallel circulation after hybrid stage I, routinely the patients are discharged home on chronic treatment with 1 × 0.1–(0.2) mg/kg bisoprolol and lisinopril, respectively; medication of digoxin and furosemide is routinely avoided. The main two indications to combine both drugs are to reduce oxygen consumption by avoiding unnecessary high heart rate and consecutively breath rate and to reduce systemic vascular resistance without endangering perfusion pressures; blocking of the neurohumoral activation reduces diastolic left-right shunt across the stented duct (Fig. 28.1).

Outpatient follow-up prior to stage II is routinely performed at 1–2-week intervals or earlier depending on the clinical condition; it includes historical information of the parents in particular how the baby is breathing during sleep, weight gain development, systolic and diastolic mean blood pressure measurements at the right arm and of the leg, which is not used by catheterization before, and pulse oximetry at arm and one leg (HLHC); after these mandatory

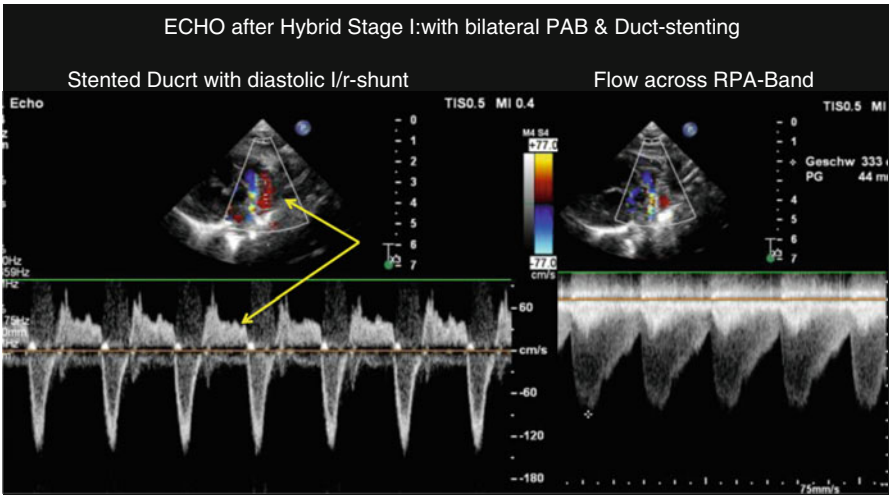

Fig. 28.1 Depicts the 2D color echocardiography of the diastolic reflow through a just implanted duct stent; additional Doppler flows show the systolic and diastolic flow pattern through the stented duct as well as across the banded right pulmonary artery

information, echocardiographic data are obtained. Patients with a hybrid approach are not referred for elective complete invasive hemodynamic and angiographic evaluation, but if a hemodynamic issue is suspected. CMRI is used, additionally to echocardiography assessment, if any unanswered diagnostic question remains open; it has to be noticed that for CMRI and elective heart catheterizations, only sedated and spontaneous breathing patients are examined, while general anesthesia is routinely avoided (Fig. 28.2).

Since 2002, as hybrid stage II was first time described by Akintuerk et al. [10], several modifications were preformed and adapted mostly based on the patient's anatomical condition. In case of an innominate subclavian artery, the artery wall is used for aortic arch reconstruction in some patients [4, 6, 11]. Additionally, some patients underwent comprehensive stage II not only without circulatory but even without cardiac arrest [4]. The stage II surgical reconstruction consisted of amalgamation of the proximal ascending aorta with the main pulmonary artery, removal or resection of the ductus/stent complex, aortic arch reconstruction, atrial septectomy, removal of the branch pulmonary artery bands with routine angioplasty or left pulmonary artery stenting in one, and superior cavo-pulmonary connection; left bidirectional Glenn is performed if a left SVC without a bridging vein is present. Considering completion of stage III in terms of Fontan circulation, a total cavo-pulmonary connection is performed without circulatory or cardiac arrest by utilizing an extracardiac conduit in most but not all with surgical fenestration. Transcatheter fenestration is performed, if necessary [26, 27]. The variants of biventricular repair are described in part previously, as well as the surgical technique of heart transplantation (HTX) with the special aspects of the morphology in patients with HLHS [6, 7, 28].

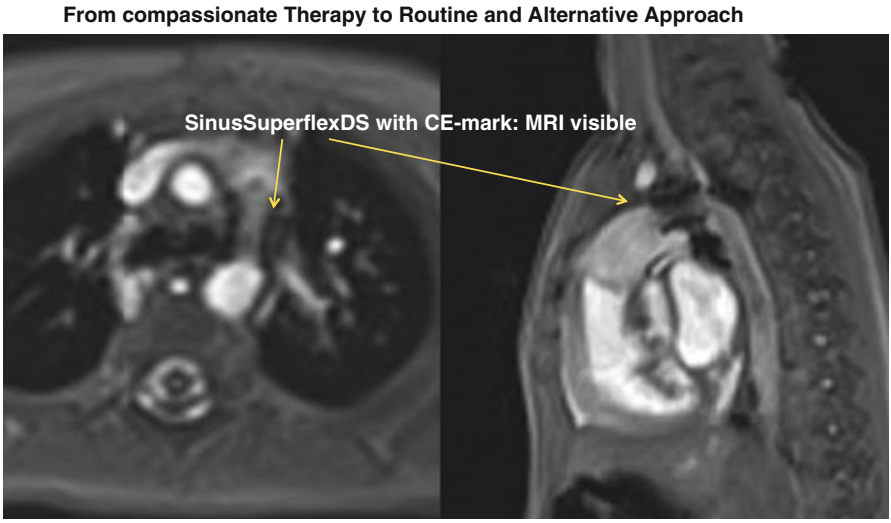

Fig. 28.2 Shows magnetic resonance imaging of the visible self-expandable Sinus-SuperFlex-DS positioned in the arterial duct in sagittal and coronary plane. Not at least based on the technical improvements, the hybrid developed from a rescue to a first-line approach in neonates with HLHS

28.3.4 Critical Patients

At least four different kinds of features are described in HLHS, HLHC, and variants:

I. HLHS with extreme hypoplastic ascending aorta without V connection to the aortic arch
II. HLHS with restrictive and/or complete obstructed atrial septum or obstructed total anomalous pulmonary venous return (TAPVR)
III. HLHS with myocardial dysfunction with or without presence of coronary sinusoids, fistulae, or dysplastic tricuspid valve
IV. HLHC with similar critical anatomical or functional issues (I–III), but in particular with residual diastolic dysfunction of the sub-aortic left or even right (ccTGA) ventricle

28.3.5 Results

Our 15-year follow-up data and further updated results are published and in press, respectively [4, 7, 11]. Between June 1998 and October 2015 meanwhile, 193 patients with the diagnosis of HLHS, HLHC, and variants received a surgical-interventional hybrid stage I in the Pediatric Heart Center Giessen. Among the

group of 193 patients, a cohort of 41 patients who have been defined to have borderline/hypoplastic left ventricular structures and seven patients with the initial diagnosis of HLHS were later amenable to receive a biventricular circulation after hybrid stage I procedure [4]. Comfort care was provided in eight patients on the basis of a family decision to abandon any therapeutic measure. 137 patients were palliated with the Giessen hybrid stage I procedure for a univentricular palliation or a primary heart transplantation ($n=8$). No patient is excluded due to complicated preoperative status such as cardiopulmonary shock or syndromatic features without an explicit family decision. Median age of patients at hybrid stage I was 6 days (0–237). Median weight at hybrid stage I procedure was 3.2 kg (1.2–7).

Operative mortality has been defined 30-day mortality postoperatively. Interstage mortality is defined for patients who died between 30 days postoperatively and the following stage of palliation. Re-interventions are defined as any surgical or interventional procedure that was required due to a cardiac or hemodynamic problem.

Figure 28.3 shows a flow chart of the number of patients at different stages, operative and interstage deaths during hybrid palliation.

Median follow-up time after hybrid stage I palliation ($n=129$) is 4.8 years (0–17.5). A comprehensive stage II operation has still to be performed in four patients, and Fontan completion is planned in 26 patients. The number of patients who underwent HTX was two and three patients after hybrid stage I and after comprehensive stage II, respectively. These patients are alive. Another two patients were listed for HTX late following Fontan operation and died on the waiting list. Two patients received HTX after Fontan completion, but both died in the follow-up.

So far, the overall mortality of all patients receiving Giessen hybrid stage I, including the eight patients with comfort therapy, is 19.6 %. The overall unadjusted cumulative operative and interstage mortality of all patients with univentricular strategy is 19.3 % (25 of 129 patients) during a 17-year follow-up. Operative mortalities were 2.2 %, 4.8 %, and 0 % at hybrid stage I, for comprehensive stage II and Fontan completion, respectively. Estimated survival of all patients who underwent hybrid stage I procedure is 79.1 % at 10-year follow-up. Similarly, patients who were directed to univentricular palliation or HTX after Giessen hybrid stage I ($n=129$) had a survival estimate of 78 % at 10-year follow-up. Birth weight (<2.5 kg) had no significant impact on survival [4, 11]. Additionally, five patients with HLHS and concomitant total anomalous pulmonary venous connection are most recently alive. Three patients received Fontan operation, one patient received biventricular correction and one patient is still awaiting Fontan operation. The Achilles heel of the hybrid approach is the fate of the left pulmonary artery; we analyzed the effect with and without stenting of the growth and size of the pulmonary arteries [11]. The freedom from pulmonary artery intervention at 1-year follow-up is 55 % and decreases at 10- and 15-year follow-up to 35 %. When the rate of interventions is separately analyzed between the years of initial experience 1998–2007 in comparison with recent practice between 2008 and 2015, no significant difference in the total number and the probability of freedom from intervention was detected. Before the year 2004 we had used a high number of aortic and pulmonary homografts for aortic reconstruction and were faced with the problem of extensive

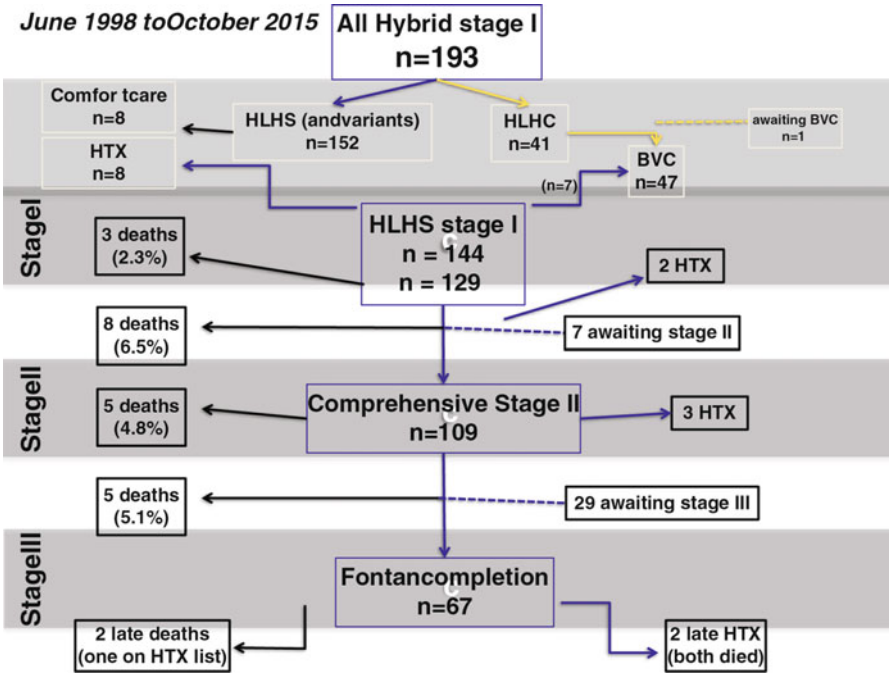

Fig. 28.3 Flow chart of patients at different stages, operative and interstage deaths during hybrid palliation

calcifications during the Fontan completion. The use of the curved porcine xenograft for the aortic arch reconstruction resulted in a non-calcified aortic arch, which eased the surgical preparation at the Fontan completion. A re-intervention on the aortic arch after the comprehensive stage II operation was needed in 17 %. These technical details are important issues with the need for continuous improvement by worldwide knowledge exchange. However at the end, the individualized quality of life, in particular the neurological outcome, and the long-term follow-up will tell us the full truth in the future.

28.4 Summary

Prenatal diagnosis of prenatally HLHS and HLHC improves the postnatal management. Neonates are not further admitted in cardiogenic shock because of severe obstruction of the arterial duct, pulmonary runoff in unrestricted interatrial communication, or by severe atrial septum restriction. Surgical options are based on a three-staged procedure or heart transplantation (HTX). Independent of the improvements of surgical, interventional, and intensive care for newborns with HLHS, the parents have to decide for classical Norwood stage I, surgical-interventional treatment (hybrid stage I) and HTX, or compassionate therapy after an intense repetitive

communication. Hybrid stage I is a lifesaving procedure in particular to high-risk HLHS patients. Presupposed, the pediatric heart team is familiar with a hybrid strategy and with any surgical and interventional step of the approach. Only then, the hybrid approach gives the chance to avoid neonatal high-risk operations, utilizing cardiopulmonary bypass with or without cardiac arrest. Hybrid approach per se has not to be associated with mortality. From the current available techniques and materials at least in Europe, there is almost no reason for death from the procedural point of view, as it was in the past, when the hybrid procedure started [5, 29]. Considering the parts of the whole hybrid approach, we are convinced that most causes of postnatal cardiovascular failure can be easliy solved by a single or orchestral surgical-interventional procedure. In case of prostaglandin refractory duct obstruction with consecutive metabolic acidosis, percutaneous duct stenting is the treatment of choice; in systemic low cardiac output due to pulmonary runoff, surgical bPAB is the most effective measure; for a restrictive or intact atrial septum, pulmonary venous decompression by catheter techniques has to be recommended at the immediate and first step before completing hybrid stage I. We emphasize that the outcome of newborns with HLHS is strictly dependent on straightforward decision-making and based on the goal to offer an effective but "gentile medicine" in terms of minimal invasiveness [30].

Perspective Hybrid stage I will be performed in a spontaneous breathing, well-sleeping newborn by percutaneous transcatheter technique. The surgeon will focus on a comprehensive stage II while preparing for stage III, so that even the transcatheter Fontan completion can be performed again in an only sedated patient. Bacha and Hijazi [31] mentioned years ago that becoming a "learning leader" is a condition sine qua non to achieve satisfactory results. In Columbus and Giessen, the surgeons and pediatric cardiologists made the decisions to change their classical programs for favoring hybrid stage I approach in most with HLHS or univentricular variants. In Giessen the hybrid stage I approach is additionally used for newborns with HLHC to postpone a high-risk operation from the neonatal period to late infancy with augmenting the options and to avoid an initial decision for a univentricular strategy.

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